Summary Table of Study Protocol

Title	Observational Study on the Safety and Effectiveness of Tepezza (teprotumumab) in South Korea
Protocol version identifier	20240224; Original, Version 1.0
Date of last version of the protocol	Not applicable (NA)
EU Post Authorization Study (PAS) Register No	Not applicable (NA)
Active Substance	Teprotumumab
Medicinal Product	TEPEZZA™ Inj (teprotumumab)
Device	NA
Product Reference	NA
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	The primary objective is to describe safety of TEPEZZA in post-marketing clinical practice within the approved indication by assessing the incidence of adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions, unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, unexpected serious adverse drug reactions, adverse events leading to discontinuation of TEPEZZA, and fatal events; as required by the Ministry of Food and Drug Safety (MFDS). The key secondary objective is to describe effectiveness of TEPEZZA at EOS in post-marketing clinical practice within the approved indication by assessing: proptosis response, change in proptosis measurement, overall response, achieving clinical activity score (CAS) value of 0 or 1; and clinical outcome assessment by the investigator.
Country(ies) of Study	South Korea
Author	PPD

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Korea Limited
MAH Contact	20th Floor, 19, Eulji-ro 5-gil, Jung-gu, Seoul, 04539 +82 2 3434 4800

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled Observational Study on the Safety and Effectiveness of Tepezza (teprotumumab) in South Korea, dated 16 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)

Title:

Name of Hospital/Site:

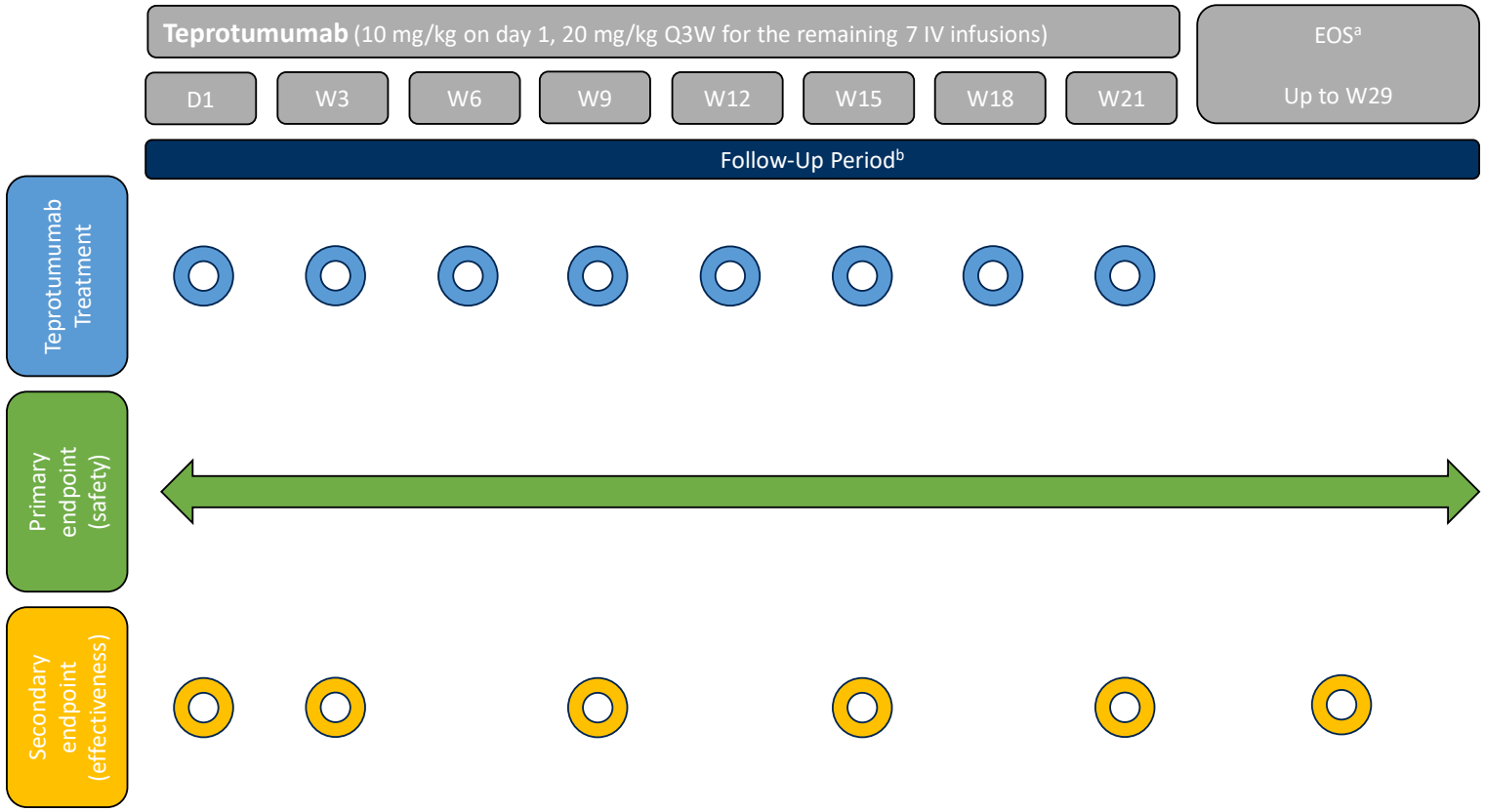
Address/City/State/Country:

Phone Number:

Email:

Study Design Schema

Figure 1. Study Design Schema



EOS = end of study; IV = intravenous; Q3W = every 3 weeks; W = week.

[a] The EOS will occur up to 8 weeks after the last dose of TEPEZZA, withdrawal of consent, death, or lost to follow-up whichever occurs first. The EOS for subjects who experience hearing impairment during the study period which has not resolved by 8 weeks after their last dose of TEPEZZA, will be the resolution of the impairment, withdrawal of consent, death, lost to follow-up, or overall EOS (last subject last visit), whichever occurs first.

[b] Patients will be followed from day 1 until EOS.

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2. List of Abbreviations

Abbreviation or Term	Definition/Explanation
CAS	Clinical Activity Score
CHO	Chinese hamster ovary
eCRF	electronic case report form
EOS	end of study
FT3	free triiodothyronine
FT4	free thyroxine
ICF	informed consent form
IEC	independent ethics committee
IGF-1R	insulin-like growth factor-1 receptor
IRB	institutional review board
MFDS	Ministry of Food and Drug Safety
NA	not applicable
PT	Preferred Term
RMP	Risk Management Plan
SOC	System Organ Class
TED	thyroid eye disease
TSH	thyroid stimulating hormone

3. Responsible Parties

The sponsor of the study is Amgen Korea Limited. The list of investigators will be determined by which sites have access to TEPEZZA. Once the list is compiled, the sponsor or delegate may provide it upon request.

4. Abstract

- **Study Title**

Observational Study on the Safety and Effectiveness of Tepezza (teprotumumab) in South Korea

- **Study Background and Rationale**

TEPEZZA is a fully human immunoglobulin G1 monoclonal antibody directed against human insulin-like growth factor-1 receptor (IGF-1R). The human variable regions of TEPEZZA were derived from a hybridoma obtained from a transgenic Hco7 mouse immunized with recombinant IGF-1R protein. The antibody is made up of 2-heterodimers, each composed of a heavy and light polypeptide chain. The 4 peptide chains are linked by disulfide bonds. The antibody bears a single carbohydrate chain in the constant region of both heavy chains. A stable antibody producing cell line was established in the Chinese hamster ovary (CHO) cell line CHO-DG44.

In South Korea, it is mandatory to conduct active pharmacovigilance surveillance as a part of Risk Management Plan (RMP) to investigate post-marketing safety and effectiveness in patients treated with newly approved drugs. To comply with the applicable regulations, Amgen Korea will conduct a prospective observational study to evaluate the safety and effectiveness of TEPEZZA in routine clinical practice. Amgen Korea will make best efforts to conduct the study using an all-patient surveillance approach by enrolling all patients prescribed TEPEZZA in accordance with the approved label.

- **Study Feasibility and Futility Considerations**

The feasibility of collecting data on the population receiving TEPEZZA in routine clinical practice in South Korea has not yet been explored. We anticipate that we will be able to recruit at least 41 subjects within the enrollment period.

- **Research Question and Objective(s)**

Objectives	**Endpoints**
Primary	
• To describe safety of TEPEZZA in post-marketing clinical practice within the approved indication (see Section 11.1 for definitions of terms)	• Incidence of adverse events • Incidence of serious adverse events • Incidence of adverse drug reactions • Incidence of serious adverse drug reactions • Incidence of unexpected adverse events • Incidence of unexpected serious adverse events • Incidence of unexpected adverse drug reactions • Incidence of unexpected serious adverse drug reactions • Incidence of adverse events leading to TEPEZZA discontinuation • Incidence of fatal events

Objectives	Endpoints
Key Secondary	
• To describe effectiveness of TEPEZZA in post-marketing clinical practice within the approved indication	• Proptosis response at EOS • The change in proptosis measurement in the study eye from baseline at EOS • Overall response at EOS (in case of acute thyroid eye disease [TED]) • Achieving Clinical Activity Score (CAS) value of 0 or 1 at EOS (in case of acute TED) • Clinical outcome assessment by the investigator at EOS
Exploratory	
• NA	• NA

- **Hypothesis(es)/Estimation**

  No hypothesis will be tested.

- **Study Design/Type**

  This is a multicenter prospective observational study in patients who are prescribed TEPEZZA within the approved indication in a post-marketing setting in South Korea.

- **Study Population or Data Resource**

  Study enrollment will be offered to patients meeting the eligibility criteria at participating medical sites in South Korea. Enrollment will start after launch of TEPEZZA in South Korea and is planned to end if enrollment targets are met. If the target enrollment can't be reached within the enrollment period, a discussion with Ministry of Food and Drug Safety (MFDS) will be needed to determine if a study period extension is required. Patients will be enrolled at participating sites and will be followed from day 1 until up to 8 weeks after their last dose of TEPEZZA, withdrawal of consent, death, or lost to follow-up, whichever occurs first. Patients with unresolved hearing impairment which has not resolved by 8 weeks after their last dose of TEPEZZA, will additionally be followed until the resolution of the impairment, withdrawal of consent, death, lost to follow-up, or the overall EOS (last subject last visit), whichever occurs first.

- **Summary of Subject Eligibility Criteria**

  Inclusion Criteria:

  - Adult subjects (aged 19 years and above) prescribed TEPEZZA in clinical practice according to the approved therapeutic indications, dosage, and administration in South Korea
  - Subjects or their authorized representative who provide written informed consent to participate in this study

  Exclusion Criteria:

  - Subjects with contraindications as listed on the approved local label
  - Subjects concurrently participating in another interventional study will not be allowed to participate in this study

- **Follow-up**

  Subjects will be followed from day 1 until up to 8 weeks after their last dose of TEPEZZA, withdrawal of consent, death, or lost to follow-up, whichever occurs first.

  Subjects who experience hearing impairment during the study period and which have not resolved by 8 weeks after the last dose of TEPEZZA, will be additionally followed until the resolution of the impairment, withdrawal of consent, death, lost to follow-up, or the overall EOS (last subject last visit), whichever occurs first.

- **Variables**
  - primary outcome measures: incidence of adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions, unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, unexpected serious adverse drug reactions, adverse events leading to TEPEZZA discontinuation, and fatal events
  - secondary outcome measure: proptosis response, overall response (in case of acute TED [CAS $\geq$ 3]), CAS response (in case of acute TED [CAS $\geq$ 3]), and clinical outcome assessment by the investigator

- **Study Sample Size**

  Per the most recent MFDS regulatory requirements, the study intends to enroll all eligible subjects in South Korea but not less than 41 subjects to collect safety and effectiveness information for the final analysis. Investigators at participating medical sites are requested to make every effort to enroll all subjects prescribed TEPEZZA during the enrollment period.

- **Data Analysis**

  The data will be summarized descriptively, unless otherwise specified.

The Safety Analysis Set will include all subjects who received at least 1 dose of TEPEZZA in accordance with the approved therapeutic indications, dosage, and administration in South Korea and completed at least 1 safety follow-up. The safety analyses will use the Safety Analysis Set, and will summarize the following measurements:

- adverse events
- serious adverse events
- adverse drug reactions
- serious adverse drug reactions
- unexpected adverse events
- unexpected serious adverse events
- unexpected adverse drug reactions
- unexpected serious adverse drug reactions
- adverse events leading to TEPEZZA discontinuation
- fatal events

The Effectiveness Analysis Set will include all subjects from the Safety Analysis Set who have at least 1 follow-up assessment to assess proptosis response, change in proptosis measurement, overall response, CAS, or clinical outcome assessment by the investigator.

5. Amendments and Updates

None.

6. Milestones

Milestones	**Planned Timelines**
Start of data collection	Commercial launch date
End of data collection	Up to 4 years and 29 weeks from the commercial launch date (end of follow-up for the last subject)
Year 1 Report*	2027
Year 2 Report*	2028
Year 3 Report*	2029
Year 4 Report*	2030
Final Report	Within 3 months following the end of the study period**

*The submission will be aligned with the timeline for periodic RMP implementation reports.

**The end date of the study period is defined as the date of completion of the final report.

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Disease State/Therapeutic Area:

Thyroid eye disease, also termed Graves' ophthalmopathy/orbitopathy and thyroid-associated ophthalmopathy, is a serious, debilitating and painful autoimmune disease that can, in severe cases, 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 involves an "active thyroid eye disease (TED)," which is an autoimmune inflammatory response targeting orbital soft tissues and "inactive TED," in which there is tissue expansion remodeling. Active TED typically lasts 1 to 3 years, and then the inflammation spontaneously subsides to leave the pathology of inactive TED (Burch and Wartofsky, 1993).

Clinical features of TED include orbital pain, swelling, dry eye, redness and discomfort of the lids and ocular surface, thickening and retraction of the eyelids and proptosis (exophthalmos) due to the expansion of tissue behind the eye (Dickinson, 2017; Bahn, 2010; Mallika et al, 2009; Burch and Wartofsky, 1993). Although TED is heterogenous and variable in presentation, proptosis is one of the most prevalent and widely known symptoms of TED. Thyroid eye disease has high morbidity (Dickinson, 2017; Bartalena et al, 2008; Gerding et al, 1997; Bartley, 1994), which takes the form of orbital pain, together with a number of serious, vision- or sight-threatening conditions, including diplopia (due to inability to correctly align the eyes), corneal ulceration (due to inability to close lids) and dysthyroid optic neuropathy (due to proptosis, tissue crowding and stress on the optic nerve). These combine to produce marked reductions in quality of life (eg physical functioning, role functioning, social functioning, mental health, health perceptions, and pain) (Terwee et al, 2002; Gerding et al, 1997). Thyroid eye disease can also produce profound psychosocial problems, in particular anxiety and depression, due to the alarming and disfiguring changes in appearance (Coulter et al, 2007; Kahaly et al, 2005; Bartley et al, 1996).

Thyroid eye disease is characterized by an autoimmune inflammatory response targeting the orbital and periocular tissues, leading to symptoms such as eyelid retraction, exophthalmos (proptosis), diplopia, and dysthyroid optic neuropathy in severe

cases (Park and Yoon, 2024). A cross-sectional study conducted at 24 general hospitals in Korea showed that Vision symptoms were presented in 10.5% of thyroid orbitopathy patients, inflammation symptoms in 43.1%, strabismus in 15.1%, and appearance and exposure symptoms in 86.3% of patients. Among the eye symptoms, proptosis was most prevalent in 56.9% of patients followed by eyelid retraction in 31.5%, diplopia in 15.1%, and optic nerve dysfunction in 2.4% of patients (Woo et al, 2008).

The prevalence of TED among dysthyroid patients in Korea is approximately 17.3% which is lower than the prevalence rate in Europe, with a higher prevalence in younger female patients (Woo et al, 2013). Risk factors for TED include female gender, young age, Graves' disease, dermopathy, anti-thyroid medication treatment, and radioiodine treatment. Smoking is also a significant risk factor, particularly in females (Sikder and Weinberg, 2010).

Pathophysiology:

The pathophysiology of TED involves the activation and proliferation of orbital fibroblasts, leading to the release of inflammatory cytokines, infiltration of immune cells into orbital tissues, excessive synthesis of extracellular matrix, and tissue expansion. The activation of fibroblasts is mediated through the insulin-like growth factor-1 receptor (IGF-1R) pathway (Shan and Douglas, 2014). Clinical features of moderate-to-severe TED include orbital pain, swelling, dry eye, redness, discomfort of the lids and ocular surface, thickening and retraction of the eyelids, and proptosis (Tanda et al, 2013).

Therapeutic Area:

The treatment of TED has traditionally involved high-dose steroids and orbital radiotherapy. However, recent advancements have introduced new therapeutic agents targeting the IGF-1R pathway, such as teprotumumab. Teprotumumab, a monoclonal antibody inhibitor of IGF-1R, has shown significant efficacy in reducing proptosis, Clinical Activity Score (CAS), diplopia, and improving quality of life in patients with TED. The drug was approved by the US Food and Drug Administration in 2020 for the treatment of TED (Park and Yoon, 2024). Since this time, teprotumumab has been approved in Brazil, Saudi Arabia, and Japan.

7.2 Rationale

In South Korea, it is mandatory to conduct active pharmacovigilance surveillance as a part of the Risk Management Plan (RMP) to investigate post-marketing safety and effectiveness in patients treated with newly approved drugs. To comply with the

applicable regulations, Amgen Korea will conduct a prospective observational study to evaluate the safety and effectiveness of TEPEZZA in routine clinical practice. Amgen Korea will make best efforts to conduct the study using an all-patient surveillance approach by enrolling all patients prescribed TEPEZZA in accordance with the approved label.

7.3 Feasibility and Futility Considerations

The feasibility of collecting data on the population receiving TEPEZZA in routine clinical practice in South Korea has not yet been explored. We anticipate that we will be able to recruit at least 41 subjects within the enrollment period.

7.4 Statistical Inference (Estimation or Hypothesis[es])

No hypothesis will be tested. This study will provide descriptive data on use of TEPEZZA and subject characteristics in the post-marketing setting in South Korea, unless otherwise specified.

8. Research Question and Objectives

The prospective observational study is conducted under routine clinical practice to collect safety and effectiveness data from all patients treated with TEPEZZA after its launch.

8.1 Primary

The primary objective is to describe safety of TEPEZZA in post-marketing clinical practice within the approved indication by assessing the incidence of adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions, unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, unexpected serious adverse drug reactions, adverse events leading to discontinuation of TEPEZZA, and fatal events; as required by the Ministry of Food and Drug Safety (MFDS).

8.2 Key Secondary

The key secondary objective is to describe effectiveness of TEPEZZA in post-marketing clinical practice within the approved indication by assessing proptosis response, change in proptosis measurement, overall response (in case of acute TED), CAS value of 0 or 1 (in case of acute TED), and clinical outcome assessment by the investigator at EOS.

9. Research Methods

9.1 Study Design

This study is an observational, prospective, cohort, multicenter study based on primary data collection in clinical practice within the approved indication.

For a full list of data elements, including the timing for each data abstraction, please refer to the schedule of data collection in Table 1.

Table 1. Schedule of Data Collection

Data Collected (if available in Medical Records)	Enrollment (Start of TEPEZZA®)		Follow-up (Data abstractions expected to occur ~every 3 weeks from first dose through EOS)	
	Baseline[a,b]	Day 1[a]	During Follow-up	End of Study[c]
Eligibility	X	-	-	-
Informed consent	X	-	-	-
Physical measurements (values most proximal to Day 1 within the Baseline Period) • Height • Weight	X	-	-	-
Demographics data • Age • Sex • Smoking history • Alcohol use history • Allergic history	X	-	-	-
Medical history • Date of initial diagnosis of TED, activity, severity • Date of initial diagnosis of endocrine disorder • History of hyperglycemia, IBD, infusion reactions, hearing impairment • Therapeutic history for TED/endocrine disorder before TEPEZZA treatment • Radiation therapy and history of surgery for TED • Other medical history including hepatic impairment and renal impairment, diabetes mellitus and chronic hypertension	X	-	-	-

Footnotes defined on last page of the table

Table 1. Schedule of Data Collection

Data Colleced (if available in Medical Records)	Enrollment (Start of TEPEZZA®)		Follow-up (Data abstractions expected to occur ~every 3 weeks from first dose through EOS)	
	Baseline[a,b]	Day 1[a]	During Follow-up	End of Study[c]
Prior and concomitant medications (including concomitant therapy) • Product name, indication, dose, unit, frequency, start and stop dates	X	-	X	X
Proptosis measurement	X	-	X	X
Clinical Activity Score (CAS) measurement	X	-	X	X
Clinical laboratory tests • Fasting chemistry (includes glucose) • Thyroid function (FT3, FT4, TSH) • Thyroid-stimulating antibody (TSAb) • Hematology • Glycated hemoglobin (HbA1c) • Other medically important lab tests	X (values most proximal to day 1)	-	X	X
Reportable events • Adverse events • Serious adverse events • Other safety findings[d] • Product complaints	-	X	X	X
Treatment with TEPEZZA® • Dosage (10 mg/kg or 20 mg/kg) • Infusion time (60 minutes or 90 minutes) • Start date/End date • Reason for termination of TEPEZZA	-	X	X	X
Clinical outcome assessment by the investigator	-	-	-	X

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EOS = end of study; FT3 = free triiodothyronine; FT4 = free thyroxine; IBD = inflammatory bowel disease; TED = thyroid eye disease; TSH = Thyroid-stimulating hormone; W = week.

[a] Baseline and day 1 may occur on the same day.

[b] Baseline period includes up to 1 year prior to first dose of TEPEZZA.

[c] End of Study: The EOS will occur up to 8 weeks after the last dose of TEPEZZA, withdrawal of consent, death, or lost to follow-up, whichever occurs first. The EOS for subjects who experience hearing impairment during the study period which has not resolved by 8 weeks after their last dose of TEPEZZA, will be the resolution of the impairment, withdrawal of consent, death, lost to follow-up, or overall EOS (last subject last visit), whichever occurs first.

[d] Other safety findings include pregnancy and lactation information.

9.2 Setting and Study Population

Physicians will evaluate patients and determine if treatment with TEPEZZA is appropriate in accordance with local standards and the approved TEPEZZA indication. The decision to treat the patient with TEPEZZA should be made independently of, and

before enrollment in the study. Once treatment with TEPEZZA has been selected, the investigator or an assigned delegate can discuss the details of the study with the prospective subject. Each prospective subject is assessed for eligibility. Once the eligibility conditions are met, which includes signing the consent, the subject will be formally enrolled into the study.

9.2.1 Study Period

This study will commence from the commercial launch date, and subject enrollment will be conducted for a period of 4 years. Each subject will be followed for up to 29 weeks. Accordingly, the data collection period for this study will be up to 4 years and 29 weeks (approximately 4 years and 7 months) from the launch date, including the completion of follow-up for the last enrolled subject.

Following completion of data collection, data cleaning and analysis will be performed, and the final report will be submitted within 3 months following the end of the study period. The end date of the study period is defined as the date of completion of the final report.

9.2.2 Selection and Number of Sites

Study sites will include approximately 20 sites that have post-market use of TEPEZZA. We aim to select almost all sites that prescribe TEPEZZA.

9.2.3 Subject/Patient/Healthcare Professional Eligibility

9.2.3.1 Inclusion Criteria

- Adult subjects (aged 19 years and above) prescribed TEPEZZA in clinical practice according to the approved therapeutic indications, dosage, and administration in South Korea
- Subjects or their authorized representative who provide written informed consent to participate in this study

9.2.3.2 Exclusion Criteria

- Subjects with contraindications as listed on the approved local label
- Subjects concurrently participating in another interventional study will not be allowed to participate in this study

9.2.4 Matching

Not applicable.

9.2.5 Baseline Period

Baseline data as close to the first administration as possible up to 1 year prior to first dose of TEPEZZA will be collected. Medical history related to TED will be collected from the time of diagnosis.

9.2.6 Study Follow-up

Subjects will be followed from day 1 until up to 8 weeks after their last dose of TEPEZZA, withdrawal of consent, death or lost to follow-up, whichever occurs first.

Subjects who experience hearing impairment during the study period and which has not resolved by 8 weeks after the last dose of TEPEZZA, will be additionally followed until the resolution, withdrawal of consent, death, lost to follow-up, or the overall EOS (last subject last visit), whichever occurs first.

9.3 Variables

Information described in Sections 9.3.1 to 9.3.3 is collected in a case report form per subject. If applicable, additional safety follow-up information for subjects who have hearing impairment during the study period and have not resolved by 8 weeks after the last dose of TEPEZZA will be collected.

9.3.1 Exposure Assessment

Dosage (10 mg/kg or 20 mg/kg), infusion time (60 minutes or 90 minutes), start date, end date, and reason for termination of TEPEZZA are collected.

9.3.2 Outcome Assessment

- Primary outcome measure: Incidence of adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions, unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, unexpected serious adverse drug reactions, adverse events leading to TEPEZZA discontinuation, and fatal events throughout the treatment/observation period along with their severity, action taken, and causal relationship with TEPEZZA will be assessed for any subject who has received at least 1 dose of TEPEZZA according to the approved therapeutic indications, dosage and administration in South Korea and completed at least 1 safety follow-up. Cumulative subject incidence of the adverse events will be reported and summarized. All adverse events will be graded using Severity Intensity Scale for Adverse Events scoring system. An adverse event and adverse drug reaction whose nature, severity, specificity, or outcome is not consistent with the term or description used in the local product labeling will be considered ‘unexpected’. Unexpected adverse events or unexpected adverse drug reactions mean adverse events or adverse drug reactions not reflected in precautions of approved local label.
- Secondary outcome measure: proptosis response, overall response (in case of acute TED [CAS $\geq$ 3]), CAS response (in case of acute TED [CAS $\geq$ 3]), and clinical outcome assessment by the investigator

9.3.3 Covariate Assessment

- Demographics and physical measurements: age, sex, height, weight, history of smoking and alcohol use, history of allergy, pregnancy or lactation status
- Medical history: Date of initial diagnosis of TED, activity, severity, medical history for endocrine disorder (Graves' disease or others), date of initial diagnosis of endocrine disorder, medical history (including history of hyperglycemia, inflammatory bowel

disease [IBD], infusion reactions, hearing impairment (baseline hearing loss or hearing impairment, co-morbidities namely diabetes mellitus, chronic hypertension and related them), therapeutic history for TED/endocrine disorder before TEPEZZA treatment, radiation therapy and history of surgery for TED

- Prior and concomitant medications
- Concurrent therapy to TED
- Clinical laboratory tests (if available): fasting chemistry (which includes glucose), thyroid function (free triiodothyronine [FT3], free thyroxine [FT4], thyroid-stimulating hormone [TSH]), thyroid-stimulating antibody (TSAb), hematology, glycated hemoglobin (HbA1c).

9.3.4 Validity and Reliability

Efforts will be made to collect complete data through the use of clear instructions to investigators regarding the completion of electronic case report forms (eCRFs). The data collected for this study will be derived from medical records that are kept per routine clinical practice for the documentation and decision-making for a subject's care. The data will be abstracted from the medical records and entered into the eCRF. A detailed data management plan will be implemented to ensure the quality of the collected data.

9.4 Data Sources

The data source for this study is subject medical records. These medical records may include a combination of paper and electronic sources. Study site staff will extract data from the medical records into the study-specific electronic database provided by the sponsor.

9.5 Study Size

Per the most recent MFDS regulatory requirements, the study intends to enroll all eligible subjects in South Korea but not less than 41 subjects to collect safety and effectiveness information for the final analysis. Investigators at participating medical sites are requested to make every effort to enroll all subjects prescribed TEPEZZA during the enrollment period.

9.6 Data Management

9.6.1 Obtaining Data Files

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and available upon request.
- Updates to eCRFs will be automatically documented through the software's audit trail.

9.6.2 Linking Data Files

Not applicable.

9.6.3 Review and Verification of Data Quality

Automatic checks within the database and further manual review by the sponsor will help to ensure quality and completeness of the data. During this review, subject data is checked for consistency, omissions, and any apparent discrepancies. Data queries will be sent to sites for clarification and resolution of discrepancies.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Interim Analysis/Analyses

According to the local regulations, interim analyses will be performed yearly for periodic reporting starting from the initial approval of TEPEZZA. The interim analyses will be conducted on subjects who have completed the study during each year.

9.7.1.2 Final Analysis

Final analysis will be performed when all enrolled subjects reach the end of study (EOS). A snapshot of the finalized database will be used for analysis. All analyses will be performed using SAS 9.4 or later versions. Safety and effectiveness data collected at scheduled time points will be used for analysis.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

The statistical analysis in this post-marketing study will be descriptive in nature, and no hypothesis testing will be performed. Categorical variables will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by the number of non-missing values, mean, standard deviation, median, lower and upper quartiles, and minimum and maximum values. Subject incidence will be summarized for adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions, unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, unexpected serious adverse drug reactions. Also, 95% CI will be presented based on exact method for the incidence proportion.

Where applicable, difference in safety results by subject's baseline characteristics can be analyzed by Chi-square test, and multivariate analysis can be conducted to estimate factors that may affect the safety results. However, this is an observational study in a real-world setting, and the study design and collection items are set according to local regulations. Due to these limited methods (total number of patients, study period, and

study method, etc), there is a risk of bias in the results of safety and effectiveness evaluation, which may make it difficult to determine clinical significance.

Additional information will be collected according to the RMP when adverse events related to the Important Safety Specification Requiring Further Evaluation Items in RMP are collected. The special investigation group (elderly, children, hepatic impairment, renal impairment, pregnancy, or lactation) will be analyzed separately where applicable.

All adverse events will be tabulated in the report using the latest version of Medical Dictionary for Regulatory Activities by System Organ Class (SOC) and Preferred Term (PT).

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Missing data will not be imputed; analysis will be based on available observed data.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrollment

All enrolled patients will be summarized in the patient disposition table showing number of patients included in the safety analysis set and effectiveness analysis set, excluded from the safety analysis set and effectiveness analysis set.

9.7.2.3.2 Description of Subject Characteristics

Characteristics of subjects in the study will be summarized using demographics, baseline and baseline disease characteristics by the investigator or a designated representative during the baseline period and will be summarized using descriptive statistics. Refer to Table 1 for the schedule of data collection.

9.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

9.7.2.4.1 Analysis of Primary Endpoint

Safety Analysis: The safety analysis set will contain all subjects who have received at least 1 dose of TEPEZZA in accordance with the approved therapeutic indication, dosage and administration in South Korea and completed at least 1 safety follow-up. The reports will use the standard System Organ Class and Preferred Term system and will use the Severity Intensity Scale for Adverse Events scoring system. All adverse events and serious adverse events will be summarized using descriptive methods, unless otherwise specified. Frequencies and percentages for categorical variables; mean standard deviation, median, minimum, and maximum values for continuous variables will be reported.

The incidence of adverse events will be summarized to include all recorded treatment-emergent adverse events from the first dose of TEPEZZA or any worsening of medical conditions initially experienced before the first dose of TEPEZZA. This summary for adverse events will be performed for the following categories:

- All adverse events and adverse drug reactions
- Serious adverse events and serious adverse drug reactions
- Unexpected adverse events and unexpected adverse drug reactions
- Unexpected serious adverse events and unexpected serious adverse drug reactions
- Adverse events leading to TEPEZZA discontinuation
- Fatal events

9.7.2.4.2 Analysis of Key Secondary Endpoint

Effectiveness analysis: If applicable, investigators will evaluate the clinical outcome of each subject according to the endpoint definition described in the table below during the follow-up period.

The Effectiveness Analysis Set will include all subjects from the Safety Analysis Set who have at least 1 follow-up assessment to assess proptosis response, change in proptosis measurement, overall response, CAS, or clinical outcome assessment by the investigator. The Effectiveness analysis will be descriptively summarized since the number of subjects is limited. Categorical variables will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by the number of non-missing values, mean, standard deviation, median, lower and upper quartiles, and minimum and maximum values.

Endpoint	Definition
proptosis response at EOS	having a ≥ 2 mm reduction in proptosis measurement from baseline in the study eye[a] without deterioration (≥ 2 mm increase) of proptosis in the fellow eye at EOS
overall response at EOS (in case of acute TED)	having ≥ 2-point reduction in clinical activity score (CAS)* AND ≥ 2 mm reduction in proptosis from baseline in the study eye, provided there is no corresponding deterioration (≥ 2-point increase in CAS or ≥ 2 mm increase in proptosis) in the fellow eye at EOS

EOS = end of study; TED = thyroid eye disease

[a] At the Baseline, the "study eye" (ie, the eye with most significant proptosis) will be identified. If both eyes are affected equally, the Investigator will choose the "study eye". Both eyes will be accessed for effectiveness, but the study eye will be used to access the primary effectiveness endpoint.

* Clinical Activity Score Assessment

Item[a]	Description
For baseline CAS	
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 that is considered to be due to Active TED
6	Chemosis
7	Inflammation of caruncle or plica
For ongoing monitoring	
8	Increase of ≥ 2 mm in proptosis
9	Decreased eye movements ≥ 5 any direction
10	Decrease of acuity ≥ 1 Snellen line

CAS = Clinical Activity Score; TED = thyroid eye disease
[a] Each item is scored (1 = present; 0 = absent) and scores for each item are summed for a total score

In addition, investigators should evaluate the clinical outcome (interpretation of signs or behaviors that can be observed related to a subject's condition) of each subject and assign 1 of the following descriptions at EOS:

- Improved
- Not changed
- Disease progression
- Unable to evaluate (with a reason)

9.7.2.5 Sensitivity Analysis

9.7.2.5.1 Subgroup Analysis

The primary and secondary endpoints will be analyzed by subgroups, where applicable. The subgroups include, but are not limited to the following:

- Sex (male, female)
- Age at baseline (years): 19 to < 65 years, ≥ 65 years
- Presence of medical history (Yes or No)
- Renal impairment at baseline (Yes or No)
- Hepatic impairment at baseline (Yes or No)
- Concurrent disease (Yes or No)
- Concomitant medication (Yes or No)

The subgroup analysis may be undertaken if enough subjects are available. If the number of subjects is insufficient, it will be replaced by subject listing.

The details of analysis methods will be specified in the Statistical Analysis Plan.

9.7.2.5.2 Stratified Analysis

Not applicable.

9.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

Not applicable.

9.7.2.5.4 Other Sensitivity Analysis

Not applicable.

9.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

Analysis of safety endpoints will be conducted as described in Section 9.7.2.4.1.

9.8 Quality Control

The Amgen representative(s) and regulatory authority inspectors are responsible for inspecting the various records of the study (eg eCRFs and other pertinent data) provided that subject confidentiality is respected.

Amgen or its designee is responsible for verifying the eCRFs to confirm adherence to the protocol, completeness, accuracy, and consistency of the data and adherence to local regulations on the conduct of surveillance studies.

9.9 Limitations of the Research Methods

The current study plans to adopt rigorous observational data collection methods for the study. This is an observational study in a real-world setting, and the study design and collection items are set according to local regulations. Due to these limited methods (total number of subjects, study period, and study method, etc), there is a risk of bias in the results of safety and effectiveness evaluation, which may make it difficult to determine clinical significance.

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Error(s)/Misclassification(s)

As with any surveillance study that relies on data entry from multiple sites, there is the potential for misclassifying adverse events and adverse drug reactions. Misclassifications can impact the validity of outcomes as well as affect overall conclusions.

9.9.1.2 Information Bias

Missing or incomplete data is a potential risk for information bias and efforts will be made to collect complete data through the use of clear instructions to investigators regarding the completion of eCRFs.

There is no systematic review or systematic method of adverse event collection. Adverse events are collected as part of a regular interaction with the subject as would be in normal practice. Therefore, adverse events collected are subject to reporting bias, but such effect is inherent to real-world surveillance.

9.9.1.3 Selection Bias

This study is an observational study in a real-world setting. The inclusion criteria are intended to enroll all patients prescribed TEPEZZA in clinical practice according to the approved therapeutic indications, dosage, and administration in South Korea. Consecutive enrollment will be performed to potentially reduce the propensity of selection bias. However, selection bias cannot be completely ruled out.

9.9.1.4 Confounding

Not applicable.

9.9.2 External Validity of Study Design

The participating medical centers are expected to represent approximately over 80% of the total patients treated with TEPEZZA in South Korea, so it is expected that the results from current study are generally extendable to the general population of patients treated with TEPEZZA in South Korea. Also, as with other studies, this study only includes patients who provide consent to participate, and patients that do not participate in this study may be different compared to those who do participate.

9.9.3 Analysis Limitations

Not applicable.

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

It is likely that there will be missing and incomplete data on key variables in this study, reflecting the lack of capture of certain data elements in routine care. Missingness and incomplete data on key variables may limit the ability to assess certain populations of interest. The level of missingness will be described and no attempts at imputation will be made in this study.

Some subjects may discontinue the study, creating missing or incomplete data for the study endpoint assessments. Such discontinuations may be related or informative to the

outcomes. Consequently, there is a risk for bias due to missing completed data and lack of robust data to analyze results.

9.10 Other Aspects

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

10. Protection of Human Subjects

10.1 Informed Consent

An initial sample informed consent form (ICF) is provided for the investigator or designee to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Clinical Study Manager to the investigator or designee. The written ICF is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the study, the investigator or designee will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study, and answer all questions regarding the study.

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

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

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

A copy of the protocol, proposed ICF, other written patient information, and any study-related material must be submitted to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for written approval. A copy of the written approval of the protocol and ICF must be received by Amgen before the study can be executed. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or

serious adverse event(s) occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures. The investigator is responsible for obtaining annual IRB approval and IRB/IEC renewal throughout the duration of the study. Copies of the investigator's reports, where applicable by local regulations and the IRB/IEC continuance of approval must be sent to Amgen.

10.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

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

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject 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 (eg signed ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with local country regulations, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject'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 subject to permit such individuals to have access to his/her study-related records, including personal information.

10.4 Subjects' Decision to Withdraw

Subjects 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 subject does not wish to or is unable to continue further study participation. Subject 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 subject has the right to request removal of their data that was collected and

not have it further processed. The investigator is to discuss with the subject appropriate steps for withdrawal of their consent from the study.

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

11.1 Definition of Reportable Events

11.1.1 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), (eg appearance of new symptoms)

An adverse drug reaction is a noxious and unintended response to a pharmaceutical product(s) administration normally. Adverse drug reactions are adverse events considered related to TEPEZZA by the investigator, including those with unknown relationship.

Unexpected adverse events or unexpected adverse drug reactions mean adverse events or adverse drug reactions not reflected in precautions of approved local label.

11.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least 1 of the following serious criteria:

- Is fatal
- Is life-threatening (places the subject 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 subject 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.

11.1.3 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).

11.1.4 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 TEPEZZA.

11.2 Safety Collection, Recording, and Submission to Amgen Requirements

This study is collecting information from healthcare professionals and patient's medical records prospectively. All reportable events (adverse events, product complaints, and other safety findings) considered to have occurred following subject exposure to TEPEZZA will be collected from the time of first dose to 8 weeks after final dose of TEPEZZA or EOS, whichever occurs first. Patients with unresolved hearing impairment which has not resolved by 8 weeks after their last dose of TEPEZZA, will additionally be followed until the resolution of the impairment, withdrawal of consent, death, lost to follow-up, or the overall EOS (last subject last visit), whichever occurs first. The Investigator is responsible for ensuring that all reportable events they become aware of

during study period, are recorded in the subject's appropriate study documentation. It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen. If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study. All reportable events must be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within the timelines stated in Table 2 below.

Table 2. Types of Safety Data to be Collected and Reported in Primary Data Collection Studies Collecting All Reportable Events

Reportable Events/Event Type	* Reporting Timeframe
• Serious Adverse Events (related and non-related) • Product Complaints (serious and non-serious) • Other Safety Findings (serious and non-serious) • Pregnancy and/or Lactation Exposure	• Within 1 business day from when Investigator first becomes aware of the event
• Non-serious Adverse Events (related and non-related)	• Within 15 calendar days from when Investigator first becomes aware of the event

Reportable events that are suspected to be related to any Amgen medicinal product, combination product or device where there is no exposure to TEPEZZA should be spontaneously reported to Amgen within 1 business day of investigator 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

See Appendix C for sample Safety Report Form(s), Appendix D for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix E for sample Pregnancy and Lactation Notification Forms. The Investigator may be asked to provide additional information for any event submitted, which may

include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded in the study documentation where safety data may also be recorded.

11.2.1 Collection of Pregnancy and Lactation Information

Female Subjects Who Become Pregnant

Investigator will collect pregnancy information on any female subject who becomes pregnant following exposure to TEPEZZA during the follow-up period (from the first dose to 8 weeks after the last dose of TEPEZZA).

Information will be recorded on the Pregnancy Notification Form (see Appendix E). The worksheet must be submitted to Amgen Safety within 1 business day of when Investigator first becomes aware of the subject's pregnancy (Note: Investigator is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide Investigator with a consent form and questionnaire to collect additional information. After obtaining the female subject's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant following exposure to TEPEZZA during the follow-up period (from the first dose to 8 weeks after the last dose of TEPEZZA). This information will be forwarded to Amgen Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of pregnancy will be reported to Amgen Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is considered another safety finding, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.

If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg female subject experiences a spontaneous abortion, stillbirth,

or neonatal death or there is a fetal or neonatal congenital anomaly) the Investigator will report the event as a serious adverse event.

Male Subjects With Partners who Become Pregnant or Were Pregnant at the Time of Enrollment

In the event a male subject fathers a child following exposure to TEPEZZA during the follow-up period (from the first dose to 8 weeks after discontinuing TEPEZZA), the information will be recorded on the Pregnancy Notification Form. The form (see Appendix E) must be submitted to Amgen Safety within 1 business day of when the Investigator first becomes aware of the pregnancy. (Note: Investigator is not required to provide any information on the Pregnancy Notification Form that violates the country or region's local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide Investigator with a consent form and questionnaire to collect additional information. The Investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.

After obtaining the female partner's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Safety.

Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of the pregnancy will be reported to Amgen Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

Investigator will collect lactation information on any female subject who breastfeeds while taking TEPEZZA during the follow-up period (from the first dose to 8 weeks after the last dose of TEPEZZA).

Information will be recorded on the Lactation Notification Form (see Appendix E) and submitted to Amgen Safety within 1 business day of when the Investigator first becomes aware of the lactation exposure.

With the female subjects' signed consent for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking TEPEZZA and during the follow-up period (from the first dose to 8 weeks after discontinuing TEPEZZA).

11.2.2 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, IRBs/IECs, or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of reportable events in accordance with local procedures and statutes.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC must be informed of all amendments and give approval. The Investigator **must** send a copy of the approval letter from the IRB/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 IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

13. Plans for Disseminating and Communicating Study Results

The final report will be submitted to the MFDS within three months following the end of study period.

13.1 Publication Policy

The results of this study will be submitted for publication. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors 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 (eg 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.

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15. Appendices

Appendix A. List of Stand-alone Documents

None.

Appendix B. ENCePP Checklist for Study Protocols

Not applicable.

Appendix C. Sample Safety Reporting Form(s)

Project ID: 20240224	A	Observational Research Safety Reporting Form	Date of Reporter Awareness: / Date Reported to Amgen:
	Reports to: Amgen Local Office	Email (preferred) svc-ags-in-kr-pm@amgen.com Fax: 080-908-0982	

1. Initial: ☐ Follow-up: ☐
2. Site Number: Subject Number:
3. Indicate event type: *(Please tick all that apply)* ☐ AE/Other Safety Finding ☐ Product Complaint (PC) ☐ Adverse Device Effect (ADE)

4. Contact Details (Vendor/Investigator)			5. Reporter ID		
Name	Phone	Fax	Name or ID	Phone	Fax
Address			Address		
City	State/Province		City	State/Province	
Postal Code	Country		Postal Code	Country	

6. HCP Contact Details (if other than reporter)			7. Patient			
Name			Initials (optional)	Sex ☐F ☐M	Age (at time of event)	Was consent obtained to follow-up with HCP? ☐Yes ☐No
Country						
Address						
City	State/Province	Postal Code	Weight ☐lbs ☐kg	Height ☐in ☐cm	Race	Is patient also reporter? ☐Yes ☐No
Phone	Fax					

8. Medical History (include primary diagnosis)	9. Suspect Product Information (include dosing details)				
	Product/Device: ___ Tepezza (Teprotumumab)_____				
	Indication: _____				
	Start Date (day month year)	Stop Date (day month year)	Dose	Route	Frequency
Pregnant? ☐Yes ☐No Lactating? ☐Yes ☐No	Prefilled Syringe? ☐Yes ☐No	Lot #_____ ☐Unknown			Vial Size
Allergy: _____	Other Device _____	Serial # _____ ☐Unavailable / Unknown			

10. AE, Other Safety Finding, or PC/ADE information									HCP ONLY		
Finding (List main event first; one event per line)	Onset Date (day month year)	Resolved Date (If patient died, list date of death) Cause of Death: (provide autopsy report) (day month year)	Hospitalization: Hospitalized? ☐Yes ☐No; Prolonged Hospitalization? ☐Yes ☐No; Admitting dx _____; Date Admitted (day month year)	Date Discharged (day month year)	Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/Prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly/birth defect; 06 Other significant medical hazard; 07 Non serious	Action Taken: 1=none; 2=dose reduced; 3=dose increased; 4=drug withdrawn; 5=drug rechallenge (state outcome)	Outcome: 01 Recovered/ Resolved; 02 Recovering/ Resolving; 03 Not recovered/not resolved; 04 Recovered/ resolved with sequelae; 05 Fatal; 06 Unknown	Severity 1=mild 2=moderate 3=severe	Relationship to Product/Device Is there a reasonable possibility that this event may have been caused by the Product/Device? Product	Device
									Y N	Y N
									Y N	Y N
									Y N	Y N

									Y N	Y N
									Y N	Y N
									Y N	Y N

11. Concomitant Medications (eg, chemotherapy)

Medication Names	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No	Co-suspect Yes	Continuing No	Continuing Yes	Dose	Route	Frequency	Treatment Meds

12. Relevant Laboratory Values (include dates, allergies, and any relevant prior therapy)

Date Day Month Year											
	Test										
	Unit										

13. Other Relevant Test (diagnostics and procedures)

Date Day Month Year	Additional Tests	Results	Units

14. Description: Provide chronological summary and details of AE symptoms, PC or ADE that are listed in section 10 (signs, diagnosis, treatment, concomitant medications including those used to treat event).

Appendix D. Additional Safety Reporting Information

Grade	Severity Intensity Scale for Adverse Events Scoring System
1	MILD: Aware of sign or symptom, but easily tolerated
2	MODERATE: Discomfort enough to cause interference with usual activity
3	SEVERE: Incapacitating with inability to work or do usual activity

Appendix E. Pregnancy and Lactation Notification Forms

AMGEN Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20240224

Study Design: ☐ Interventional ■Observational (If Observational: ■ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (____)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject age (at onset):____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm_____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐Yes ☐No ☐Unknown ☐N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20240224

Study Design: ☐ Interventional ■ Observational (If Observational: ■ Prospective ☐ Retrospective)

Investigator Name _____ Site # _____

Phone (____)_____ Fax (____)_____ Email _____

Institution _____

Subject ID # _____ Subject age (at onset): ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm_____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Approval Signatures

Document Name: Protocol Original teprotumumab-trbw 20240224

Document Description: Tepezza 20240224 Original Protocol (South Korea PMS)

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