Teprotumumab (thyroid eye disease)

Addendum to Project A26-18 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
AESI	adverse event of special interest
CAS	clinical activity score
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
EUGOGO	European Group on Graves' Orbitopathy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GO-QoL	Graves' Ophthalmopathy Quality of Life
HLT	High Level Term
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
PT	Preferred Term
RCT	randomised controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardised mean difference
SMQ	Standardised MedDRA Query
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 7 July 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A26-18 (Teprotumumab – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprised the assessment of the HZNP-TEP-403 study for research question 3 (chronic disease phase) presented by the pharmaceutical company (hereinafter referred to as 'the company') in the dossier, as well as an evaluation of the criteria for disease severity on the basis of the information provided by clinicians during the oral hearing [2] with reference to the patients included in HZNP-TEP-403.

The responsibility for this assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Assessment and evaluation of the criteria for disease severity in patients enrolled in HZNP-TEP-403

It was explained in dossier assessment A26-18 that the data submitted by the company in Module 4 B of the dossier concerning the total population of the HZNP-TEP-403 study were unsuitable for the benefit assessment because it was assumed that fewer than 80% of the patients included in the study had moderate to severe thyroid eye disease.

No new data on this matter were submitted during the commenting procedure on teprotumumab. During the oral hearing, the criteria for assessing the severity of the disease were discussed [2]. Against this background, the available data were reassessed.

Inclusion criteria for the HZNP-TEP-403 study specified no restrictions regarding disease severity

Whilst the chronic disease stage was represented by the inclusion criteria for the HZNP-TEP-403 study, the study population was not restricted to patients with moderate to severe thyroid eye disease on the basis of these inclusion criteria. In contrast to one of the pivotal studies for the acute disease stage – the HZNP-TEP-301 (OPTIC) study [3], in which one of the inclusion criteria was the presence of moderate to severe disease as defined by the 2008 consensus statement of the European Group on Graves' Orbitopathy (EUGOGO) [4] – the HZNP-TEP-403 study did not have a comparable inclusion criterion. The investigators were therefore free to enrol patients with mild thyroid eye disease in the HZNP-TEP-403 study. There was no evidence to suggest that the study was designed to include patients with moderate to severe thyroid eye disease. The EUGOGO criteria, which were cited in both the 2008 consensus statement and the 2021 guideline [5] to classify disease severity, were not fully recorded in the HZNP-TEP-403 study at baseline.

Assessment of the severity of the study population based on the available data

No information was available on the severity of the disease in the patients included in the HZNP-TEP-403 study. As part of the dossier assessment, the 2021 EUGOGO classification was used to assess the severity of thyroid eye disease. The 2021 EUGOGO guideline differs from the 2008 consensus statement with regard to the assessment of the severity of thyroid eye disease. Since 2021, a rating as 'moderate to severe' generally requires 2 or more of the criteria listed below to be met, whereas previously meeting one or more of the criteria was sufficient.

The first version of the protocol for the HZNP-TEP-403 study was dated June 2020, and patient enrolment in the study began in August 2021. The 2 pivotal studies for the acute disease stage (HZNP-TEP-301 [OPTIC] and TED01RV [6]), on the other hand, were conducted prior to 2021

and employed the 2008 EUGOGO consensus statement. For the European authorisation procedure, subgroup analyses for the studies in the acute phase were therefore conducted and submitted based on the number of criteria met at baseline (≥2 criteria versus 1 criterion) [7]. No such analyses were available for the HZNP-TEP-403 study. Presence of the EUGOGO criteria was not a requirement for the inclusion of patients in the HZNP-TEP-403 study and was not recorded. During the oral hearing on A26-18, it was discussed whether it could be assumed that at least 2 of the EUGOGO criteria were met in the patient population of HZNP-TEP-403, and whether other factors were taken into account in the assessment of severity.

Classification of severity according to the 2021 EUGOGO guideline

The 2021 EUGOGO guideline defines moderate to severe thyroid eye disease in adults as a condition that is not sight-threatening but has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). These patients usually have 2 or more of the following:

- lid retraction ≥2 mm
- moderate or severe soft-tissue involvement
- proptosis of ≥3 mm above normal for family origin and sex
- inconstant or constant diplopia

Proptosis

As described in dossier assessment A26-18, one of the inclusion criteria of HZNP-TEP-403 was 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 was still assumed that the criterion of proptosis was met in a large proportion of patients included in the study.

During the oral hearing, proptosis was described as a surrogate outcome for moderate to severe thyroid eye disease, which always occurs in conjunction with involvement of the eye muscles. It is plausible that proptosis is associated with involvement of the eye muscles. However, rating the severity of the condition as moderate to severe on the basis of proptosis alone is not in line with the currently valid classification set out in the 2021 EUGOGO guideline.

There are no data to show that proptosis of ≥3 mm above normal for family origin and sex in the therapeutic indication to be assessed is always associated with soft-tissue involvement of moderate to severe severity.

Soft-tissue involvement

During the oral hearing, the clinicians involved explained that soft-tissue involvement is always present in cases of proptosis and that a clinical activity score (CAS) of 0 does not rule out soft-

tissue involvement. However, soft-tissue involvement – including an assessment of its severity – was not recorded in the HZNP-TEP-403 study. It therefore remained unclear to what extent the criterion of moderate to severe soft-tissue involvement was met in the patients included in the study.

Diplopia

During the oral hearing, proptosis and diplopia (double vision) were described as hard criteria indicating a certain degree of severity of the disease, which, if the diagnosis is correct, do not occur in isolation. As stated in dossier assessment A26-18, constant or inconstant diplopia was present in only 16% of the patients included in the study. Given the inclusion criterion for proptosis listed above, it was assumed that these patients met 2 or more criteria and had moderate to severe thyroid eye disease in accordance with the 2021 EUGOGO guideline. Neither in the dossier nor in the commenting procedure did the company provide any analyses on this subpopulation.

Lid retraction

Lid retraction is the most common clinical sign of thyroid eye disease. During the discussion on determining disease severity, the clinicians also pointed out that lid retraction is a typical sign even in mild forms of the disease. As stated in dossier assessment A26-18, only one participant in the HZNP-TEP-403 study had a documented history of lid retraction (of unknown severity).

Impact on daily life

It was emphasised both in the EUGOGO guideline and in the oral hearing that the impact on daily life is an important criterion for assessing the severity of the disease.

In HZNP-TEP-403, health-related quality of life was assessed using the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire. With this questionnaire, patients themselves assess the extent of the impairment in their visual function and appearance. The 'visual function' domain covers questions regarding impairments in bicycling, driving, reading and watching TV, for example. Values ranging from 0 to 100 can be achieved here, with a domain score of 100 indicating no impairment. At baseline, the median [Q1; Q3] domain score was 93.8 [81; 100] in the teprotumumab arm and 84.4 [72; 97] in the placebo arm. A large proportion of patients enrolled in HZNP-TEP-403 therefore had only a mild impairment of visual function at baseline.

The 'appearance' domain of the GO-QoL represents impairments in psychosocial well-being (also on a scale of 0 to 100; a higher domain score corresponds to a lesser degree of impairment). At baseline, the median [Q1; Q3] domain score was 50.0 [19; 75] in the teprotumumab arm and 37.5 [13; 66] in the placebo arm.

Although the visual function and psychosocial well-being of the patients included in the study were limited on the basis of this information, it was unclear whether these impairments were of such severity that they would – in accordance with the above-mentioned EUGOGO definition of moderate to severe disease – justify the potential risks of surgical intervention.

Conclusion

Overall, therefore, there was still no suitable data available to show that patients with moderate to severe thyroid eye disease were included in the HZNP-TEP-403 study. On the contrary, the data on lid retraction, diplopia and visual function, in particular, suggested that a large proportion of patients included in HZNP-TEP-403 did not have moderate to severe thyroid eye disease. The data on the total study population presented by the company with the dossier were therefore not suitable for answering research question 3, even when taking into account all the information provided in the written comments and at the oral hearing.

In compliance with the commission, the total population of the HZNP-TEP-403 study is assessed below.

2.2 Assessment of study HZNP-TEP-403

2.2.1 Study characteristics

A characterisation of the HZNP-TEP-403 study and the study population can be found in dossier assessment A26-18.

Risk of bias across outcomes

Table 1 shows the risk of bias across outcomes (risk of bias at study level).

Table 1: Risk of bias across outcomes (study level) – RCT, direct comparison: teprotumumab vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
HZNP-TEP-403	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomised controlled trial							

The risk of bias across outcomes was rated as low for HZNP-TEP-403.

Transferability of the study results to the German health care context

The company stated that the characteristics of the patients in HZNP-TEP-403 corresponded to those of patients with thyroid eye disease treated in Germany. Furthermore, treatment in HZNP-TEP-403 was carried out in accordance with the international 2021 EUGOGO guideline, which is also valid in Germany. The company considered the results to be transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.2.2 Results

2.2.2.1 Presented outcomes

The following patient-relevant outcomes are presented in this addendum:

- Mortality
  - All-cause mortality
- Morbidity
  - Freedom from diplopia
  - Orbital pain, recorded using a visual analogue scale (10 cm VAS)
- Health-related quality of life
  - recorded using the GO-QoL
- Side effects
  - Serious AEs (SAEs)
  - Severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥3)
  - Discontinuation due to AEs
  - Hearing disorder (Standardised Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ] hearing impairment, High Level Term [HLT] hearing losses, AEs)
  - Infusion related reactions
  - Other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 B) [8].

Table 2 shows the outcomes for which data were available in the study.

Table 2: Matrix of outcomes – RCT, direct comparison: teprotumumab vs. placebo

Study	Outcomes									
	All-cause mortality[a]	Freedom from diplopia	Orbital pain (VAS)	Health-related quality of life (GO-QoL)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Hearing impairment (SMQ, HLT, AEs)[c]	Infusion related reactions	Other specific AEs
HZNP-TEP-403	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	No[e]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalised as CTCAE grade ≥3.
c. Operationalised using the SMQ hearing impairment and the HLT hearing losses.
d. No suitable data available; see section 'Notes on outcomes' below for reasons.
e. No further specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; GO-QoL: Graves' Ophthalmopathy Quality of Life questionnaire; HLT: High Level Term; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomised controlled trial; SAE: serious adverse event; SMQ: Standardised MedDRA Query; VAS: visual analogue scale

Notes on outcomes

Proptosis does not necessarily represent noticeable symptoms

For the primary outcome of proptosis, in Module 4 B the company presented both responder analyses, defined as a reduction in proptosis of ≥2 mm from baseline in the study eye and without concurrent worsening (an increase in proptosis of ≥2 mm) in the other eye at Week 24, and continuous analyses using a mixed-effects model with repeated measures (MMRM) for the mean change from baseline to Week 24.

In the HZNP-TEP-403 study, proptosis (protrusion of the eyeball) was measured using a Hertel exophthalmometer. Proptosis does not necessarily represent patient-noticeable symptoms of the disease. A factor that may be relevant to the benefit assessment is any tangible improvement in functional symptoms or psychosocial burden that patients may experience as a result of a reduction in proptosis. These patient-relevant symptoms were directly assessed in the HZNP-TEP-403 study using the 2 domains of the GO-QoL (see below, section on health-related quality of life). Neither in the dossier nor during the commenting procedure did the company submit a surrogate validation of a reduction in proptosis as a surrogate for a patient-relevant outcome. The outcome proptosis is therefore not presented in this addendum.

Freedom from diplopia

The presence of diplopia (including its severity) was assessed in the HZNP-TEP-403 study using the Bahn-Gorman score [9]:

- **Grade 0:** no diplopia
- **Grade 1:** intermittent, i.e. diplopia in primary position of gaze when tired or when first awakening
- **Grade 2:** inconstant, i.e. diplopia in extreme directions of gaze
- **Grade 3:** constant, i.e. continuous diplopia in the primary or reading position

The outcome defined by the company as a complete binocular diplopia response at Week 24 corresponded to freedom from diplopia (grade 0) at Week 24. In both Module 4 B and the study protocol, complete response was defined as the percentage of participants with baseline diplopia >0 and freedom from diplopia (grade 0) at Week 24. Deviating from this, the company presented an analysis in Module 4 B that included all randomised patients, regardless of whether or not they had diplopia at baseline. This was appropriate, as, in principle, all patients with thyroid eye disease may develop diplopia (grade >0). The operationalisation of this outcome predefined in the HZNP-TEP-403 study protocol would have resulted in the exclusion of a large proportion of the patient population (patients without diplopia at baseline: 67% in the teprotumumab arm and 80% in the placebo arm). However, a critical point to note regarding the analysis presented by the company in Module 4 B was that patients without diplopia at baseline (grade 0) were classified as non-responders if they remained diplopia-free at Week 24. It would have been appropriate to classify these patients as responders. For the outcome 'freedom from diplopia' (grade 0 at Week 24), the Institute therefore conducted calculations on the basis of the data available in the dossier, in which the aforementioned patients were classified as responders (see Table 4).

Health-related quality of life (GO-QoL)

The GO-QoL is a validated questionnaire used for recording health-related quality of life in patients with thyroid eye disease [10-12]. The questionnaire comprises the domains of visual function and appearance, with a total of 16 questions. For each domain, 8 questions (covering a 1-week period) are answered on a 3-point Likert scale. To calculate the domain scores, the scores for questions 1 to 8 (visual function) and questions 9 to 16 (appearance) are added and then converted to a scale of 0 to 100, with a higher domain score indicating better health-related quality of life. The calculation of a total score across all 16 questions is unvalidated.

In Module 4 B of the dossier, the company presented post-hoc responder analyses for both domains, showing improvements and deteriorations of at least 15 points (corresponding to

15% of the scale range) at Week 24. In addition, prespecified continuous analyses using MMRM were available on the mean change from baseline to Week 24.

The treatment goal in the patient population under consideration here, who are in the chronic disease phase, is to improve health-related quality of life. It would therefore generally be useful to carry out analyses of the improvement at Week 24 for both domains. It should be noted, however, that there were relevant ceiling effects in the domain of visual function in both groups. As already shown in Section 2.1, at baseline, the median [Q1; Q3] domain score was 93.8 [81; 100] in the teprotumumab arm and 84.4 [72; 97] in the placebo arm. Consequently, an improvement of ≥15 points compared with baseline was not achievable in over 50% of the patients enrolled in the HZNP-TEP-403 study. For this reason, this addendum presents the continuous analyses of the 2 domains.

Side effects

Hearing impairment (SMQ, HLT, AEs)

In Module 4 B of its dossier, the company presented analyses for the outcome hearing impairment. The company explained that it had predefined the outcome as an AE of special interest (AESI) via the SMQ 'hearing and vestibular disorders' (broad search) and had coded it using MedDRA, version 26.0. However, according to the information provided in the statistical analysis plan for the HZNP-TEP-403 study, the AESI was predefined as SMQ 'hearing impairment' and HLT 'hearing losses' in accordance with MedDRA, version 24.0. Consequently, there were discrepancies in the information on the operationalisation of the AESI hearing impairment between Module 4 B of the dossier and the study documents; however, the figures on event rates were the same. The operationalisation from the study documents was used in this addendum.

Infusion related reactions

In HZNP-TEP-403, infusion related reactions were predefined as the AESI 'infusion reactions' and were to be recorded in the electronic case report form (eCRF). According to the information in the study protocol, potential infusion related reactions after the first 3 infusions were to be monitored over a period of 60 minutes after completion of the infusion. From the fourth infusion onwards, the duration could be reduced to at least 30 minutes if no previous infusion related reactions had occurred. If immediate hypersensitivity reactions or infusion related reactions were noted, it was specified in HZNP-TEP-403 that premedication was to be administered prior to subsequent infusions to prevent infusion related reactions. It should be pointed out in general that the period specified in the study for monitoring patients for potential infusion reactions appeared to be too short. This is also supported by the recommendation in the SmPC for teprotumumab [13] that patients should be monitored closely throughout the infusion and for 90 minutes after completion of infusion.

The eCRF showed that an AE entry was first made, and that a query was then raised as to whether this was an infusion related reaction. Analyses regarding this query were not available. One point of criticism is that, in the HZNP-TEP-403 study, no specific criteria were provided for the investigators to assess whether an AE was to be classified as an infusion related reaction (e.g. a predefined list of Preferred Terms [PTs]). The structure of the eCRF suggested that the underlying symptoms were coded using the relevant PT in accordance with MedDRA, and that there was no provision of a coding using the PT 'infusion related reaction'. In Module 4 B of the dossier, the company explained that it had operationalised the AESI 'infusion reactions' post hoc as the SMQ 'infusion related reactions', in accordance with MedDRA, version 26.0. However, the SMQ referred to by the company did not exist in MedDRA, version 26.0. A comparison with the clinical study report showed that the results presented in Module 4 B for the AESI corresponded to the results for the PT 'infusion related reaction': An infusion related reaction was documented in only 2 (4.9%) patients in the teprotumumab arm and 3 (15.0%) patients in the placebo arm during the double-blind treatment phase of HZNP-TEP-403. However, given the aforementioned approach to recording data in the eCRF, it was likely that infusion related reactions were under-reported.

The data presented by the company in Module 4 B therefore did not allow for a comprehensive assessment of infusion related reactions. Although there were therefore no suitable data available for the outcome, it was assumed, on the basis of the available information, that the symptoms that occurred as infusion reactions in HZNP-TEP-403 were included in the analyses of the AEs.

2.2.2.2 Risk of bias

Table 3 describes the risk of bias for the results of the relevant outcomes.

Table 3: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: teprotumumab vs. placebo

Study	Study level	Outcomes									
		All-cause mortality[a]	Freedom from diplopia	Orbital pain (VAS)	Health-related quality of life (GO-QoL)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Hearing impairment[c] (SMQ, HLT, AEs)	Infusion related reactions	Other specific AEs
HZNP-TEP-403	L	L	L	L	H[d]	L	L	L	L	–[e]	–[f]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalised as CTCAE grade ≥3.
c. Operationalised using the SMQ hearing impairment and the HLT hearing losses
d. Large difference between the treatment groups (>5 percentage points) in the proportion of patients without a post-baseline recording for whom the change from baseline to the first timepoint of recording after baseline was set to 0.
e. No suitable data available; see Section 2.2.2.1 of this addendum for reasons.
f. No further specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; GO-QoL: Graves' Ophthalmopathy Quality of Life questionnaire; H: high; HLT: High Level Term; L: low; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomised controlled trial; SAE: serious adverse event; SMQ: Standardised MedDRA Query; VAS: visual analogue scale

For the results on outcomes from the mortality, morbidity and side effects categories, the risk of bias was assessed as low. For the health-related quality of life outcome (GO-QoL), the risk of bias in the results was assessed as high. This was due to a large difference between the treatment groups (>5 percentage points) in the proportion of patients without a post-baseline recording for whom the change from baseline to the first timepoint of recording after baseline was set to 0.

2.2.2.3 Results

Table 4 and Table 5 summarise the results of the comparison of teprotumumab with placebo from the HZNP-TEP-403 study. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. In case of a statistically significant mean difference, a standardised mean difference (SMD) was used to assess the clinical relevance.

Results on common AEs, SAEs, severe AEs (CTCAE grade ≥3) and discontinuations due to AEs are presented in Appendix A.

Table 4: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: teprotumumab vs. placebo

Study	teprotumumab		placebo		teprotumumab vs. placebo
Outcome category Outcome Week 24	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
HZNP-TEP-403					
Mortality					
All-cause mortality[b]	41	0 (0)	20	0 (0)	–
Morbidity					
Freedom from diplopia	39	31 (79.5)[c]	20	16 (80.0)[c]	0.99 [0.76; 1.30][c]; >0.999
Side effects					
AEs[d] (supplementary information)	41	33 (80.5)	20	16 (80.0)	–
SAEs	41	1 (2.4)	20	1 (5.0)	0.49 [0.03; 7.40]; 0.734
Severe AEs[e]	41	1 (2.4)	20	1 (5.0)	0.49 [0.03; 7.40]; 0.734
Discontinuation due to AEs	41	1 (2.4)	20	1 (5.0)	0.49 [0.03; 7.40]; 0.734
Hearing impairment[f] (SMQ, HLT, AEs)	41	9 (21.9)	20	2 (10.0)	2.20 [0.52; 9.23]; 0.299
Infusion related reactions	No suitable data[g]				

a. Institute's calculation, unconditional exact test (CSZ method according to [14]).
b. The results on all-cause mortality are based on the data on fatal AEs.
c. Institute's calculation; patients with freedom from diplopia (grade 0) at Week 24 are classified as responders, regardless of whether or not they had diplopia (grade >0) at baseline.
d. Including events that may be attributed to both side effects and symptoms of the underlying condition.
e. Operationalised as CTCAE grade ≥3.
f. Operationalised using the SMQ hearing impairment and the HLT hearing losses.
g. See Section 2.2.2.1 of this addendum for reasons.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HLT: High Level Term; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardised MedDRA Query

Table 5: Results (morbidity, continuous) – RCT, direct comparison: teprotumumab vs. placebo

Study Outcome category Outcome	teprotumumab			placebo			teprotumumab vs. placebo
	N[a]	Values at baseline Mean (SD)	Mean change by Week 24 Mean[b] (SE)	N[a]	Values at baseline Mean (SD)	Mean change by Week 24 Mean[b] (SE)	MD [95% CI]; p-value[b]
HZNP-TEP-403							
Morbidity							
Orbital pain (VAS)[c]	42	6.8 (13.7)	−5.6 (1.3)[d]	20	15.9 (27.0)	−2.4 (2.0)[e]	−3.27 [−8.07; 1.54]; 0.179
Health-related quality of life							
GO-QoL[f]							
Visual function	42	86.4 (20.0)	7.4 (1.4)[g]	20	81.4 (18.8)	2.5 (2.0)[e]	4.94 [0.00; 9.87]; 0.050[h] SMD: 0.54 [−0.00; 1.08]
Appearance	42	46.4 (29.5)	8.2 (2.3)[g]	20	40.0 (28.6)	5.2 (3.3)[e]	2.92 [−5.25; 11.09]; 0.478

a. Number of patients considered in the effect estimation.
b. MMRM of mean changes, with baseline value, visit, treatment, interaction between visit and treatment, and interaction between visit and baseline value as covariates; for patients without a post-baseline recording, the change from baseline to the first timepoint of recording after baseline was set to 0.
c. Lower (decreasing) values indicate better symptoms; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 mm to 100 mm).
d. No post-baseline recordings were available for a maximum of 2 (5) patients.
e. At least one post-baseline recording was available for all patients.
f. Higher (increasing) values indicate better health-related quality of life; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 100).
g. No post-baseline recordings were available for 3 (7) patients.
h. Unrounded p-value <0.05.

CI: confidence interval; GO-QoL: Graves' Ophthalmopathy Quality of Life; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; SMD: standardised mean difference; VAS: Work visual analogue scale

Mortality

All-cause mortality

There were no deaths in either treatment group up to Week 24.

Morbidity

Freedom from diplopia

At Week 24, no statistically significant difference between treatment groups was shown for the outcome of freedom from diplopia.

Orbital pain (VAS)

By Week 24, no statistically significant difference between treatment groups was found for the outcome of orbital pain, recorded using a 10 cm VAS.

Health-related quality of life (GO-QoL)

Health-related quality of life was recorded using the 'visual function' and 'appearance' domains of the GO-QoL.

For the visual function domain, a statistically significant difference between the treatment groups was observed up to Week 24; however, when considering the SMD, this difference was not relevant, as the 95% CI for the effect did not lie entirely outside the irrelevance threshold of [−0.2; 0.2]. Up to Week 24, no statistically significant difference between treatment groups was shown for the appearance domain.

Side effects

SAEs, severe AEs (CTCAE grade ≥3) and discontinuation due to AEs

At Week 24, no statistically significant difference between treatment groups was shown for the outcomes of SAEs, severe AEs and discontinuation due to AEs.

Specific AEs

Hearing impairment (SMQ, HLT, AEs)

At Week 24, no statistically significant difference between treatment groups was shown for the outcome of hearing impairment.

Infusion related reactions

No suitable data were available for the outcome of infusion related reactions.

2.2.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered in this addendum:

- Age (<65 years versus ≥65 years)
- Sex (male versus female)

No suitable characteristic was available for disease severity.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value <0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

When applying the above-described methods, the available subgroup results show no effect modifications.

2.2.3 Summary of the results

Overall, the HZNP-TEP-403 study showed no advantages or disadvantages of teprotumumab compared with placebo in any of the outcomes presented.

The G-BA decides on the added benefit.

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Appendix A Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥3), the following tables present results for System Organ Classes (SOCs) and Preferred Terms (PTs) according to MedDRA, each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity): events that occurred in at least 10% of patients in one study arm
- Overall rate of severe AEs (e.g. CTCAE grade ≥3) and SAEs: events that occurred in at least 5% of patients in one study arm
- Additionally, for all events irrespective of severity: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 6: Common AEs[a] – RCT, direct comparison: teprotumumab vs. placebo

Study	Patients with event n (%)	
SOC[b] PT[b]	teprotumumab N=41	placebo N=20
HZNP-TEP-403		
Overall AE rate[c]	33 (80.5)	16 (80.0)
Musculoskeletal and connective tissue disorders	19 (46.3)	4 (20.0)
Muscle spasms	17 (41.5)	2 (10.0)
Gastrointestinal disorders	11 (26.8)	7 (35.0)
Diarrhoea	8 (19.5)	4 (20.0)
Infections and infestations	14 (34.1)	5 (25.0)
COVID-19	6 (14.6)	2 (10.0)
Upper respiratory tract infection	1 (2.4)	2 (10.0)
Nervous system disorders	11 (26.8)	6 (30.0)
Headache	7 (17.1)	2 (10.0)
Dizziness	2 (4.9)	2 (10.0)
Eye disorders	12 (29.3)	4 (20.0)
Eye pain	5 (12.2)	1 (5.0)
Ear and labyrinth disorders	11 (26.8)	4 (20.0)
Ear discomfort	2 (4.9)	2 (10.0)
Tinnitus	2 (4.9)	2 (10.0)
Injury, poisoning and procedural complications	5 (12.2)	5 (25.0)
Infusion related reaction	2 (4.9)	3 (15.0)
General disorders and administration site conditions	10 (24.4)	3 (15.0)
Fatigue	9 (21.9)	2 (10.0)
Skin and subcutaneous tissue disorders	10 (24.4)	0 (0)
Dry skin	5 (12.2)	0 (0)
Metabolism and nutrition disorders	6 (14.6)	3 (15.0)
Investigations	4 (9.8)	3 (15.0)
Respiratory, thoracic and mediastinal disorders	4 (9.8)	2 (10.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (2.4)	2 (10.0)

a. Events that occurred in at least one study arm in ≥10% of patients.
b. MedDRA version 26.0; SOCs and PTs taken from Module 4 B.
c. Including events that may be attributed to both side effects and symptoms of the underlying condition.

AE: adverse event; COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomised controlled trial; SOC: System Organ Class

Table 7: Common SAEs[a] – RCT, direct comparison: teprotumumab vs. placebo

Study	Patients with event n (%)	
SOC[b] PT[b]	teprotumumab N=41	placebo N=20
HZNP-TEP-403		
Overall SAE rate	1 (2.4)	1 (5.0)
Metabolism and nutrition disorders	0 (0)	1 (5.0)
Diabetic ketoacidosis	0 (0)	1 (5.0)

a. Events that occurred in at least one study arm in ≥5% of patients.
b. MedDRA version 26.0; SOCs and PTs taken from Module 4 B.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomised controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 8: Common severe AEs[a] (CTCAE grade ≥3) – RCT, direct comparison: teprotumumab vs. placebo

Study	Patients with event n (%)	
SOC[b] PT[b]	teprotumumab N=41	placebo N=20
HZNP-TEP-403		
Overall rate of severe AEs (CTCAE grade ≥3)	1 (2.4)	1 (5.0)
Metabolism and nutrition disorders	0 (0)	1 (5.0)
Diabetic ketoacidosis	0 (0)	1 (5.0)

a. Events that occurred in at least one study arm in ≥5% of patients.
b. MedDRA version 26.0; SOCs and PTs taken from Module 4 B.

CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomised controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 9: Discontinuations due to AEs – RCT, direct comparison: teprotumumab vs. placebo

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**teprotumumab** **N=41**	**placebo** **N=20**
HZNP-TEP-403		
Overall rate of discontinuations due to AEs	1 (2.4)	1 (5.0)
Injury, poisoning and procedural complications	0 (0)	1 (5.0)
Infusion related reaction	0 (0)	1 (5.0)
Ear and labyrinth disorders	1 (2.4)	0 (0)
Conductive deafness	1 (2.4)	0 (0)

a. MedDRA version 26.0; SOCs and PTs taken from Module 4 B.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomised controlled trial; SOC: System Organ Class