Summary Table of Study Protocol

Title	Real World Use, Effectiveness and Safety of Teprotumumab among Thyroid Eye Disease Patients treated in China BOAO Pilot Zone: A Retrospective Cohort Study
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Date of last version of the protocol	Not Applicable (NA)
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Medicinal Product	TEPEZZA®
Device	Not Applicable (NA)
Product Reference	Not Applicable (NA)
Procedure Number	Not Applicable (NA)
Joint PASS	No
Research Question and Objectives	**Primary Objective:** • Assess proportion of patients with proptosis response as of last intravenous infusion of teprotumumab **Secondary objective:** • Describe baseline characteristics of patients at teprotumumab initiation, and the teprotumumab use at follow-up • Describe real-world effectiveness of clinical outcomes of interest • Describe patient-reported outcomes • Describe real-world safety of teprotumumab
Country of Study	China
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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled Real World Use, Effectiveness and Safety of Teprotumumab among Thyroid Eye Disease Patients treated in China BOAO Pilot Zone, dated 26 December 2024 and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Investigator: Date (DD Month YYYY)

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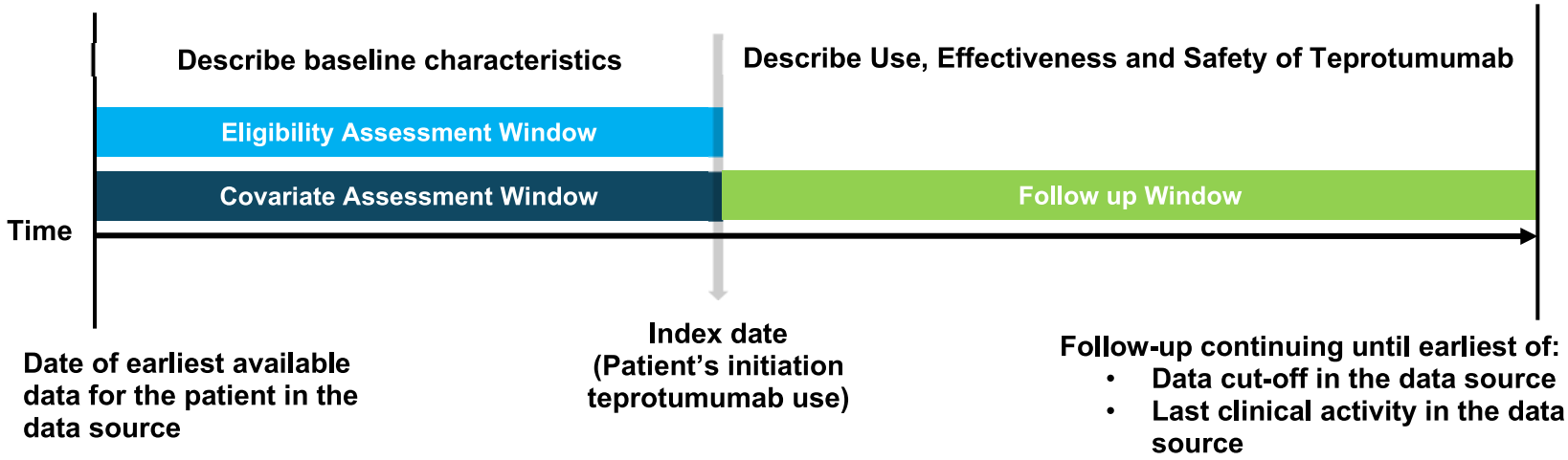
Study Design Schema



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2. List of Abbreviations

AE	Adverse Events
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CAS	Clinical Activity Score
CRF	Case Report Form
EC	Ethics Committee
EHR	Electronic Health Records
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
SOP	Standard Operating Procedure
TED	Thyroid Eye Disease
TEAE	Treatment-emergent Adverse Events

3. Responsible Parties

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4. Abstract

- Study Title

Real world use, effectiveness and safety of teprotumumab among thyroid eye disease patients treated in China BOAO Pilot Zone.

- Study Background and Rationale

In China, the prevalence of Graves' disease among adults is 0.53% based upon a population-based assessment of thyroid ultrasonography and serum concentrations of thyroid hormones, thyroid antibodies, and urine iodine concentration. Among patients with Graves' disease, an estimated 25% to 40% have some symptoms of thyroid eye disease (TED). The severe cases of TED can manifest as pronounced proptosis, diplopia (due to uneven motility restriction), and optic nerve compression leading to

potential vision loss. TED is quite heterogeneous in symptoms and severity between patients – in part based on age, sex, genetics, specific characteristics of each person's autoimmune response. Hence, managing TED often involves tailoring therapies to each patient's specific symptom profile and severity, with ongoing monitoring to adjust therapy along as symptoms evolve. Common ocular symptoms include proptosis (eye bulging), pain, irritation, and diplopia (double vision) resulting from muscle involvement and restriction. Other manifestations may include eyelid retraction and swelling, as well as vision impairment due to optic nerve compression.

Two randomized controlled trials among subjects with moderate-to-severe, high activity TED (TED01RV phase 2 & OPTIC phase 3) demonstrated that teprotumumab resulted in better outcomes than placebo with respect to proptosis, inflammation quantified according to Clinical Activity Score (CAS), diplopia, and quality of life. Teprotumumab received US FDA approval for the treatment of TED in January 2020. In 2023, the FDA approved indication was updated to "TEPEZZA is indicated for the treatment of Thyroid Eye Disease regardless of Thyroid Eye Disease activity or duration". No inter-ethnic differences of teprotumumab were observed between global TED subjects and East Asian TED patients in the combined analyses of randomized controlled trials (TED01RV phase 2, OPTIC phase 3, OPTIC-J phase 3 for Japanese population). Real-world studies of teprotumumab in North America clinical practice have further informed the therapy's safety and effectiveness.

Since April 2022, teprotumumab has been available in China through pre-registration use per FDA prescribing information in the China Hainan BOAO Pilot Zone at the Rare Disease Clinical Medical Center. This study aims to describe the use, effectiveness and safety of teprotumumab among Chinese patients treated with teprotumumab at BOAO Pilot Zone.

- Study Feasibility

Following "Guidelines for real-world data used to generate real-world evidence" (NMPA 2021), Amgen has conducted feasibility assessment for the available infrastructure in BOAO Pilot Zone to support study execution, the data accessibility, the ethical and security process, availability of key variables of interest, lab and imaging reports, adverse events, and study specific outcomes. Based upon this evaluation, the data source (described below) should support addressing the study objectives.

- Objectives

Objectives:	**Endpoints**
Primary	
• Assess proportion of patients with proptosis response as of last intravenous infusion of teprotumumab.	• Proptosis response[1] as of the last infusion
Secondary	

• Describe baseline characteristics of patients at teprotumumab initiation, and the teprotumumab use at follow-up.	• Baseline characteristics
	  ○ Demographic
	  ○ Clinical characteristics[2]
	  ○ Medical history[3]
	• Teprotumumab use
	  ○ Dose and dosing schedule
	  ○ Total number of infusions and duration
	  ○ Dose reduction and modification, interruption, discontinuation and causes

• Describe real-world effectiveness of clinical outcomes of interest.	• Proptosis
	  ○ All available proptosis measurements by eye for each patient
	  ○ The change in proptosis measurement between baseline and the last infusion by eye
	• Clinical Activity Score (CAS)
	  ○ All available measures of CAS items by eye for each patient
	  ○ Achieving CAS value of 0 or 1 as of the last infusion among patients with active TED at baseline[4]
	• Overall response[5,6] as of the last infusion among patients with active TED[4]
	• Diplopia
	  ○ All available measures of diplopia for each patient
	  ○ The binocular diplopia response[7] as of the last infusion
	  ○ The complete diplopia response[8] as of the last infusion.

• Describe patient-reported outcomes.	• Quality of life ○ All available patient-reported quality of life for each patient, overall and at subscale level ○ The change in quality of life between baseline and the last infusion, overall and at subscale level
• Describe real-world safety of teprotumumab.	• The incidence of adverse events (AE)[9] between the administration of the first dose and 30 days after the last dose of teprotumumab • Status of specific AEs[10] up to 6 months after last infusion of teprotumumab

Notes:

1. Proptosis response is defined as having a ≥ 2 mm reduction in proptosis measurement from baseline in the more severely affected eye without deterioration (≥ 2 mm increase) of proptosis in the fellow eye following the last infusion.
2. Clinical characteristics include body mass index; smoking status; TED-related clinical characteristics include disease duration, activity and the according CAS items if available, severity, eye symptoms (e.g., eyelid retraction if available, proptosis, diplopia, ocular motility), CAS, CT/MRI measurement (e.g., optic nerve involvement), and quality of life.
3. Medical history includes history of compressive optic neuropathy, hyperglycemia, inflammatory bowel disease (IBD), infusion reactions, and hearing impairment; therapeutic history for thyroid disease (Graves' disease or others) before teprotumumab administration; therapeutic history for TED before teprotumumab administration and complications if any; comorbidities; concomitant treatments; lab tests.
4. Active TED is defined as CAS≥3 on a 7-point scale at baseline.
5. Overall response is defined as having ≥ 2-point reduction in CAS AND ≥ 2 mm reduction in proptosis from baseline in the most severely affected eye, provided there is no corresponding deterioration (≥ 2-point increase in CAS or ≥ 2 mm increase in proptosis) in the fellow eye following the last infusion.
6. The more severely affected eye is defined as the one with the greater proptosis. If both eyes have equal proptosis, the eye with the higher CAS score will be considered more severely affected. If both proptosis and CAS scores are equal, the right eye will be chosen.
7. The binocular diplopia response is defined as having baseline binocular diplopia grade > 0 and a reduction of ≥ 1 grade between baseline and the last infusion.
8. Complete diplopia response is defined as having baseline binocular diplopia grade > 0 and achieving grade of 0 as of the last infusion.
9. Adverse events to be collected include any AE; specific AEs, inclusive of infusion-related reactions, hyperglycemia, hearing impairment, and new onset or exacerbation of inflammatory bowel disease (IBD); serious adverse event (SAE); AE leading to treatment discontinuation; AE leading to death.
10. Specific AEs include infusion-related reactions, hyperglycemia, hearing impairment, and new onset or exacerbation of IBD.

– Hypothesis

  Study objectives are descriptive in nature.

- Study Design

A retrospective cohort will be followed longitudinally for endpoints.

- Study Population and Data Source

The target population is patients with TED that have received teprotumumab treatment in BOAO Pilot Zone. A case report form will be used to extract the relevant structured

and unstructured data from the electronic health records of Hainan BOAO Rare Disease Clinical Medical Center.

For a patient, typically residing within mainland China, to receive teprotumumab in the BOAO Pilot Zone, the patient needs to be admitted to the Rare Disease Clinical Medical Center and return in person for administration of therapy per FDA approved prescribing information (10 mg/kg for the first infusion and 20 mg/kg for subsequent infusions every 3 weeks over a period of 24 weeks). The interval between infusions or assessment is typically 3 weeks, though it may vary slightly based on the patient's feasibility. As teprotumumab is in the pre-registration program, close monitoring and reporting of safety events is required by the government. Hence, expectation that safety endpoints will be well captured. At each visit, including baseline visit, key evaluations of the treatment outcomes (e.g., proptosis, diplopia, CAS, quality of life) are always performed using the same apparatus/form and performed by the same healthcare providers, minimizing inter-apparatus or inter-provider heterogeneity in rating before and post treatment. Eye socket (orbital) CT/MRI were conducted at least baseline and at the end of treatment to assess the extent of orbital involvement, detect optic nerve involvement, evaluate disease activity and progression. The effectiveness endpoints are expected to be sufficiently captured in this study.

- Summary of Patient Eligibility Criteria

Inclusion Criteria

  - Receipt of at least 1 infusion of teprotumumab for the treatment of TED
  - Obtained study specific informed consent form (ICF), if required

Exclusion Criteria

  - Documentation of non-Chinese ethnicity.

- Follow-up

Index date per patient: Date of initial teprotumumab use.
Follow-up per patient will continue through earliest date of:

  - Data cut-off in the data source, i.e., ethics committee (EC) submission date (~ Q2 2025)
  - Last clinical activity in the data source

- Variables

Endpoints listed in the table above will be extracted during study period.

- Study Sample Size

By the time of data cut-off, an estimated 10 teprotumumab treated patients will be eligible for study inclusion. For proptosis response rate consistent with clinical trials and real-world studies (≈ 70%), the estimated 95% Clopper-Pearson exact interval is [34.8%, 93.3%] based on the sample size as 10.

- Data Analysis

All analyses will be descriptive in nature. Summary statistics for available continuous variables (e.g., proptosis measurement and change, CAS, diplopia, quality of life and change) will include number of patients, mean, standard deviation (SD), median, and range (min, max). Categorical variables (e.g., proptosis response, overall response, achieving CAS value of 0 or 1, binocular diplopia response, complete diplopia response, incidence of AEs, status of AEs) will be summarized using frequencies and percentages.

In addition to descriptive statistics, all available patient level data will be presented to understand the richness of available data, and the variability of these patients in great detail.

For safety outcomes, all patients in the study who meet the eligibility criteria will be included in the analysis.

For all effectiveness outcomes and patient-reported outcomes, endpoints including proptosis response, change in proptosis measurement, achieving CAS value of 0 or 1, overall response rate, binocular diplopia response and complete diplopia response, and change in quality of life, will be evaluated as of the last infusion. The endpoints will be evaluated based on assessments conducted in BOAO Pilot Zone to avoid inter-apparatus or inter-provider heterogeneity before and after treatment.

For all effectiveness outcomes and patient-reported outcomes, those who received $\geqslant$4 infusions of teprotumumab and have completed corresponding assessments following the last infusion will be included. Subsequent infusions must be within 120 days following the previous one. Any infusion administered 120 days or more after the previous one will be classified as retreatment and excluded from the effectiveness analysis.

A subgroup analysis of effectiveness outcomes will be conducted for patients completed 8 infusions.

5. Amendments and Updates

None

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Thyroid eye disease (TED), also known as Graves' ophthalmopathy or Graves' orbitopathy and thyroid-associated ophthalmopathy, is a rare, serious, debilitating, and painful autoimmune disease associated with major comorbidities that can lead to blindness. Thyroid eye disease is commonly associated with Graves' hyperthyroidism/disease, but also occurs in a proportion of patients with other autoimmune thyroid diseases, including Hashimoto's thyroiditis. The natural history usually involves an "active TED" phase which is an autoimmune inflammatory response targeting orbital soft tissues leading to retro-orbital expansion of muscle and fat tissue and an "chronic TED," phase in which the inflammation has mostly subsided and transitioned to tissue expansion remodeling. Active TED typically lasts 1 to 3 years, and then the inflammation spontaneously subsides to leave the pathology of chronic TED (Bartalena et al, 2016). The severe cases of TED can manifest as pronounced proptosis, diplopia (due to uneven motility restriction), and optic nerve compression, leading to potential vision loss. Hence, managing TED often involves tailoring therapies to each patient's specific symptom profile and severity, with ongoing monitoring to adjust therapy along as symptoms evolve. The severity of symptoms can range from mild discomfort or cosmetic concerns to more debilitating conditions that impair vision. Common ocular symptoms include proptosis (eye bulging), pain, irritation, and diplopia (double vision) resulting from muscle involvement and restriction. Other manifestations may include eyelid retraction and swelling, as well as vision impairment due to optic nerve compression.

Studies have shown that the incidence and prevalence of TED in the Asian population are similar to those observed in the Caucasian population. In China, the prevalence of Graves' disease among adults is 0.53% based on thyroid ultrasonography and serum concentrations of thyroid hormones, thyroid antibodies, and urine iodine concentration (Li et al. 2020; Wang et al 2020). Among patients with Graves' disease, an estimated 25% to 40% can have some symptoms of TED (Bartalena et al, 2020).

According to the Chinese guideline on the diagnosis and treatment of thyroid-associated ophthalmopathy (OODGCOSCMA, 2022), the first-line treatment for moderate to severe active TED in China is IV corticosteroid pulse therapy, which demonstrated a 70% to

80% improvement in ocular symptoms (OODGCOSCMA, 2022). However, glucocorticoids have limited efficacy in reducing proptosis and may cause side effects that impact various organ systems, such as osteoporosis and infection (Moleti et al, 2016; Miśkiewicz et al, 2014; Bartalena et al, 2012; Marcocci et al, 2012; Wichary and Gasińska, 2012). While surgical options are available for inactive TED to address proptosis and strabismus, they require clinical stability and euthyroid status and is with surgical complication risk (OODGCOSCMA, 2022). The current therapeutic landscape highlights an urgent medical need for more effective treatments for TED.

6.2 Rationale

Teprotumumab is a fully human monoclonal antibody that targets IGF-1R. Two randomized controlled trials (phase II trial TED01RV and phase III trial OPTIC) among subjects with moderate-to-severe and high activity TED (Douglas et al. 2020, Douglas et al. 2022) demonstrated that teprotumumab resulted in better outcomes than placebo with respect to proptosis, inflammation quantified according to Clinical Activity Score (CAS), diplopia. Teprotumumab received FDA approval for the treatment of TED. In 2023, the FDA approved indication was updated to “TEPEZZA is indicated for the treatment of Thyroid Eye Disease regardless of Thyroid Eye Disease activity or duration”. No inter-ethnic differences were observed of teprotumumab between global TED subjects and East Asian TED patients in the combined analyses of randomized controlled trials (TED01RV, OPTIC, OPTIC-J [phase 3 of active TED in Japan]). Real-world studies of teprotumumab in North America clinical practice have further informed the therapy’s safety and effectiveness (Table 1).

Since April 2022, teprotumumab has been available in China through pre-registration use per FDA prescribing information at the China Hainan BOAO Pilot Zone providing an opportunity to assess the use, safety, and effectiveness of teprotumumab among Chinese patients in real-world clinical settings.

Table 1. Overview of Real-world Studies of Teprotumumab

Study	Country	Population	N	Proptosis Response Definition	Proptosis Response Rate (%)	Proptosis - Change from Baseline (mean [SD/CI], mm)
1 (Ho et al, 2023)	USA	TED	74	Proptosis reduction >2mm	Partial treatment exam: 73% Final follow-up: 77%	NR
		Active TED	62	Proptosis reduction >2mm	Partial treatment exam: 73% Final follow-up: 77%	Partial treatment exam: -2.9
		Inactive TED	12	Proptosis reduction >2mm	Partial treatment exam: 75% Final follow-up: 75%	Partial treatment exam: -2.8
2 (Ugradar et al, 2023)	USA	TED	20	NA	NA	-4.3 (1.6)
		Acute TED	10	NA	NA	-4 (1.9)
		Chronic TED	10	NA	NA	-2.9 (2.9)
3 (Lu et al, 2022)	USA	TED	48	Responder: proptosis reduction ≥2mm at post-treatment Regressor: proptosis regression (≥2mm increase from post-treatment to long-term follow-up)	Responder: 70.2% Regressor: 28.2%	Post-treatment: -2.91 (2.18)
4 (Diniz et al, 2021)	USA	TED	21	Proptosis reduction >2mm	71.4%	-2.5 (1.8)
		Mild	6	NA	NA	-1.6 (0.9)
		Moderate to severe TED	12	NA	NA	-3.0 (1.6)
		Stable TED	11	NA	NA	-2.3 (1.4)
		Active TED	10	NA	NA	-2.0 (2.2)
5 (Ugradar et al, 2022)	USA	Chronic TED	31	Proptosis reduction ≥2mm	90%	-3.5 (0.4)
6 (Ting et al, 2023)	USA	TED	22	NR	NA	-2.91 (1.97)
7 (Reshef et al, 2023)	USA	TED	24	Proptosis reduction ≥2mm	79.2% orbits	-3.47 (2.26)
8 (Adetunji et al, 2022)	USA	TED	17	NA	NA	6 weeks: -3.7 (-6.4 to -1) 12 weeks: -1.9 (-3 to -0.8) 24 weeks: -3.4 (-5.6 to -1.3) Last follow-up: -2.1 (-3 to -1.2)
9 (O'dell et al, 2023)	USA	TED	15	NA	NA	Right eye: -2.3 (2) Left eye: -3.2 (1.9)
10 (Ugradar, 2022)	NA	TED	21	NA	NA	-3

CI = Confidence Interval, NA = Not available, SD = standard deviation.

6.3 Feasibility (fit-for-purpose evaluation)

Active and accessible data

Teprotumumab became available in Hainan BOAO Rare Disease Clinical Medical Center in April 2022 through a pre-registration program. Teprotumumab will be continuously available at BOAO Pilot Zone before data cut-off (approximately Q2 2025). Patient-level data in BOAO Pilot Zone will be available and can be submitted to enable review and result reproducibility by regulatory authorities.

Ethical and security requirements

The study will follow requirements of the governance and sites. All data extracted will be anonymized. The study protocol will be reviewed by the EC of the site. In addition to governance and the EC, the study will comply with Amgen's global standard operating procedures and technical governance for observation research.

Coverage of critical variables

The electronic health record database in BOAO Rare Disease Clinical Medical Center includes patient clinical history, demographic, treatments, diagnosis, lab, imaging, and also a pre-specified hospital department tracking form. As part of the database, this form was used to record more granularity of the treatment and outcomes at practice.

Accuracy of the definition of exposure, outcomes, and covariates

Eligible patients need to be physically at BOAO Rare Disease Clinical Medical Center to receive treatments, enabling complete teprotumumab exposure assessment in electronic health record database. As teprotumumab is used through the pre-registration program, local government authorities require close monitoring. Clinicians are required to report safety events of special drugs used in BOAO Pilot Zone, which enables describing the reported safety event in the database. The pre-specified hospital department tracking form, contains follow-up evaluation (both within and outside BOAO) of the treatment outcomes (e.g., eye socket [orbital] CT/MRI, proptosis, diplopia, CAS, quality of life). Specifically, these exams for effectiveness assessment are always performed using the same apparatus/form and performed by the same healthcare providers, minimizing inter-apparatus or inter-provider heterogeneity in rating before and post treatment.

Sample size

This is a descriptive study in which patient-level data on effectiveness and safety will be analyzed. By the time of data cut-off, approximately 10 teprotumumab-treated patients in BOAO Pilot Zone, will be eligible for enrollment. This number is in the same magnitude of other real-world studies published (Diniz, Cohen et al. 2021, Adetunji, Nguyen et al. 2022, Ugradar 2022, O'Dell, Mussatto et al. 2023, Reshef, Marsiglia et al. 2023, Ting, Ozzello et al. 2023, Ugradar, Zimmerman et al. 2023), which we believe is adequate to generate clinical meaningful results.

For proptosis response rate consistent with clinical trials and real-world studies (≈ 70%), the estimated 95% Clopper-Pearson exact interval is [34.8%, 93.3%] based on the sample size as 10.

6.4 Statistical Inference (Estimation)

Study objectives are descriptive in nature.

7. Research Question and Objectives

7.1 Primary

The primary objective is to assess proportion of patients with proptosis response as of last intravenous infusion of teprotumumab.

7.2 Secondary

The secondary objectives are to:

- Describe baseline characteristics of patients at teprotumumab initiation, and the teprotumumab use at follow-up.
- Describe real-world effectiveness of clinical outcomes of interest.
- Describe patient-reported outcomes.
- Describe real-world safety of teprotumumab.

8. Research Methods

8.1 Study Design

A retrospective cohort will be followed longitudinally for endpoints. RWE guidance documents were used to inform the planning and design of this study (NMPA, 2023a; ICH M14, 2024), data curation (NMPA, 2021) and communication of this study (NMPA, 2023b)

8.2 Setting and Study Population

The target population is patients with TED that have received teprotumumab treatment in BOAO Pilot Zone. By the time of data cut-off, approximately 10 teprotumumab treated patients will be eligible for enrollment. Details of data sources are provided in Section 8.4.

8.2.1 Study Period

The study eligibility period extends from the patients' index date (i.e., the initiation teprotumumab use) to the end of study period, defined as the earliest occurrence of data cut-off date or patient's last activity date in the data source. The first available teprotumumab use in BOAO Pilot Zone is around April 2022 through a pre-registration program. The data cut-off will be the Ethics Committee (EC) submission date (~ Q2 2025).

8.2.2 Selection and Number of Sites

Hainan BOAO Rare Disease Clinical Medical Center, the only facility providing treatment of teprotumumab in China mainland, will be included.

8.2.3 Patient Eligibility

Eligibility criteria will be evaluated during data extraction and reasons for ineligibility will be extracted in the case report form (CRF).

8.2.3.1 Inclusion Criteria

- Receipt of at least 1 infusion of teprotumumab for treatment of the TED
- Obtained study specific informed consent form (ICF), if required

8.2.3.2 Exclusion Criteria

- Documentation of non-Chinese ethnicity.

8.2.4 Matching

Not applicable

8.2.5 Baseline Period

The baseline period is defined as the period starting from date of earliest available data for the patients to the index date (inclusive). Data during this period will be extracted, including baseline demographics, clinical characteristics and medical history (see details in Section 8.3.3).

8.2.6 Study Follow-up

Follow-up per patient will continue through earliest date of:

- Data cut-off in the data source, i.e., EC submission date (~ Q2 2025)
- Last clinical activity in the data source

8.3 Variables

8.3.1 Outcome Assessment

- Primary:

  Proptosis response

  The more severely affected eye is defined as the one with the greater proptosis. If both eyes have equal proptosis, the eye with the higher CAS score will be considered more severely affected. If both proptosis and CAS scores are equal, the right eye will be chosen.

  - Proptosis response is defined as having a $\geqslant$ 2 mm reduction in proptosis measurement from baseline in the more severe eye without deterioration ($\geqslant$ 2 mm increase) of the fellow eye as of the last infusion.

- Secondary:

  Baseline characteristics

  Demographic and clinical characteristics are needed to understand the generalizability of study results. The variables will be assessed during the baseline period. For variables that can change over time recorded at the index date or the value nearest to the index date will be utilized.

  - Demographic
    - Age in years at index date
    - Sex (male, female, unknown)
  - Clinical characteristics:
    - Height in cm, weight in kg, and body mass index (BMI) in kg/m^2 at index date
    - Smoking status (current smoker, former smoker, never smoker, unknown/not documented) at index date
    - TED-related clinical characteristics at index date
      - Disease duration

- Activity, i.e., active vs chronic phase: A CAS ⩾3 on a 7-point scale is indicative of active disease, and the according CAS items if available.
- Severity of TED (mild, moderate-to-severe, sight-threatening, according to EUGOGO classification[1])
- Eye symptoms (e.g., eyelid retraction if available, proptosis, diplopia, ocular motility)
- CAS
- Orbital CT/MRI measurement (e.g., optic nerve involvement if any)
- Quality of life

- Medical history
  - History of compressive optic neuropathy, hyperglycemia, inflammatory bowel disease (IBD), infusion reactions, and hearing impairment
  - Therapeutic history for thyroid disease (Graves' disease or others) before teprotumumab administration
  - Therapeutic history for TED before teprotumumab administration and complications if any.
  - Co-morbidities
  - Concomitant treatments
  - Lab tests

<u>Teprotumumab use</u>

Patients will be considered as exposed from time of their initial date of teprotumumab administration through last administration in the EHRs by data cut-off date. Treatment information of teprotumumab will be extracted through follow-up.

- Dose and dosing schedule
- Total number of infusions and duration

- Dose reduction and modification, including causes.
- Treatment interruption and causes, time interval from interruption to re-initiation, and subsequent re-initiation of treatment (if any)
- Treatment discontinuation, including causes

Effectiveness outcomes

- Proptosis
  - All available proptosis measurement by eye for each patient
  - The change in proptosis measurement between baseline and the last infusion by eye.
- Clinical Activity Score (CAS)[2]

  Active TED is defined as CAS≥3 on a 7-point scale at baseline.
  - All available measures of CAS items by eye for each patient
  - Achieving CAS value of 0 or 1 as of the last infusion among patients with active TED at baseline.
- Overall response

  The more severely affected eye is defined as the one with the greater proptosis. If both eyes have equal proptosis, the eye with the higher CAS score will be considered more severely affected. If both proptosis and CAS scores are equal, the right eye will be chosen.

  Active TED is defined as CAS≥3 on a 7-point scale at baseline.
  - Overall response as of the last infusion among patients with active TED is defined as having ≥ 2-point reduction in CAS AND ≥ 2 mm reduction in proptosis from baseline in the more severely affected eye, provided there is no corresponding deterioration (≥ 2-point increase in CAS or ≥ 2 mm increase in proptosis) in the fellow eye.
- Diplopia
  - All available measures of diplopia for each patient

- The binocular diplopia response as of the last infusion is defined as having baseline binocular diplopia grade[3] > 0 and a reduction of ⩾ 1 grade between baseline and the last infusion.
- Complete diplopia response is defined as having baseline binocular diplopia grade > 0 and achieving grade of 0 as of the last infusion.

Patient-report outcomes

- Quality of life
  - All available patient-reported quality of life for each patient, overall and at subscale level
  - The change in quality of life between baseline and the last infusion, overall and at subscale level.

Safety outcomes

- The incidence of adverse events (AE) between the administration of the first dose and 30 days after the last dose of teprotumumab, including
  - Any AE
  - Specific AEs, inclusive of infusion-related reactions, hyperglycemia, hearing impairment, and new onset or exacerbation of inflammatory bowel disease (IBD)
  - Serious adverse event (SAE)
  - AE leading to treatment discontinuation
  - AE leading to death
- Status of specific AEs up to 6 months after last infusion of teprotumumab

Notes:

1. Classification of severity of TED (EUGOGO, 2021)

Classification	Features
Mild	Patients whose features of GO have only a minor impact on daily life that have insufficient impact to justify immunomodulation or surgical treatment. They usually have one or more of the following: • minor lid retraction (<2 mm) • mild soft-tissue involvement • exophthalmos • <3 mm above normal for race and gender • no or intermittent diplopia and corneal exposure responsive to lubricants
Moderate-to-severe	Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive).

	They usually have two or more of the following: • lid retraction ≥ 2 mm • moderate or severe soft-tissue involvement • exophthalmos ≥ 3 mm above normal for race and gender • inconstant or constant diplopia
Sight-threatening (very severe)	Patients with dysthyroid optic neuropathy and/or corneal breakdown.

2. Clinical Activity Score Assessment (Mourits et al, 1997)

Item Each item is scored (1 = present; 0 = absent) and scores for each item are summed for a total score	Description
1	Spontaneous orbital pain
2	Gaze evoked orbital pain
3	Eyelid swelling that is considered to be due to Active TED
4	Eyelid erythema
5	Conjunctival redness considered to be due to active (inflammatory phase) thyroid eye disease/Graves' ophthalmopathy (ignore "equivocal" redness)
6	Chemosis
7	Inflammation of caruncle or plica

3. Subjective Diplopia score (EUGOGO, 2006)

Subjective diplopia score:
0 = no diplopia 1 = intermittent (diplopia in primary position of gaze, when tired or when first awakening) 2 = inconstant (diplopia at extremes of gaze) 3 = constant (continuous diplopia in primary or reading position)

8.3.2 Validity and Reliability

In BOAO Pilot Zone, both structured and unstructured data elements will be extracted and validated. Any suspected data abstraction errors will be checked, confirmed or corrected with the clinical investigators responsible for the study operation, by checking the original copy. Unstructured data, which include details not directly captured in a structured electronic health record field, such as description of AEs in the medical records will require some level of manual abstraction. All abstractors will undergo systematic training before performing data extraction.

8.4 Data Sources

A case report form will be used to extract the relevant structured and unstructured data from the electronic health records of Hainan BOAO Rare Disease Clinical Medical Center.

For a patient, typically residing within mainland China, to receive teprotumumab in the BOAO Pilot Zone; the patient needs to be admitted to the Rare Disease Clinical Medical Center and return in person for administration of therapy per FDA approved prescribing information (10 mg/kg for the first infusion and 20 mg/kg for subsequent infusions every 3 weeks over a period of 24 weeks). The interval between infusions is typically 3 weeks, though it may vary slightly based on the patient's feasibility. As teprotumumab is in the pre-registration program, close monitoring and reporting of safety events is required by the government. Hence, expectation that safety endpoints will be well captured. At each visit, including baseline visit, key evaluations of the treatment outcomes (e.g., proptosis, diplopia, CAS, quality of life) are always performed using the same apparatus/form and performed by the same healthcare providers, minimizing inter-apparatus or inter-provider heterogeneity in rating before and post treatment. Eye socket (orbital) CT/MRI were conducted at least baseline and at the end of treatment to assess the extent of orbital involvement, detect optic nerve involvement, evaluate disease activity and progression. Thus, the effectiveness endpoints are expected to be sufficiently captured in this study.

8.5 Study Size

This is a descriptive study in which patient-level data on effectiveness and safety will be analyzed. By the time of data cut-off, an estimated 10 teprotumumab treated patients will be eligible for study inclusion. The following table (Table 2) provides the estimated confidence intervals for primary endpoint proptosis response rate based on the sample size of patients who received teprotumumab (N = 10, tentatively) and various proportions of interest. Given the small sample size, Clopper-Pearson exact method was used.

Table 2. Expected confidence intervals of proptosis response rate based on the sample size by various proportions

Proportion of interest	Sample size of patients	Observed number of cases	90% Clopper-Pearson exact interval	95% Clopper-Pearson exact interval
90%	10	9	[60.6%, 99.5%]	[55.5%, 99.7%]
80%	10	8	[49.3%, 96.3%]	[44.4%, 97.5%]
70%	10	7	[39.3%, 91.3%]	[34.8%, 93.3%]

The sample size of patients treated with teprotumumab will be confirmed during data cleaning and data analysis phase.

8.6 Data Management (Curation)

Data curation is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study and will comply with applicable international regulatory guidelines. The data curation and quality assurance processes for this study will be outlined in the data curation plan.

Data relevant for the study will be extracted in the CRF specifically designed for this study. Case report forms must be completed for each patient enrolled in the study. All data recorded will be anonymized. Before data extraction begins, the CRF will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements for the study before it is used to capture data from this study. This validation will confirm that the form is capable of accurately capturing the necessary data. All personnel involved in data collection will receive training on the CRF, as well as study-specific training to familiarize them with the protocols and objectives of the study. Data extraction will be conducted at the investigational center by designated and trained staff members. To maintain data integrity, the study monitor team will monitor data extraction both through remotely and in an on-site manner. The detailed review and verification of data quality is described in Section 8.6.3.

After data extraction, applicable terms will be coded according to the coding conventions for this study. All medical and health related terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Medical and health related terms include AEs, medical procedures, clinical characteristics, clinical diagnosis, names and qualitative results of laboratory tests, etc. All prior and ongoing therapy and medications

will be coded according to the Anatomical Therapeutic Chemical (ATC) Classification System based on generic names. Other social-economic characteristics and geospatial information are coded according to dictionaries published by the government.

Data extraction, curation and analysis will be performed according to the applicable practices of vendor's and Amgen's and will be performed by dedicated personnel trained to work for this study. These personnel will be responsible for data curation, accuracy, quality, completeness, and internal consistency.

8.6.1 Obtaining Data Files

Not applicable

8.6.2 Linking Data Files

Not applicable

8.6.3 Review and Verification of Data Quality

Data received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. The monitor will verify the extracted data against the original data sources. A detailed data validation plan will be developed and updated during study to document errors found, corrections made, and the rationale for decisions. Additionally, all data extracted will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate. In addition to a planned proactive outreach, the data curation will continue to manage investigator-initiated study-related enquiries as needed.

8.7 Data Analysis

The analyses of all objectives will be performed using descriptive statistical methods. All analyses will be descriptive in nature. In addition to descriptive statistics, all available patient level data will be presented.

8.7.1 Planned Analyses

8.7.1.1 Primary Analysis

The primary analyses will be conducted after completing data extractions of all eligible patients to describe real-world use, effectiveness and safety of teprotumumab.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

All data analyses will be performed using appropriate software such as SAS statistics software version 9.3 or higher (SAS Institute Inc., Cary, NC). Despite the study is

descriptive in nature, an analysis plan with a detailed description of analyses to be performed will be developed.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

This is a retrospective chart review study. Information which is not included in the patient medical charts cannot be reported. Missing data will not be replaced by imputation methods. All analyses will be conducted in patients with available information.

Outcome assessment up to the end of follow-up defined in Section 8.2.6 will be included in the analysis.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

Patients will be selected by reviewing the medical charts and enrolling those who meet the eligibility criteria and sign ICF, if required.

8.7.2.3.2 Description of Patient Characteristics

Patients who have TED and have been treated with at least 1 infusion of teprotumumab in clinical practice will be included in the study.

8.7.2.4 Analysis of the Primary and Secondary Endpoints

All analyses will be descriptive in nature. Summary statistics for available continuous variables (e.g., proptosis measurement and change, CAS, diplopia, quality of life and change) will include number of patients, mean, standard deviation (SD), median, and range (min, max). Categorical variables (e.g., proptosis response, overall response, achieving CAS value of 0 or 1, binocular diplopia response, complete diplopia response, incidence of AEs, status of AEs) will be summarized using frequencies and percentages.

In addition to descriptive statistics, all available patient level data will be presented to understand the richness of available data and variability of these patients in great detail.

For safety outcomes, all patients in the study who meet the eligibility criteria will be included in the analysis.

For all effectiveness outcomes and patient-reported outcomes, endpoints including proptosis response, change in proptosis measurement, achieving CAS value of 0 or 1, overall response rate, binocular diplopia response and complete diplopia response, and change in quality of life, will be evaluated as of the last infusion. The endpoints will be evaluated based on assessments conducted in BOAO Pilot Zone to avoid different measurement errors before and after treatment.

For all effectiveness outcomes and patient-reported outcomes, those who received ⩾4 infusions of teprotumumab and have completed corresponding assessments following the last infusion will be included. Subsequent infusions must be within 120 days following the previous one. Any infusion administered 120 days or more after the previous one will be classified as retreatment and excluded from the effectiveness analysis.

A subgroup analysis of effectiveness outcomes will be conducted for patients completed 8 infusions.

8.7.2.5 Sensitivity Analysis

8.7.2.5.1 Subgroup Analysis

A subgroup analysis of effectiveness outcomes (i.e.., proptosis, CAS, diplopia, quality of life) will be conducted for all patients who completed 8 infusions.

8.7.2.5.2 Stratified Analysis

Not applicable

8.7.2.5.3 Other Sensitivity Analysis

If assessments after last infusions within or outside of BOAO Pilot Zone are available, all available patient level data will be presented to understand the richness of available data and variability of these patients in great detail.

8.7.3 Analysis of Safety Endpoints

All patients participating in the study who meet the eligibility criteria will be included in the safety analysis. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). For safety outcomes defined in Section 8.3.2, count and proportions will be calculated, respectively.

8.8 Quality Control

At the study level, all aspects of the study from protocol development to the reporting of the results are conducted following Standard Operating Procedures (SOPs) developed by Amgen and/or the vendor. These procedures include internal quality audits of the data, accuracy and consistency of extracted data, validation of coding, rules for secure and confidential data storage, methods to maintain and archive documents, quality control procedure for programming, standards for writing analysis plans, and requirement for senior scientific review.

The investigator, co-investigator(s) and all site staff involved in the study will be trained on the conduct of the study at the time of site initiation. All functions, processes, and

specifications for data extraction, cleaning and validation will be described in a data curation plan. Written programming will be reviewed independently. The secure storage of data, study programs, log files, output files and back up will be ensured as required by regulatory guidelines. All key study documents, such as the statistical plan and study reports, will undergo quality control and review.

8.9 Limitations of the Research Methods

8.9.1.1 Internal Validity of Study Design

Inconsistent practices among healthcare providers can lead to variability in how patient data is assessed and recorded, resulting in incomplete or ambiguous information. Based on feasibility assessment, proptosis exams for primary effectiveness assessment are always performed using the same apparatus and performed by the same healthcare providers, minimizing inter-apparatus or inter-provider heterogeneity in rating before and post treatment. Evaluations conducted by same healthcare providers in BOAO Pilot Zone will be used for analysis. Additionally, data extraction and curation will be carried out by dedicated personnel specifically trained for this study, further enhancing the validity of the data.

8.9.1.2 Confounding

Not applicable.

8.9.2 External Validity of Study Design

All Chinese patients with TED who were treated with teprotumumab in BOAO Pilot Zone will be included, unless demonstrated operationally unfeasible. Since teprotumumab is not available in mainland China outside of BOAO pilot zone, the early adopters included in this study may not be fully representative of the broader population that may eventually receive this treatment. For instance, the high cost and the need for patients to travel to the BOAO Pilot Zone for therapy may mean they generally have a higher socioeconomic status than the average patient.

8.9.3 Analysis Limitations

With limited exclusion criteria, the patients included in this study may have a heterogeneous history of TED. For example, some patients may have undergone surgical interventions, while others may have received only medical therapy prior to enrollment.

Additionally, since patients typically do not return to the BOAO Pilot Zone after their last infusion for further endpoint assessments, endpoints (including proptosis response,

change in proptosis measurement, achieving CAS value of 0 or 1, overall response rate, binocular diplopia response and complete diplopia response, and change in quality of life) will be evaluated as of the last infusion, not allowing enough time for the last infusion to take effect. However, if assessments after last infusions (both within and outside BOAO) are available, all available patient level data will be presented to understand the richness of available data and variability of these patients in great detail.

For safety outcomes, all patients in the study who meet the eligibility criteria will be included in the analysis. For effectiveness and patient-reported outcomes analysis, patients who have received ⩾4 infusions of teprotumumab and completed the corresponding assessments after the last infusion will be included. As of the data cut-off date, some patients may still be undergoing treatment and have not yet completed 8 infusions. The analysis may produce descriptive statistics for patients with varying numbers of infusions.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

A limitation of retrospective chart review studies is that only data documented in patient medical records can be transmitted in the CRF. Missing or incomplete data may introduce information bias.

To mitigate this risk, clear instructions will be provided to investigators on completing CRFs. During the data abstraction phase, missing information in mandatory variables will be carefully checked and any inconsistencies will be corrected when feasible.

As teprotumumab is being used in BOAO Pilot Zone under the pre-registration program, it is expected this study will have limited missing data in terms of patient demographic, clinical characteristics, teprotumumab exposure. As for the effectiveness and safety outcomes, as described in Section 6.3 and Section 8.4, close monitoring of AE is required for special medications used in BOAO Pilot Zone. Therefore, AE capture should be relatively complete. Physicians proactively follow-up with patients to document patients' treatment outcomes both within and outside the BOAO Pilot Zone. Key evaluations of the treatment outcomes occur at each visit, including the baseline visit. The level of missingness will be described and no attempts at imputation will be made in this study.

8.10 Other Aspects

Not applicable.

9. Protection of Patients

9.1 Informed Consent

Where an informed consent is required per local regulations and sites, an initial sample informed consent form is provided for the investigator or designee to then prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Study Manager to the investigator or designee. The informed consent form is to be prepared in the language(s) of the potential patient population.

Where an informed consent is required per local regulations and sites, the investigator or designee will explain to the patient, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study, and answer all questions regarding the study prior to the patient's participation.

The acquisition of informed consent is to be documented in the patient's medical records. The informed consent form is to be signed and personally dated by the patient or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the patient or the patient's legally authorized representative.

If local regulations do not require an informed consent to be signed but mandate that the patient is notified about the study, the investigator or designee should document the notification process in the patient's medical record.

9.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The study protocol will be reviewed by the IEC of the Hainan BOAO Future Hospital.

9.3 Patient Confidentiality

De-identified patient records will be transferred to Amgen by the investigator. The investigator must ensure that the patient's confidentiality is maintained for documents submitted to Amgen.

Patient will be assigned a unique identifier. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

For serious AEs reported to Amgen, patients are to be identified by their unique patient identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (e.g., signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB, direct access to review the patient's original medical records for verification of data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit such individuals to have access to his/her study-related records, including personal information.

9.4 Patients Decision to Withdraw

Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the patient does not wish to or is unable to continue further study participation. Patient data up to withdrawal of consent will be included in the analysis of the study and, where permitted, publicly available data can be included after withdrawal of consent. As per local regulations, upon withdrawal of consent, the patient has the right to request removal of their data that was extracted and not have it further processed. The investigator is to discuss with the patient appropriate steps for withdrawal of their consent from the study.

10. Collection, Recording, and Reporting of Safety Information and Product Complaints

10.1 Definition of Reportable Events

10.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a subject/patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease

- Events associated with the discontinuation of the use of a product(s), (e.g., appearance of new symptoms)

10.1.2 Serious Adverse Events

A serious AE is any AE as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an “other medically important serious event” that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for “serious” is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.
“Other medically important serious events” refer to important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

10.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse event) include:

- Medication errors, overdose/underdose, whether accidental or intentional, misuse, addiction, or abuse involving an Amgen product,
- Use of an Amgen product while pregnant and/or breast feeding,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Accidental or Occupational exposure,
- Any lack or loss of intended effect of the product(s).

10.1.4 Product Complaints

Product Complaints include any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution

to market or clinic. This includes any drug(s), device(s) or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) or combination product(s) includes investigational product.

10.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is analyzing secondary data from electronic health record databases. The safety outcomes that are listed in Section 8.3.2 will be documented and analyzed in this study. These will be reported in aggregate in the final study report as counts and proportions. See Section 8.3.2 for safety outcomes and definitions. Reportable events suspected to be related to any Amgen medicinal product, combination product or device should be spontaneously reported to Amgen within 1 business day of investigator/vendor awareness. A list of all Amgen medicinal products can be found in the following link: https://wwwext.amgen.com/amgen-worldwide

To spontaneously report a reportable event to Amgen, refer to the following link to locate your Local Amgen contact information by country: https://wwwext.amgen.com/contact-us/product-inquiries

Additional details on what to collect and report to Amgen for the reportable event can be found in the following link: https://wwwext.amgen.com/products/global-patient-safety/adverse-event-reporting Reportable events suspected to be related to any non-Amgen medicinal product should be reported to the local authority in line with the local country requirements.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. When Amgen amends the protocol and distributes the protocol amendment to the sites, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IEC must be informed of all amendments and give approval for all protocol amendments that Amgen provides to the site. The Investigator **must** send a copy of the approval letter from the IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

12. Plans for Disseminating and Communicating Study Results

The study will be submitted for publication in a peer-reviewed journal.

12.1 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

13. Compensation

If ICF is required by specific site regulation, patients participating in this study will be provided a one-time compensation for the time and effort spent for signing and delivering ICF for this chart review study. Compensation will be in accordance with Amgen's Fair Market Value.

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15. Appendices

Appendix A. List of Stand-alone Documents

None.

Approval Signatures

Document Name:	Protocol Original teprotumumab-trbw 20240345
Document Description:	Real World Use, Effectiveness and Safety of Teprotumumab among Thyroid Eye Disease Patients treated in China BOAO Pilot Zone
Document Number:	CLIN-000361102
Approval Date:	10 Apr 2025
Type of Study Protocol:	Original
Protocol Amendment No.:	

Document Approvals	
Reason for Signing: Functional Area	Name: PPD Date of Signature: 10-Apr-2025 13:43:51 GMT+0000