Teprotumumab (thyroid eye disease)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A26-18 Version: 1.0 Status: 22 May 2026 DOI: 10.60584/A26-18_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Teprotumumab (endokrine Orbitopathie) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Teprotumumab (thyroid eye disease) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

2 March 2026

Internal Project No.

A26-18

DOI-URL

https://doi.org/10.60584/A26-18_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
Email: info@iqwig.de
Internet: www.iqwig.de

Recommended citation

Institute for Quality and Efficiency in Health Care. Teprotumumab (thyroid eye disease); Benefit assessment according to §35a SGB V; Extract [online]. 2026 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A26-18_en.

Keywords

Teprotumumab, Graves Ophthalmopathy, Benefit Assessment, NCT04583735

Medical and scientific advice

- Daniela Claessens, Augenheilkunde Lindenthal, Cologne, Germany

IQWiG thanks the medical and scientific advisor for their contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received within the framework of this dossier assessment.

IQWiG employees involved in the dossier assessment

- Caroline Wöhl
- Annalena Dunkel
- Judith Kratel
- Jaqueline Krüger
- Torben Lütkehermölle
- Daniela Preukschat
- Leonie Schürmeyer
- Claudia Selbach
- Franziska Sende

Part I: Benefit assessment

I Table of contents

Page

I List of tables I.3
I List of abbreviations I.4
I 1 Executive summary of the benefit assessment I.1
I 2 Research question I.6
I 3 Research questions 1 and 2: adults in the acute disease phase receiving first-line treatment (research question 1) or who are eligible for second-line treatment (research question 2) I.8
I 3.1 Information retrieval and study pool I.8
I 3.2 Results on added benefit I.9
I 4 Research question 3: adults in the chronic disease phase I.10
I 4.1 Information retrieval and study pool I.10
I 4.1.1 Evidence provided by the company I.10
I 4.1.2 Assessment of the evidence presented by the company I.13
I 4.2 Results on added benefit I.15
I 5 Probability and extent of added benefit I.16
I 6 References for English extract I.17

I List of tables[2]

Page

Table 2: Research questions for the benefit assessment of teprotumumab I.2
Table 3: Teprotumumab – probability and extent of added benefit I.5
Table 4: Research questions for the benefit assessment of teprotumumab I.6
Table 5: Characteristics of the study included by the company – RCT, direct comparison: teprotumumab vs. placebo I.11
Table 6: Characteristics of the intervention – RCT, direct comparison: teprotumumab vs. placebo I.12
Table 7: Teprotumumab – probability and extent of added benefit I.16

[2] Table numbers start with ‘2’ as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CAS	clinical activity score
EPAR	European Public Assessment Report
EUGOGO	European Group on Graves' Orbitopathy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IV	intravenous
RCT	randomised controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug teprotumumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 2 March 2026.

Research question

The aim of this report is to assess the added benefit of teprotumumab in comparison with the appropriate comparator therapy (ACT) in adults with moderate to severe thyroid eye disease.

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions for the benefit assessment of teprotumumab

Research question	Therapeutic indication	ACT[a, b]
Adults with moderate to severe thyroid eye disease		
1	in the acute disease phase receiving first-line treatment	Individualised treatment[c] from a choice of ▪ methylprednisolone ▪ methylprednisolone in combination with mycophenolate mofetil
2	in the acute disease phase who are eligible for second-line treatment	Individualised treatment[c] from a choice of ▪ methylprednisolone ▪ glucocorticoids in combination with orbital radiotherapy, cyclosporine or azathioprine ▪ rituximab (monotherapy)
3	in the chronic disease phase	Watchful waiting[d]

a. Presented is the respective ACT specified by the G-BA.
b. In both study arms, it is assumed that any underlying conditions that may be present (e.g. Graves' disease) are treated in accordance with the current state of medical knowledge and that any concomitant treatments are documented.
c. For the implementation of individualised treatment in a study of direct comparison, study physicians are expected to have a choice of several treatment options at their disposal, enabling them to make individualised treatment decisions (multi-comparator study). The decision on individualised treatment with regard to the comparator therapy should be made before group allocation (e.g. randomisation). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). A rationale must be provided for the choice and any limitation of treatment options.
Further comments from the G-BA:
▫ According to the guideline, intravenously administered methylprednisolone and the orally available options prednisolone and prednisone are recommended for the treatment of thyroid eye disease.
▫ For patients with eye movement disorders, the preferred treatment is methylprednisolone in combination with orbital radiotherapy.
d. It is assumed that patients in the chronic stage of the disease in both study arms are offered rehabilitative surgery, such as orbital decompression, correction of eye misalignment or eyelid correction, as required.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company followed the ACT specified by the G-BA for the treatment of adults with moderate to severe thyroid eye disease in the acute disease phase receiving first-line treatment (research question 1) and in the chronic disease phase (research question 3). With regard to research question 2, the company stated that it was following the G-BA's specification of the ACT and named tocilizumab as an additional treatment option within the ACT for adults in the acute disease phase who are eligible for second-line treatment. As the company used broader inclusion criteria for research question 2 than necessary for this benefit assessment, the company's approach had no consequences.

The company's deviation from the G-BA's ACT is not discussed further, as the company did not present any relevant studies in the acute disease phase for the benefit assessment (research questions 1 and 2).

The assessment was conducted in comparison with the ACT specified by the G-BA by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Research questions 1 and 2: adults in the acute disease phase receiving first-line treatment (research question 1) or who are eligible for second-line treatment (research question 2)

Results

Neither for research question 1 nor for research question 2 were any randomised controlled trials (RCTs) identified for the direct comparison of teprotumumab with the ACT specified by the G-BA. For research question 1, the company conducted an additional information retrieval for RCTs for an indirect comparison. However, it did not identify any RCTs that would be suitable for an indirect comparison using an appropriate common comparator.

In its conclusion on the added benefit (Section 4.4.2 of Module 4 A of the dossier), the company took into account the results of the pivotal studies TED01RV and HZNP-TEP-301 (as separate individual studies and in a pooled analysis) for both research questions. Both studies are double-blind RCTs comparing teprotumumab versus placebo. In both RCTs, neither non-steroidal immunosuppressants nor glucocorticoids (oral or IV) were permitted as concomitant medication (with the exception of premedication with ≤20 mg of IV dexamethasone following infusion reactions).

As none of the treatment options specified by the G-BA were permitted in either study, the data submitted by the company were not suitable for deriving conclusions on the added benefit of teprotumumab compared with the ACT in adults with thyroid eye disease in the acute disease phase.

Results on added benefit

Since no relevant studies were available for research questions 1 and 2, in each case, there is no hint of an added benefit of teprotumumab in comparison with the ACT; an added benefit is therefore not proven.

Research question 3: adults in the chronic disease phase

Results

A review of the completeness of the study pool identified the HZNP-TEP-403 study. Although it was assumed that the study included a subpopulation relevant to research question 3, the data presented by the company were not suitable for drawing conclusions on the added benefit for the patient population covered by research question 3.

HNZP-TEP-403 is a completed, double-blind RCT comparing teprotumumab versus placebo. Adults with chronic (inactive) thyroid eye disease were included in the study. To be included, patients had to show an increase in proptosis of ≥3 mm from the value prior to the diagnosis of thyroid eye disease and/or proptosis ≥3 mm above normal for family origin and sex. In addition, they had to have either a clinical activity score (CAS) of ≤1 in both eyes for ≥1 year prior to screening, or meet the following 3 criteria for ≥1 year prior to screening: no progression in proptosis, no progression in diplopia (if present) and no new inflammatory symptoms. Furthermore, they were not allowed to have a medical indication for immediate surgery, or be planning rehabilitative surgery and/or orbital irradiation.

A total of 62 patients were enrolled and randomly allocated in a 2:1 ratio to either treatment with teprotumumab (N=42) or placebo (N=20). Treatment with teprotumumab in the double-blind phase (24 weeks) was in compliance with the recommendations of the summary of product characteristics (SmPC).

The primary outcome of the HNZP-TEP-403 study was the change in proptosis at Week 24 from baseline. According to the information provided by the company in Module 4 B of the dossier, patient-relevant secondary outcomes were outcomes from the categories of morbidity, health-related quality of life and side effects.

In accordance with the therapeutic indication, research question 3 covers adult patients with moderate to severe thyroid eye disease in the chronic disease phase. Whilst the chronic disease phase was represented in the inclusion criteria of HZNP-TEP-403, the study was not designed for moderate to severe disease. No information was available on the severity of the disease in the patients included. On the basis of the available information on patient characteristics, it was assumed that fewer than 80% of the patients included in the study belonged to the relevant population for research question 3 (moderate to severe thyroid eye disease in the chronic disease phase). The data on the total population presented by the company with the dossier were therefore unsuitable for answering research question 3.

Results on added benefit

Since no relevant data were available for research question 3, there is no hint of an added benefit of teprotumumab in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 summarises the probability and extent of added benefit of teprotumumab.

Table 3: Teprotumumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
Adults with moderate to severe thyroid eye disease			
1	in the acute disease phase receiving first-line treatment	Individualised treatment[c] from a choice of ▪ methylprednisolone ▪ methylprednisolone in combination with mycophenolate mofetil	Added benefit not proven
2	in the acute disease phase who are eligible for second-line treatment	Individualised treatment[c] from a choice of ▪ methylprednisolone ▪ glucocorticoids in combination with orbital radiotherapy, cyclosporine or azathioprine ▪ rituximab (monotherapy)	Added benefit not proven
3	in the chronic disease phase	Watchful waiting[d]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. In both study arms, it is assumed that any underlying conditions that may be present (e.g. Graves' disease) are treated in accordance with the current state of medical knowledge and that any concomitant treatments are documented.
c. For the implementation of individualised treatment in a study of direct comparison, study physicians are expected to have a choice of several treatment options at their disposal, enabling them to make individualised treatment decisions (multi-comparator study). The decision on individualised treatment with regard to the comparator therapy should be made before group allocation (e.g. randomisation). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). A rationale must be provided for the choice and any limitation of treatment options.
Further comments from the G-BA:
  - According to the guideline, intravenously administered methylprednisolone and the orally available options prednisolone and prednisone are recommended for the treatment of thyroid eye disease.
  - For patients with eye movement disorders, the preferred treatment is methylprednisolone in combination with orbital radiotherapy.

d. It is assumed that patients in the chronic stage of the disease in both study arms are offered rehabilitative surgery, such as orbital decompression, correction of eye misalignment or eyelid correction, as required.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) 'proof', (2) 'indication', (3) 'hint', or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or lesser benefit). For further details see [1,2].

I 2 Research question

The aim of this report is to assess the added benefit of teprotumumab in comparison with the appropriate comparator therapy (ACT) in adults with moderate to severe thyroid eye disease.

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions for the benefit assessment of teprotumumab

Research question	Therapeutic indication	ACT[a, b]
Adults with moderate to severe thyroid eye disease		
1	in the acute disease phase receiving first-line treatment	Individualised treatment[c] from a choice of ▪ methylprednisolone ▪ methylprednisolone in combination with mycophenolate mofetil
2	in the acute disease phase who are eligible for second-line treatment	Individualised treatment[c] from a choice of ▪ methylprednisolone ▪ glucocorticoids in combination with orbital radiotherapy, cyclosporine or azathioprine ▪ rituximab (monotherapy)
3	in the chronic disease phase	Watchful waiting[d]

a. Presented is the respective ACT specified by the G-BA.
b. In both study arms, it is assumed that any underlying conditions that may be present (e.g. Graves' disease) are treated in accordance with the current state of medical knowledge and that any concomitant treatments are documented.
c. For the implementation of individualised treatment in a study of direct comparison, study physicians are expected to have a choice of several treatment options at their disposal, enabling them to make individualised treatment decisions (multi-comparator study). The decision on individualised treatment with regard to the comparator therapy should be made before group allocation (e.g. randomisation). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). A rationale must be provided for the choice and any limitation of treatment options.
Further comments from the G-BA:
▫ According to the guideline, intravenously administered methylprednisolone and the orally available options prednisolone and prednisone are recommended for the treatment of thyroid eye disease.
▫ For patients with eye movement disorders, the preferred treatment is methylprednisolone in combination with orbital radiotherapy.
d. It is assumed that patients in the chronic stage of the disease in both study arms are offered rehabilitative surgery, such as orbital decompression, correction of eye misalignment or eyelid correction, as required.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company followed the ACT specified by the G-BA for the treatment of adults with moderate to severe thyroid eye disease in the acute disease phase receiving first-line treatment (research question 1) and in the chronic disease phase (research question 3). With regard to research question 2, the company stated that it was following the G-BA's specification of the ACT and named tocilizumab as an additional treatment option within the

ACT for adults in the acute disease phase who are eligible for second-line treatment. The company justified its expansion of the ACT on the grounds that tocilizumab is listed in the 2021 guideline of the European Group on Graves' Orbitopathy (EUGOGO) [3] as a further option of second-line treatment. As the company used broader inclusion criteria in research question 2 than necessary for this benefit assessment, the company's approach had no consequences.

The company's deviation from the G-BA's ACT is not discussed further, as the company did not present any relevant studies in the acute disease phase for the benefit assessment (research questions 1 and 2) (see Chapter I 3). Accordingly, the assessment of research questions 1 and 2 is presented below in joint sections of the report.

The assessment was conducted in comparison with the ACT specified by the G-BA by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the inclusion criterion of the company.

I 3 Research questions 1 and 2: adults in the acute disease phase receiving first-line treatment (research question 1) or who are eligible for second-line treatment (research question 2)

I 3.1 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on teprotumumab (status: 15 December 2025)
- Bibliographical literature search on teprotumumab (last search on 15 December 2025)
- Search of trial registries / trial results databases for studies on teprotumumab (last search on 15 December 2025)
- Search on the G-BA website for teprotumumab (last search on 19 December 2025)
- Bibliographical literature search on the ACT (last search on 15 December 2025)
- Search of trial registries / trial results databases for studies on the ACT (last search on 15 December 2025)
- Search on the G-BA website for the ACT (last search on 19 December 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on teprotumumab (last search on 12 March 2026); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, neither for research question 1 nor for research question 2 were any randomised controlled trials (RCTs) identified for the direct comparison of teprotumumab with the ACT specified by the G-BA. For research question 1, the company conducted an additional information retrieval for RCTs for an indirect comparison. However, it did not identify any RCTs that would be suitable for an indirect comparison using an appropriate common comparator.

In its conclusion on the added benefit (Section 4.4.2 of Module 4 A of the dossier), the company took into account the results of the pivotal studies TED01RV [4] and HZNP-TEP-301 (hereinafter referred to as OPTIC) [5], both as separate individual studies and in a pooled analysis, for both research questions. TED01RV and OPTIC are double-blind RCTs comparing teprotumumab versus placebo. In both RCTs, neither non-steroidal immunosuppressants nor glucocorticoids (oral or IV) were permitted as concomitant medication (with the exception of premedication with ≤20 mg of IV dexamethasone following infusion reactions). Although the company stated that it would refrain from carrying out a formal assessment in accordance

with the requirements for dossier assessments according to §35a Social Code Book V because there was no comparison in each case versus the ACT specified by the G-BA, it derived an indication of a non-quantifiable added benefit on the basis of the available evidence.

As none of the treatment options specified by the G-BA were permitted in either study, the data submitted by the company were not suitable for deriving conclusions on the added benefit of teprotumumab compared with the ACT in adults with thyroid eye disease in the acute disease phase.

I 3.2 Results on added benefit

No suitable data were available to assess the added benefit of teprotumumab compared with the ACT in adults with moderate to severe thyroid eye disease in the acute disease phase – neither for patients receiving first-line treatment (research question 1) nor for patients who are eligible for second-line treatment (research question 2). In each case, there is no hint of an added benefit of teprotumumab in comparison with the ACT; an added benefit is therefore not proven.

I 4 Research question 3: adults in the chronic disease phase

I 4.1 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on teprotumumab (status: 15 December 2025)
- Bibliographical literature search on teprotumumab (last search on 15 December 2025)
- Search of trial registries / trial results databases for studies on teprotumumab (last search on 15 December 2025)
- Search on the G-BA website for teprotumumab (last search on 22 December 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on teprotumumab (last search on 12 March 2026); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the study HZNP-TEP-403 [6-8] was identified in the review. Although it was assumed that the study included a subpopulation relevant to research question 3, the data presented by the company were not suitable for drawing conclusions on the added benefit for the patient population covered by research question 3.

Below, the study is first described and then reasons are provided as to why the data presented by the company were unsuitable for the benefit assessment.

I 4.1.1 Evidence provided by the company

Design of the HZNP-TEP-403 study

Table 5 and Table 6 describe the HNZP-TEP-403 study presented by the company in Module 4 B of the dossier (for a characterisation of the study population, see Table 8 in I Appendix B of the full dossier assessment).

Table 5: Characteristics of the study included by the company – RCT, direct comparison: teprotumumab vs. placebo

Study	Study design	Population	Interventions (number of randomised patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
HZNP-TEP-403	RCT, double-blind, parallel	Adults (≥18 years) with chronic thyroid eye disease[b] ▪ Thyroid eye disease diagnosed ≥2 and <10 years[c] ▪ Proptosis ≥3 mm increase from the value prior to the diagnosis of thyroid eye disease[d] and/or proptosis ≥3 mm above normal for family origin and sex	teprotumumab (N=42) placebo (N=20)	Screening: 28 days Treatment: ▪ 24 weeks (double-blind) ▪ 24 weeks (open-label)[e] Follow-up: 30 days[f]	11 centres in the United States Period: 8/2021–10/2023 Data cuts: ▪ 30 March 2023 (double-blind)[g] ▪ 13 October 2023 (open-label)[h]	Primary: change in proptosis at Week 24 in the study eye Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes comprise exclusively data based on the information provided by the company's Module 4 B of the dossier.
b. Clinical diagnosis of chronic (inactive) thyroid eye disease, defined as a CAS of ≤1 in both eyes for ≥1 year prior to screening, or as meeting the following 3 criteria:
   - No progression in proptosis for ≥1 year prior to screening
   - No progression in diplopia (if present) for ≥1 year prior to screening
   - No new inflammatory symptoms for ≥1 year prior to screening
c. Before protocol amendment 3 (version 4.0) dated 10 March 2022, the diagnosis had to be made ≥3 years and <8 years prior to screening.
d. Assessed by the treating physician.
e. After a double-blind treatment phase, patients in both groups without clinical response, defined as a <2 mm reduction in proptosis from baseline at Week 24, could continue treatment with teprotumumab in a 24-week open-label treatment phase.
f. Follow-up continued until 30 days after Week 24 or until 30 days after Week 48 (in case of continued treatment with teprotumumab in the open-label treatment phase).
g. Prespecified primary analysis following the final visit of the last patient (17 March 2023) in the double-blind treatment phase.
h. Prespecified (descriptive) follow-up analysis of data from the open-label treatment phase, after all patients completed the 30-day follow-up period or discontinued the study prematurely.

AE: adverse event; CAS: clinical activity score; n: relevant subpopulation; N: number of randomised patients; RCT: randomised controlled trial

Table 6: Characteristics of the intervention – RCT, direct comparison: teprotumumab vs. placebo

Study	Intervention	Comparison
HZNP-TEP-403	teprotumumab IV[a], initial dose 10 mg/kg body weight, followed by 7 doses of 20 mg/kg body weight, administered at 3-week intervals	placebo IV[a] every 3 weeks
	Dose modification: A reduction in infusion rate, dose interruptions[b] and discontinuation of treatment were allowed due to adverse events (e.g. infusion related reactions or events associated with hyperglycaemia), depending on the severity	
	Prior and concomitant treatment <u>Recommended</u> ▪ Premedication with an antihistamine (diphenhydramine, famotidine, ranitidine), an antipyretic (paracetamol) and/or a corticosteroid (dexamethasone)[d] ▪ Concomitant treatment with drugs that are ototoxic and may cause muscle spasms should be avoided <u>Allowed</u> ▪ Topical or inhaled steroids (except for thyroid eye disease) ▪ Local supportive measures for thyroid eye disease ▪ Simple analgesics (e.g. paracetamol) and dietary supplements (except for thyroid eye disease treatment) ▪ Symptomatic treatment of infusion related reactions (e.g. with antipyretics, antihistamines, beta-2 adrenoceptor agonists, glucocorticoids, oxygen or IV fluid) ▪ Non-steroidal eye drops (e.g. saline, methylcellulose, antihistamines and vasoconstrictors)[e] <u>Disallowed</u> ▪ Orbital irradiation, orbital decompression or strabismus surgery prior to screening and during the study ▪ Systemic (IV or oral) steroids (except for the treatment of infusion related reactions) and steroid eye drops ≤3 weeks prior to screening and during the study ▪ rituximab ≤12 months prior to the first infusion of the study drug and during the study ▪ tocilizumab ≤6 months prior to the first infusion of the study drug and during the study ▪ Monoclonal antibodies ≤3 weeks prior to screening ▪ Non-steroidal immunosuppressants ≤3 weeks prior to screening and during the study ▪ Drugs targeting the neonatal Fc receptor	

a. The first 2 infusions were administered over approximately 90 minutes (not <80 minutes). If these were well tolerated, infusions 3 to 8 were each administered over approximately 60 minutes (not <50 minutes) every 3 weeks.
b. Treatment was restarted upon complete resolution of symptoms.
c. For the first 3 infusions, patients were monitored for infusion related reactions during the infusions and for up to 60 minutes after completion of the infusion. If these were well tolerated, for the subsequent infusions, patients were monitored during the infusions and for ≥30 minutes after completion of the infusion.
d. In patients who had immediate hypersensitivity reactions or infusion related reactions during the first 2 infusions; all subsequent infusions were administered over approximately 90 minutes (not <80 minutes) and vital signs were monitored every 15 minutes up to 60 minutes after completion of the infusion.
e. Not permitted on the day of the visit.

IV: intravenous; RCT: randomised controlled trial

HNZP-TEP-403 is a completed, double-blind RCT comparing teprotumumab versus placebo. Adults with chronic (inactive) thyroid eye disease were included in the study. To be included, patients had to show an increase in proptosis of ≥3 mm from the value prior to the diagnosis of thyroid eye disease and/or proptosis ≥3 mm above normal for family origin and sex. In addition, they had to have either a clinical activity score (CAS) of ≤1 in both eyes for ≥1 year prior to screening, or meet the following 3 criteria for ≥1 year prior to screening: no progression in proptosis, no progression in diplopia (if present) and no new inflammatory symptoms. Furthermore, they were not allowed to have a medical indication for immediate surgery, or be planning rehabilitative surgery and/or orbital irradiation.

A total of 62 patients were enrolled and randomly allocated in a 2:1 ratio to either treatment with teprotumumab (N=42) or placebo (N=20). In the randomised patients, the eye that was more severely affected at baseline (i.e. the eye with greater extent of proptosis) was defined as the study eye on Day 1. After completion of the double-blind phase (24 weeks), patients in both groups without clinical response (i.e. with a <2 mm reduction in proptosis from baseline) could continue treatment with teprotumumab in the open-label treatment phase.

Treatment with teprotumumab in the double-blind phase was in compliance with the recommendations of the summary of product characteristics (SmPC) [9].

The primary outcome of the HNZP-TEP-403 study was the change in proptosis at Week 24 from baseline. According to the information provided by the company in Module 4 B of the dossier, patient-relevant secondary outcomes were outcomes from the categories of morbidity, health-related quality of life and side effects.

I 4.1.2 Assessment of the evidence presented by the company

The HZNP-TEP-403 study data presented by the company were unsuitable for drawing any conclusions on the added benefit of teprotumumab in comparison with the ACT for research question 3 of this benefit assessment. It was assumed that fewer than 80% of the patients included belonged to the relevant population for research question 3 of this benefit assessment (moderate to severe thyroid eye disease in the chronic disease phase). This is explained below.

Data on the total population of the HZNP-TEP-403 study unsuitable for this benefit assessment

In accordance with the therapeutic indication, research question 3 covers adult patients with moderate to severe thyroid eye disease in the chronic disease phase. Whilst the chronic disease phase was represented in the inclusion criteria of HZNP-TEP-403, the study was not designed for moderate to severe disease.

The severity of thyroid eye disease is usually assessed in accordance with the classification set out in the 2021 EUGOGO guideline [3]. In this classification, patients with moderate to severe thyroid eye disease usually meet 2 or more of the following 4 criteria:

- Lid retraction ≥2 mm
- Moderate or severe soft-tissue involvement
- Proptosis ≥3 mm above normal for family origin and sex
- Inconstant or constant diplopia

No information was available on the severity of the disease in the patients included in the HZNP-TEP-403 study.

Criterion 1: lid retraction ≥2 mm

Lid retraction is the most common clinical sign of thyroid eye disease and occurs in approximately 90% of patients [10,11].

According to the information in the clinical study report, a history of lid retraction (of unknown severity) was documented in only one of the participants. The criterion 'lid retraction ≥2 mm' was therefore considered as not met (based on the available information).

Criterion 2: moderate or severe soft-tissue involvement

In accordance with the EUGOGO, soft tissue signs were assessed that are characteristic of inflammation, e.g. redness and swelling of eyelids, redness of conjunctiva and chemosis [12]. In the HZNP-TEP-403 study, soft-tissue involvement (objective signs of inflammation) was assessed using the CAS, together with subjective signs of activity (pain or a feeling of pressure behind the eyeball and pain during eye movements) [13]. The CAS consists of 7 items, each of which is rated with 1 point if applicable; the total score is calculated by adding up all the points (range 0 to 7). Higher values indicate higher disease activity. The HZNP-TEP-403 study included patients with a CAS ≤1. The company dossier did not specify how many patients had a CAS of 0 or a CAS of 1. According to the European Public Assessment Report (EPAR), at baseline, 69% versus 50% of the patients enrolled had a CAS of 0 (i.e. no soft-tissue involvement) and 31% versus 50% had a CAS of 1 (teprotumumab versus placebo, respectively) [14]. Neither the EPAR nor the company dossier contained any information on which item was present in a CAS of 1 or on its severity.

Criterion 3: proptosis ≥3 mm above normal for family origin and sex

The HZNP-TEP-403 study included patients with an increase in proptosis of ≥3 mm from the value prior to the diagnosis of thyroid eye disease (each assessed by the treating physician) and/or proptosis ≥3 mm above normal for family origin and sex. It could not be inferred from the documents submitted by the company how many patients met only the latter criterion.

According to the literature, the following upper limits of normal (for exophthalmometry) apply to adults [15]:

- 19 mm (women) and 21 mm (men) for people of white family origin
- 23 mm (women) and 24 mm (men) for people of Black/African-American family origin
- 16 mm for Thai women, 17 mm for Thai men, or 18.6 mm for people with Chinese family origin

The characteristics of the total population used by the company showed that the majority of adults included in HZNP-TEP-403 were female (76% versus 90%) and of white or Asian family origin (69% versus 65%) (see I Appendix B of the full dossier assessment). At baseline, the median extent of proptosis (in the more severely affected eye) was [first quartile; third quartile] 25.0 mm [23.0 mm; 26.0 mm] in patients in the intervention group and 23.0 mm [21.8 mm; 27.0 mm] in patients in the control group. Based on the normal values mentioned above (for family origin and sex), it can therefore be assumed that the criterion 'proptosis ≥3 mm above normal for family origin and sex' was met by the majority of patients included in the study. However, it was not possible to estimate the exact proportion of patients on the basis of the information available.

Criterion 4: inconstant or constant diplopia

At the start of the HZNP-TEP-403 study, 5% of patients in each group had inconstant diplopia (score 2) and 11% (14% vs. 5%) had constant diplopia (score 3) (see I Appendix B of the full dossier assessment). The criterion of 'inconstant or constant diplopia' was therefore not met by the majority of the patients included in the study (84%).

Summary

The HZNP-TEP-403 study enrolled adults with thyroid eye disease in the chronic (inactive) disease phase. The documents submitted by the company did not indicate the severity of the condition. Based on the available information on patient characteristics, it was assumed that fewer than 80% of the patients included in the study belonged to the relevant population for research question 3 of the benefit assessment (moderate to severe thyroid eye disease in the chronic disease phase). In summary, the data on the total population presented by the company were not suitable for answering research question 3.

I 4.2 Results on added benefit

No suitable data were available to assess the added benefit of teprotumumab compared with the ACT in adults with moderate to severe thyroid eye disease in the chronic disease phase. There is no hint of an added benefit of teprotumumab in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of teprotumumab in comparison with the ACT is summarised in Table 7.

Table 7: Teprotumumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
Adults with moderate to severe thyroid eye disease			
1	in the acute disease phase receiving first-line treatment	Individualised treatment[c] from a choice of ▪ methylprednisolone ▪ methylprednisolone in combination with mycophenolate mofetil	Added benefit not proven
2	in the acute disease phase who are eligible for second-line treatment	Individualised treatment[c] from a choice of ▪ methylprednisolone ▪ glucocorticoids in combination with orbital radiotherapy, cyclosporine or azathioprine ▪ rituximab (monotherapy)	Added benefit not proven
3	in the chronic disease phase	Watchful waiting[d]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. In both study arms, it is assumed that any underlying conditions that may be present (e.g. Graves' disease) are treated in accordance with the current state of medical knowledge and that any concomitant treatments are documented.
c. For the implementation of individualised treatment in a study of direct comparison, study physicians are expected to have a choice of several treatment options at their disposal, enabling them to make individualised treatment decisions (multi-comparator study). The decision on individualised treatment with regard to the comparator therapy should be made before group allocation (e.g. randomisation). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). A rationale must be provided for the choice and any limitation of treatment options.
Further comments from the G-BA:
  - According to the guideline, intravenously administered methylprednisolone and the orally available options prednisolone and prednisone are recommended for the treatment of thyroid eye disease.
  - For patients with eye movement disorders, the preferred treatment is methylprednisolone in combination with orbital radiotherapy.
d. It is assumed that patients in the chronic stage of the disease in both study arms are offered rehabilitative surgery, such as orbital decompression, correction of eye misalignment or eyelid correction, as required.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above differed from that of the company, which derived an indication of a non-quantifiable added benefit for the acute disease phase and an indication of a minor added benefit for the chronic disease phase (research question 3).

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 8.0 [online]. 2025 [Accessed: 07.01.2026]. URL: https://doi.org/10.60584/Allgemeine-Methoden_V8.0.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Bartalena L, Kahaly GJ, Baldeschi L et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol 2021; 185(4): G43-G67. https://doi.org/10.1530/EJE-21-0479.

4. Smith TJ, Kahaly GJ, Ezra DG et al. Teprotumumab for Thyroid-Associated Ophthalmopathy. N Engl J Med 2017; 376(18): 1748-1761. https://doi.org/10.1056/NEJMoa1614949.

5. Douglas RS, Kahaly GJ, Patel A et al. Teprotumumab for the Treatment of Active Thyroid Eye Disease. N Engl J Med 2020; 382(4): 341-352. https://doi.org/10.1056/NEJMoa1910434.

6. Douglas RS, Couch S, Wester ST et al. Efficacy and Safety of Teprotumumab in Patients With Thyroid Eye Disease of Long Duration and Low Disease Activity. J Clin Endocrinol Metab 2024; 109(1): 25-35. https://doi.org/10.1210/clinem/dgad637.

7. Horizon Therapeutics USA. A Phase 4, Randomized, Double-masked, Placebo-controlled, Multicenter Trial to Evaluate the Efficacy and Safety of TEPEZZA in Treating Patients with Chronic (Inactive) Thyroid Eye Disease; study HZNP-TEP-403; Clinical Study Report (Double-masked Treatment Period) [unpublished]. 2023.

8. Amgen. A Study Evaluating TEPEZZA Treatment in Patients With Chronic (Inactive) Thyroid Eye Disease [online]. 2024 [Accessed: 13.04.2026]. URL: https://clinicaltrials.gov/study/NCT04583735.

9. Amgen. Tepezza 500 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung [online]. 03.2026 [Accessed: 27.04.2026]. URL: https://www.fachinfo.de/.

10. Bartley GB, Fatourechi V, Kadrmas EF et al. Clinical features of Graves' ophthalmopathy in an incidence cohort. Am J Ophthalmol 1996; 121(3): 284-290. https://doi.org/10.1016/s0002-9394(14)70276-4.

11. Burch HB, Perros P, Bednarczuk T et al. Management of Thyroid Eye Disease: A Consensus Statement by the American Thyroid Association and the European Thyroid Association. Thyroid 2022; 32(12): 1439-1470. https://doi.org/10.1089/thy.2022.0251.

12. European Group on Graves' Orbitopathy. EUGOGO initial assessment proforma [online]. 2004 [Accessed: 08.04.2026]. URL: https://www.eugogo.eu/downloadfiles/610/?tmstv=1775647666.

13. Mourits MP, Koornneef L, Wiersinga WM et al. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. Br J Ophthalmol 1989; 73(8): 639-644. https://doi.org/10.1136/bjo.73.8.639.

14. European Medicines Agency. Tepezza; Assessment report [online]. 2025 [Accessed: 08.04.2026]. URL: https://www.ema.europa.eu/en/documents/assessment-report/tepezza-epar-public-assessment-report_en.pdf.

15. Ross DS, Burch HB, Cooper DS et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid 2016; 26(10): 1343-1421. https://doi.org/10.1089/thy.2016.0229.

The full report (German version) is published at https://www.iqwig.de/en/projects/a26-18.html.