Teplizumab
(stage 2 type 1 diabetes mellitus, ≥8 years)

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

EXTRACT

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Medical and scientific advice

- Andreas Barthel

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Patient and family involvement

The questionnaire on the disease and its treatment was answered by Thomas Roth.

IQWiG thanks the respondent and the patient organisation 'Deutsche Diabetes Föderation e. V.' for participating in the written exchange and for their support. The respondent and the 'Deutsche Diabetes Föderation e. V.' were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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[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
ADA	American Diabetes Association
AE	adverse event
AUC	area under the curve
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DDG	Deutsche Diabetes Gesellschaft (German Diabetes Society)
EMA	European Medicines Agency
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GAD65	glutamic acid decarboxylase 65
HbA1c	glycated haemoglobin
IA-2A	insulinoma-associated antigen-2 antibodies
ICA	islet cell antibodies
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mIAA	micro-insulin autoantibodies
OGTT	oral glucose tolerance test
PT	Preferred Term
RCT	randomised controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
WHO	World Health Organization
ZnT8	zinc transporter 8 antibodies

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 teplizumab. 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 16 February 2026.

Research question

The aim of this report is to assess the added benefit of teplizumab in comparison with the appropriate comparator therapy (ACT) in patients with stage 2 type 1 diabetes mellitus, to delay the onset of stage 3.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of teplizumab

Therapeutic indication	**ACT**[a]
Adult and paediatric patients 8 years of age and older with stage 2 type 1 diabetes mellitus[b], to delay the onset of stage 3	Watchful waiting
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, the criteria apply to people who do not (yet) have clinically manifest type 1 diabetes mellitus, but who have persistent autoantibodies in conjunction with a fasting plasma glucose level of between 100 and 125 mg/dL or an HbA1c level of between 5.7% and 6.4%. According to current guidelines, these people are classified as having stage 2 type 1 diabetes mellitus [1,2]. People with stage 1 and 2 type 1 diabetes mellitus are assumed to not be insulin-dependent. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HbA1c: glycated haemoglobin	

The company named watchful waiting as the ACT and thus followed the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. In this therapeutic indication, randomised controlled trials (RCTs) with an event-driven study duration are preferable for the derivation of the added benefit. Nevertheless, the review of the completeness of the study pool was based on RCTs with a minimum duration of 24 weeks.

Study pool and study design

The RCT TN-10 was used for this benefit assessment. TN-10 is a completed, double-blind RCT comparing teplizumab versus placebo. The study included patients with stage 2 type 1 diabetes mellitus aged 8 years and older who had previously been enrolled in the TN-01 study

at an age of 1 to 45 years. All patients in the TN-10 study had at least one relative with type 1 diabetes mellitus. Furthermore patients had to have abnormal glucose tolerance in order to be included in the TN-10 study. Abnormal glucose tolerance could be confirmed by the fasting plasma glucose level, a 2-hour plasma glucose level, or a 30, 60, or 90 minute value after an oral glucose tolerance test (OGTT). In addition at least 2 diabetes-related antibodies had to be present, confirmed in 2 independent measurements. The measurements had to be taken within 6 months prior to the first study drug administration. The autoantibodies that were to be confirmed were anti glutamic acid decarboxylase 65 (GAD65), insulinoma-associated antigen-2 antibodies (IA-2A), micro-insulin autoantibodies (mIAA), zinc transporter 8 antibodies (ZnT8) and/or islet cell antibodies (ICA). Patients with clinically manifest type 1 diabetes mellitus were excluded from the study.

The study included a total of 76 patients, randomised in a 1:1 ratio to treatment with teplizumab (N=44) or to placebo (N=32).

Treatment with teplizumab in the study was largely in compliance with the recommendations of the summary of product characteristics (SmPC).

The primary outcome of the TN-10 study was the time to onset of type 1 diabetes mellitus (stage 3). Further patient-relevant outcomes were recorded in the side effects category.

Limitations of the TN-10 study

Restriction of the study population to individuals with stage 2 type 1 diabetes mellitus and a family history of the condition

The authorised therapeutic indication for teplizumab covers all patients 8 years of age and older with stage 2 type 1 diabetes mellitus regardless of a family history. The company argued that the results of the TN-10 study were transferable from patients without a family history to patients with a family history. It based this argument on analyses of the Fr1da study carried out in Germany. The aim of this study was to diagnose children whilst they were still in the prediabetic stage. In the article cited by the company, a group from the Fr1da cohort comprising patients with stage 2 type 1 diabetes mellitus was compared with the TN-10 placebo arm. However, the analyses of the presented study and the company's reasoning were insufficient to assume the transferability of the results of the TN-10 study to patients without a family history. This was due to differences in the median time to progression to stage 3 (Fr1da group: 32 months versus placebo arm of the TN-10 study: 26 months) and differences in the compared patient populations in terms of age and family history (the Fr1da study included patients with and without relatives with type 1 diabetes mellitus). Furthermore, the Fr1da group was not treated with teplizumab and, consequently, no comparison with the intervention arm of the TN-10 study was presented. The TN-10 study

only allowed conclusions to be drawn regarding patients with stage 2 type 1 diabetes mellitus who have a family history of the condition.

Deviations in the diagnostic criteria for stage 2 type 1 diabetes mellitus

The inclusion criteria in the TN-10 study for the diagnosis of stage 2 type 1 diabetes mellitus differed in some aspects from those set out in the S3 guidelines of the German Diabetes Society (DDG).

There was a difference in the determination of abnormal glucose tolerance. In TN-10, the plasma glucose level at 30, 60 and 90 minutes after an OGTT was used. This diagnostic/inclusion criterion does not comply with the guidelines; according to WHO guidelines, the 2-hour plasma glucose level following an OGTT is recommended. Due to the lack of information by the company, it was unclear how many patients were included on the basis of this non-recommended diagnostic criterion. The resulting uncertainty did not completely call into question the suitability of the TN-10 study, but was taken into account in the assessment of the certainty of conclusions.

Uncertainties regarding the dosage of teplizumab

The formulation of teplizumab used in the TN-10 study differed from the authorised commercial product due to a change of manufacturer and an associated change in the manufacturing process. Patients in TN-10 received a cumulative dose of teplizumab that was approximately 20% lower. Due to missing data, it remained unclear whether and to what extent the different dosage had an impact on patient-relevant outcomes. This uncertainty was taken into account when assessing the certainty of conclusions.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT for the research question. The TN-10 study used placebo as the comparator therapy. The study involved regular tests to assess the symptoms and clinical signs of type 1 diabetes mellitus. In this therapeutic indication, the interventions were therefore regarded, on the whole, as a sufficient approximation of the ACT watchful waiting.

Risk of bias and certainty of conclusions

The risk of bias across outcomes was rated as low for TN-10.

The risk of bias was rated as high for the results for the outcomes all-cause mortality and severe AEs. This was due to incomplete observations for potentially informative reasons with different observation periods. The risk of bias for the outcomes of onset of type 1 diabetes mellitus and discontinuation due to AEs was rated as low. No data or no suitable data were available for the remaining outcomes, so the risk of bias was not assessed.

The TN-10 study enrolled patients with stage 2 type 1 diabetes mellitus. The following aspects were taken into account in the assessment of the certainty of conclusions:

- Deviations from the guideline recommendations regarding the diagnosis of stage 2 type 1 diabetes mellitus at the time of enrolment, based on abnormal glucose tolerance
- Deviations in the dosage of teplizumab in the TN-10 study compared with the authorised commercial product

In view of the aspects mentioned above, the certainty of conclusions regarding the research question at hand was reduced overall. Based on the available information from the TN-10 study, at most hints, e.g. of an added benefit, could be derived for all outcomes presented.

Results

Mortality

No deaths occurred in the TN-10 study. There is no hint of an added benefit of teplizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Onset of type 1 diabetes mellitus

For the outcome 'onset of type 1 diabetes mellitus', the analysis of the time to onset of type 1 diabetes mellitus (stage 3) showed a statistically significant advantage of teplizumab compared with placebo. The median delay in the onset of type 1 diabetes mellitus (stage 3) was 2 years. The observation period was too short to investigate whether teplizumab can completely prevent the onset of type 1 diabetes mellitus. In addition, it was unclear to what extent the observed delay has a positive effect on the long-term course of the disease (particularly the occurrence of micro- and macrovascular late complications). The effects of the delay on health-related quality of life and symptoms were not recorded.

There is no hint of an added benefit of teplizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

Data for the category of health-related quality of life were not recorded. There is no hint of an added benefit of teplizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

Severe AEs

A statistically significant difference between treatment groups to the disadvantage of teplizumab was found for the outcome of severe AEs. There is a hint of greater harm of teplizumab in comparison with watchful waiting.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm of teplizumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Infections (AEs), serious infections (SAEs)

No suitable data were available for the outcomes of infections (AEs) and serious infections (SAEs) due to missing time-to-event analyses. In each case, there is no hint of greater or lesser harm of teplizumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug teplizumab versus the ACT was assessed as follows:

In this benefit assessment, based on the TN-10 study, it was only possible to draw conclusions on patients who have a family history of type 1 diabetes mellitus. No data were available for patients with no family history of the condition.

Overall, there is a negative effect in the category of serious/severe side effects for patients with stage 2 type 1 diabetes mellitus and with a family history of the condition. There is a hint of greater harm with major extent. The outcomes in the side effects category could not be fully taken into account due to the analyses presented in Module 4 A regarding the relative risk in the presence of different observation periods; however, disadvantages regarding specific AEs were suggested.

[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 [3,4].

For the outcome 'onset of type 1 diabetes mellitus', there was a statistically significant advantage of teplizumab in comparison with watchful waiting, with a median delay in onset of 2 years. However, it is unclear to what extent this delay has a positive effect on the long-term course of the disease (particularly the occurrence of micro- and macrovascular late complications). The effects of the delay on health-related quality of life and symptoms were not recorded. As there is some uncertainty regarding the effects of teplizumab on morbidity and health-related quality of life due to missing data, the negative effect observed in the side effects category is not sufficient to justify a conclusion that there is a lesser benefit.

In summary, there is no hint of an added benefit of teplizumab in comparison with the ACT for adult and paediatric patients 8 years of age and older, with a family history, with stage 2 type 1 diabetes mellitus, to delay the onset of stage 3. An added benefit is therefore not proven for this patient group.

For adult and paediatric patients 8 years of age and older, without a family history, with stage 2 type 1 diabetes mellitus, the TN-10 study provided no data to assess the added benefit of teplizumab in comparison with the ACT. An added benefit is therefore not proven for this patient group.

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

Table 3: Teplizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult and paediatric patients 8 years of age and older with stage 2 type 1 diabetes mellitus[b], to delay the onset of stage 3	watchful waiting	▪ For patients with a family history[c]: added benefit not proven (based on the results of the relevant study) ▪ For patients without a family history: added benefit not proven (no relevant study[d])
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, the criteria apply to people who do not (yet) have clinically manifest type 1 diabetes mellitus, but who have persistent autoantibodies in conjunction with a fasting plasma glucose level of between 100 and 125 mg/dL or an HbA1c level of between 5.7% and 6.4%. In accordance with current guidelines, these people are classified as having stage 2 type 1 diabetes mellitus. People with stage 1 and 2 type 1 diabetes mellitus are assumed to not be insulin-dependent. c. TheTN-10 study only included patients from the age of 8 to a maximum of 49.5 years. It remains unclear whether the observed effects can be transferred to patients older than 49.5 years. d. The research question of teplizumab in comparison with watchful waiting in patients without a family history was not investigated in the TN-10 study. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HbA1c: glycated haemoglobin		

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of teplizumab in comparison with the appropriate comparator therapy (ACT) in patients with stage 2 type 1 diabetes mellitus, to delay the onset of stage 3.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of teplizumab

Therapeutic indication	**ACT**[a]
Adult and paediatric patients 8 years of age and older with stage 2 type 1 diabetes mellitus[b], to delay the onset of stage 3	Watchful waiting
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, the criteria apply to people who do not (yet) have clinically manifest type 1 diabetes mellitus, but who have persistent autoantibodies in conjunction with a fasting plasma glucose level of between 100 and 125 mg/dL or an HbA1c level of between 5.7% and 6.4%. According to current guidelines, these people are classified as having stage 2 type 1 diabetes mellitus [1,2]. People with stage 1 and 2 type 1 diabetes mellitus are assumed to not be insulin-dependent. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HbA1c: glycated haemoglobin	

The company named watchful waiting as the ACT and thus followed the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. In this therapeutic indication, randomised controlled trials (RCTs) with an event-driven study duration are preferable for the derivation of the added benefit. Nevertheless, the review of the completeness of the study pool was based on RCTs with a minimum duration of 24 weeks. This concurs with the inclusion criterion of the company.

I 3 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 teplizumab (status: 24 November 2025)
- Bibliographical literature search on teplizumab (last search on 24 November 2025)
- Search of trial registries / trial results databases for studies on teplizumab (last search on 24 November 2025)
- Search on the G-BA website for teplizumab (last search on 24 November 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on teplizumab (last search on 26 February 2026); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: teplizumab vs. watchful waiting

Study	Study category			Available sources		
	Study for the marketing authorisation of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
TN-10	Yes	Yes	No	Yes [5]	Yes [6,7]	Yes [8,9]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomised controlled trial

The TN-10 study was used for the benefit assessment. The study pool was consistent with that selected by the company.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT, direct comparison: teplizumab vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomised patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
TN-10	RCT, double-blind, parallel	Children and adults (≥8–45 years) with stage 2 type 1 diabetes mellitus[b] ▪ Confirmed[c] abnormal glucose tolerance[d] ▪ ≥2 diabetes-related antibodies (GAD65A, IA-2A (=ICA512), mIAA, ZnT8A and/or ICA)[e]	teplizumab (N=44) placebo (N=32)	Screening: up to 7 weeks Treatment: 14 days Observation: Until reaching the primary outcome[f] or until the end of the study[g]	30 centres in Australia, Canada, Germany, United Kingdom and United States 7/2011–11/2018 Data cut: 30 Nov 2018[h]	Primary: time to onset of type 1 diabetes mellitus[i] Secondary: AEs

Table 6: Characteristics of the included study – RCT, direct comparison: teplizumab vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomised patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. The study included only children and adults who were also participants in the TN-01 study and who had one or more relatives with type 1 diabetes mellitus. The relatives must have been diagnosed with diabetes before age 40 and started on insulin therapy within one year of diagnosis. If the relatives were diagnosed with type 1 diabetes based on other criteria, the study protocol required the TrialNet Eligibility Committee to approve enrolment in TN01.
c. In patients <18 years of age by a TrialNet-conducted OGTT within 7 weeks before the baseline visit (Day 0), and in patients ≥18 years of age by 2 consecutive TrialNet-conducted OGTTs, the most recent within 7 weeks before the baseline visit (Day 0).
d. Defined as fasting plasma glucose ≥110 mg/dL and <126 mg/dL, or 2-hour plasma glucose ≥140 mg/dL and <200 mg/dL, or 30, 60, or 90 minute value on OGTT ≥200 mg/dL.
e. Confirmed by 2 measurements; the second measurement must have taken place within 6 months prior to the first dose of the study medication, but did not need to involve the same autoantibodies as were found in the first measurement.
f. Patients who reached the primary outcome were offered follow-up for a minimum of 2 years.
g. According to the amendment to the study protocol dated 25 June 2014, the study ended once 40 patients had been diagnosed with clinically manifest type 1 diabetes mellitus. Patients who did not have manifest type 1 diabetes mellitus by study end were continued to be followed as part of the TN-01 (TrialNet Natural History/Pathway to Prevention Study) protocol.
h. The final analysis was carried out after ≥40 events in the primary outcome. An additional interim analysis was conducted; according to the SAP, this was to take place after 18 events in the primary outcome.
i. The criteria for type 1 diabetes mellitus onset are based on glucose testing (according to American Diabetes Association criteria), or the presence of unequivocal hyperglycaemia with acute metabolic decompensation (diabetic ketoacidosis). The glucose tests had to be carried out at 2 timepoints, no less than one day apart, and one of the following criteria had to be met: classic symptoms of diabetes mellitus (polyuria, polydipsia and unexplained weight loss) and casual (i.e. without regard to time since last meal) plasma glucose concentration ≥200 mg/dL (11.1 mmol/L) or fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) or 2-hour plasma glucose after OGTT ≥200 mg/dL (11.1 mmol/L).

AE: adverse event; GAD65A: glutamic acid decarboxylase-65 antibodies; IA-2A: insulinoma-associated antigen-2 antibodies; ICA: islet cell antibodies; mIAA: micro-insulin autoantibodies; N: number of randomised patients; OGTT: oral glucose tolerance test; RCT: randomised controlled trial; ZnT8A: zinc transporter 8 antibodies

Table 7: Characteristics of the interventions – RCT, direct comparison: teplizumab vs. placebo

Study	Intervention	Comparison
TN-10	teplizumab once daily, IV, for 14 days[a] (total dose: 9034 µg/m² BSA) ▪ Day 0: 51 µg/m² BSA ▪ Day 1: 103 µg/m² BSA ▪ Day 2: 207 µg/m² BSA ▪ Day 3: 413 µg/m² BSA ▪ Days 4–13: 826 µg/m² BSA	placebo once daily, IV, for 14 days
	Dose modification: ▪ Treatment interruptions possible[b]	
	Required pretreatment ▪ ibuprofen and antihistamines as prophylaxis prior to the infusion on the first 5 days **Allowed concomitant treatment** ▪ ibuprofen, antihistamines and paracetamol for the treatment of fever, malaise, headache, arthralgia or rash **Prohibited prior and concomitant treatment** ▪ Live vaccines within 8 weeks after randomisation and up to 1 year after treatment ▪ Killed virus vaccines within 4 weeks after randomisation and, if possible, not within 4 weeks after treatment ▪ Chronic use of steroids or immunosuppressants[c] ▪ Non-insulin-based drugs that affect glycaemic control ▪ Monoclonal antibodies within 1 year prior to randomisation ▪ Previous OKT3 or other anti-CD3 treatments	

a. The 14-day course of treatment had to begin within 7 weeks of the confirmatory OGTT except in the event of intercurrent illness.
b. During the 14-day treatment cycle patients were monitored daily for hepatic abnormalities, thrombocytopenia, neutropenia, anaemia, coagulopathy, fever (grade 3 on Day 0 or 1) and grade ≥3 adverse events, regardless of relatedness to study drug (except for lymphopenia, hypoglycaemia, hyperglycaemia, fatigue/malaise, insomnia, cheilitis, dry skin, nail changes, hot flushes, headache, myalgia, flu-like symptoms). Where relevant findings or other events occurred, at the discretion of the investigator, administration of the study medication was temporarily interrupted.
c. Patients were instructed not to use prednisone, immunosuppressants or chronic inhaled or nasal corticosteroids during the study in order to reduce infectious risks and to prevent possible impact on diabetes progression.

BSA: body surface area; CD: cluster of differentiation; IV: intravenous; OGTT: oral glucose tolerance test; RCT: randomised controlled trial

Study design

TN-10 is a completed, double-blind RCT comparing teplizumab versus placebo. The study included patients with stage 2 type 1 diabetes mellitus aged 8 years and older (at the time of randomisation) who had previously been enrolled in the TN-01 study (where patients were aged 1 to 45 years). At the time of enrolment in the TN-10 study the patients were aged 49.5 years or younger. The TN-01 study (TrialNet Pathway To Prevention Study) is a screening

and monitoring study with the primary aim of identifying patients for prevention or intervention studies. All patients in the TN-10 study had at least one relative with type 1 diabetes mellitus. Patients with stage 2 diabetes mellitus who did not have any relatives with type 1 diabetes mellitus were excluded from the study. Furthermore patients had to have abnormal glucose tolerance in order to be included in the TN-10 study. Abnormal glucose tolerance was defined as a fasting plasma glucose between ≥110 mg/dL and <126 mg/dL, or a 2-hour plasma glucose between ≥140 mg/dL and <200 mg/dL, or a 30, 60, or 90 minute value after an oral glucose tolerance test (OGTT) ≥200 mg/dL. At the time of randomisation the abnormal glucose tolerance in patients 18 years of age or older must have been confirmed by 2 consecutive TrialNet-conducted OGTTs (TrialNet is a network of 19 clinical centres worldwide dedicated to the research, prevention and early treatment of type 1 diabetes mellitus). The most recent OGTT must have taken place within 7 weeks before the baseline visit (Day 0). For patients under the age of 18 years, determination of abnormal glucose tolerance could be obtained with a confirmed OGTT carried out within 7 weeks before the baseline visit (Day 0). In addition at least 2 diabetes-related antibodies had to be present, confirmed in 2 independent measurements. The measurements had to be taken within 6 months prior to the first study drug administration. The autoantibodies that were to be confirmed were anti glutamic acid decarboxylase 65 (GAD65), insulinoma-associated antigen-2 antibodies (IA-2A), micro-insulin autoantibodies (mIAA), zinc transporter 8 antibodies (ZnT8) and/or islet cell antibodies (ICA).

Patients with clinically manifest type 1 diabetes mellitus were excluded from the study.

The study included a total of 76 patients, randomised in a 1:1 ratio to treatment with teplizumab (N=44) or to placebo (N=32). Randomisation was stratified by study centre and age at the time of recruitment (<18 years versus ≥18 years).

Treatment with teplizumab in the study was largely in compliance with the recommendations of the summary of product characteristics (SmPC) [10]. Uncertainties regarding the dosage are described in the section entitled ‘Uncertainties regarding the dosage of teplizumab’.

The primary outcome of the TN-10 study was the time to onset of type 1 diabetes mellitus (stage 3). Further patient-relevant outcomes were recorded in the side effects category.

The final data cut-off for the TN-10 study was on 30 November 2018; it had been planned for the timepoint after 40 patients reached the primary outcome. An additional interim data analysis had been planned for the timepoint after 18 patients reached the primary outcome. The final data cut was used for this benefit assessment.

Planned duration of follow-up

Table 8 shows the planned duration of patient follow-up for the individual outcomes.

Table 8: Planned duration of follow-up – RCT, direct comparison: teplizumab vs. placebo

Study **Outcome category** **outcome**	**Planned follow-up**
TN-10	
Mortality	
All-cause mortality[a]	Until the primary outcome is reached[b] or until the end of the study[c] or until study discontinuation
Morbidity	
Onset of type 1 diabetes mellitus	Until the end of the study[c]
Health-related quality of life	No data on health-related quality of life were recorded
Side effects	
All outcomes in the side effects category	Until the primary outcome is reached[b], until the end of the study[c] or until study discontinuation

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Once a patient reached the primary outcome, i.e. the onset of clinically manifest type 1 diabetes mellitus, the study ended for this patient. Nevertheless, these patients were offered follow-up for a minimum of 2 years in the TN-10 Extension study.
c. The study ended after 40 patients had reached the primary outcome. Patients who had not reached the primary outcome before the end of the study were followed up in accordance with the TN-01 study protocol.

AE: adverse event; RCT: randomised controlled trial

Patients were followed up for all recorded outcomes until the primary outcome was reached – the onset of clinically manifest type 1 diabetes mellitus – or until the end of the study. Patients who had not reached the primary outcome before the end of the study were offered a follow-up in accordance with the TN-01 study protocol. The company stated that the results of the TN-01 study as a follow-up analysis were not directly relevant for presentation in the dossier. However patients could still be monitored regularly for progression of type 1 diabetes mellitus to stage 3. According to the European Public Assessment Report (EPAR), the company had access only to publicly available data from the TN-01 study [11]. According to Sims' publication on the follow-up [9] metabolic analyses based on OGTTs and immune response were investigated and followed up. There was no information as to whether patient-relevant outcomes were also recorded. There were therefore no suitable data available from the TN-01 study.

Patients who reached the primary outcome could continue follow-up for another 2 years in the TN-10 Extension study.

Limitations of the TN-10 study

Restriction of the study population to individuals with stage 2 type 1 diabetes mellitus and a family history of the condition

The authorised therapeutic indication for teplizumab covers all patients 8 years of age and older with stage 2 type 1 diabetes mellitus regardless of a family history [10]. However the TN-10 study included only patients who had relatives with clinically manifest type 1 diabetes mellitus.

More than 80% of patients with type 1 diabetes mellitus have no relatives with the condition and therefore no family history of the disease [1,2]. To support the argument that the study results are transferable with regard to family history, the company drew on analyses of the Fr1da study carried out in Germany [12]. As part of the Fr1da study children aged 2 to 11 years were offered screening for type 1 diabetes mellitus by testing for islet autoantibodies. The aim was to diagnose children whilst they were still in the prediabetic stage. Children in this age cohort were tested regardless of whether or not they had a family history. Children and adults aged 1 to 21 years who had a relative with type 1 diabetes mellitus were also included. The outcome of the study was a diagnosis of stage 3 type 1 diabetes mellitus. In the article cited by the company, a group from the Fr1da cohort comprising patients with stage 2 type 1 diabetes mellitus was compared with the TN-10 placebo arm [12]. For the retrospective analysis presented in the article, the patients in the Fr1da group were selected based on the evidence of abnormal glucose tolerance assessed using the same methods and criteria used in TN-10, and on the confirmed presence of ≥2 autoantibodies, in line with the TN-10 inclusion criteria. In total, the Fr1da group comprised 152 patients, and 32 patients from the TN-10 study were included in the analyses. Although the company argued that the progression of type 1 diabetes mellitus from stage 2 to stage 3 in children and adolescents in the Fr1da group was comparable to that in the TN-10 placebo arm, the median time to progression in the Fr1da group (32 months) differed from that in the TN-10 placebo arm (26 months). Furthermore, the entire Fr1da group with stage 2 was used for the comparison. This group included both patients with and without a family history of the condition and, with a median age of 5 years, was notably younger than the patients in the TN-10 placebo arm (13 years). In the Fr1da group, the time to stage 3 was operationalised as the number of days between the age at stage 2 diagnosis of type 1 diabetes mellitus and the age at stage 3 diagnosis. In TN-10, it was defined as the number of days between the stage 2 diagnosis of type 1 diabetes mellitus and the stage 3 diagnosis. Additional sensitivity analyses, which take into account age and family history, revealed differences between the groups compared, which, whilst not statistically significant, were nonetheless substantial (age group 8 to 15 years: Fr1da group (n = 40): 32 months versus the TN-10 placebo arm (n = 24): 15 months; Fr1da group with (n = 45) versus without (n = 107) family history: 42 months versus 27 months). There was no comparison between the Fr1da group with no family history versus patients in the TN-10 study.

Furthermore, the Fr1da group was not treated with teplizumab and, consequently, no comparison with the intervention arm of the TN-10 study could be presented. It was therefore not possible to draw any conclusions regarding patients treated with teplizumab. According to the authors themselves, the study only had sufficient power to detect large differences. The lack of statistical significance in the comparative analyses did not, therefore, necessarily imply that the groups were comparable, particularly in view of the differences listed.

Overall, based on the company's reasoning, the transferability of the results of the TN-10 study to patients without a family history could not be assumed. The TN-10 study therefore only allowed conclusions to be drawn regarding patients with stage 2 type 1 diabetes mellitus who have a family history of the condition.

Deviations in the diagnostic criteria for stage 2 type 1 diabetes mellitus

The inclusion criteria in the TN-10 study for the diagnosis of stage 2 type 1 diabetes mellitus differed in some aspects from those set out in the S3 guidelines of the German Diabetes Society (DDG) [1,2]. The discrepancies related to the ICA demonstrating islet autoimmunity and to the values used as inclusion criteria to demonstrate abnormal glucose tolerance (fasting plasma glucose level and the 30, 60 and 90-minute plasma glucose levels following an OGTT).

In the TN-10 study, autoimmunity was determined, amongst other things, based on the ICA. According to the German S3 guideline on the treatment of type 1 diabetes, ICA testing yields non-specific results and is no longer recommended [2]. However, the S3 guideline on the diagnosis, treatment and monitoring of diabetes mellitus in children and adolescents still includes the determination of autoimmunity via ICA [1]. In the TN-10 study, ≥2 antibodies had to be determined on 2 different occasions. The first occasion was within the TN-01 study, in which participants with relatives with type 1 diabetes mellitus were screened for autoantibodies. Patients who tested positive had an OGTT and were then assessed further for meeting the inclusion criteria for the TN-10 study. The second occasion had to occur within 6 months prior to the first study drug administration. However, it did not need to involve the same autoantibodies as were found on the first occasion. The fact that this diagnostic criterion differed from the S3 guideline for adults had no consequences.

The range for fasting plasma glucose levels for inclusion in the TN-10 study was ≥110 to <126 mg/dL, which was somewhat narrower than the definition in the guidelines (≥100 to <126 mg/mL) [2,13]. According to the S3 guideline, a glycated haemoglobin (HbA1c) value of between 5.7% and 6.4%, or an increase of ≥10%, would also be suitable for determining abnormal glucose tolerance (see also Table 4). Although the HbA1c value was recorded in the TN-10 study, it was not used as a criterion for inclusion in the study. The described deviations had no consequence for this benefit assessment.

Another difference in the determination of abnormal glucose tolerance was the plasma glucose level at 30, 60 and 90 minutes after an OGTT. This diagnostic/inclusion criterion does not comply with the guidelines. According to WHO guidelines, the 2-hour plasma glucose level following an OGTT is taken into account [1,2,14], which could also be used in the study. However, according to the cited recommendations, plasma glucose levels at 30, 60 and 90 minutes should not be used to diagnose abnormal glucose tolerance. Due to the lack of information by the company, it was unclear how many patients were included on the basis of this non-recommended diagnostic criterion. The resulting uncertainty did not completely call into question the suitability of the TN-10 study, but was taken into account in the assessment of the certainty of conclusions (see Section I 4.2).

Uncertainties regarding the dosage of teplizumab

The formulation of teplizumab used in the TN-10 study differed from the authorised commercial product due to a change of manufacturer and an associated change in the manufacturing process. Pharmacokinetic studies showed differences in the clearance of the products, among other things. The clearance of the formulation used in the TN-10 study was lower than that of the commercial product, which explains why the dosing regimen in the TN-10 study differed from that of the authorised product [11]. Differing from the dosing regimen set out in Table 7, the authorised formulation of teplizumab is administered as follows: Day 1: 65 µg/m^2, Day 2: 125 µg/m^2, Day 3: 250 µg/m^2, Day 4: 500 µg/m^2 , Days 5 to 14: 1030 µg/m^2 [10]. Patients in TN-10 received a total of 9034 µg/m^2 body surface area of teplizumab, and thus a cumulative dose of teplizumab that was approximately 20% lower. The different dosing regimen was calculated on the basis of a pharmacokinetic model submitted by the company for marketing authorisation in the United States, where it was approved. According to the assessment report by the European Medicines Agency (EMA), these data alone were not sufficient, and uncertainties therefore remained in this regard. However, based on post-marketing safety data for the authorised commercial product in the United States, the adjusted dose was accepted by EMA [11]. In conclusion, due to missing comparative data, it remained unclear whether and to what extent the different dosage had an impact on patient-relevant outcomes. This uncertainty was taken into account when assessing the certainty of conclusions (see Section I 4.2).

Implementation of the ACT

The G-BA specified watchful waiting as the ACT for the research question. The TN-10 study used placebo as the comparator therapy. It was not designed for a comparison with watchful waiting. However, the study was suitable for such a comparison. This is explained below.

The following tests were conducted in the TN-10 study to assess the symptoms and clinical signs of type 1 diabetes mellitus:

- Regular OGTTs and HbA1c measurements
- Regular physical examinations and enquiries about symptoms and side effects

OGTTs, HbA1c measurements and physical examinations were performed at 3, 6 and 12 months and every 6 months thereafter. Random plasma glucose levels were measured every 3 months, where no OGTT was scheduled. According to the study protocol, the study staff asked the participants questions about symptoms and side effects, but it was unclear at what intervals this took place. According to the American Diabetes Association's (ADA) 'Consensus Guidance for Monitoring Individuals With Islet Autoantibody-Positive Pre-Stage 3 Type 1 Diabetes', individuals with presymptomatic type 1 diabetes mellitus should be monitored regularly for disease progression [15]. For adults with stage 2, it is recommended that the HbA1c value be measured every 6 months, in conjunction with either blinded continuous glucose monitoring or a 2-hour plasma glucose value following OGTT [15]. For children with stage 2, monitoring of glucose metabolism is recommended; this includes, amongst other things, measuring the HbA1c value and performing an OGTT. For children with stage 2, it is explicitly recommended to measure the HbA1c value every 6 months in children aged between 3 and 9 years, and at least every 12 months in children older than 9 years [15]. The German guideline also recommends that children and adolescents with stages 1 or 2 have their HbA1c values measured as part of examinations every 3 to 6 months, in order to determine the appropriate time to commence insulin therapy within 2 years [1].

In this therapeutic indication, the interventions in the comparator arm were therefore regarded, on the whole, as a sufficient approximation of the ACT watchful waiting.

Characteristics of the study population

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: teplizumab vs. placebo (multipage table)

Study **Characteristic** **Category**	**teplizumab** **N=44**	**placebo** **N=32**
TN-10		
Age [years]		
Mean (SD)	19 (12)	18 (11)
Median [min; max]	14 [9; 50]	13 [9; 45]
Age group, n (%)		
<18 years	29 (66)	26 (81)
≥18 years	15 (34)	6 (19)
Sex [F/M], %	43/57	47/53
Family origin, n (%)		
Caucasian	44 (100)	30 (94)
Asian	0	1 (3)
Multiple	0	1 (3)
Body weight [kg]		
Mean (SD)	57.9 (24.7)	57.0 (19.5)
Median [min; max]	52.0 [26.6; 143.5]	61.0 [27.2; 117.1]
BMI [kg/m^2],		
Mean (SD)	22.0 (6.4)	22.1 (4.4)
Median [min; max]	20.0 [14.7; 43.7]	21.6 [16.0; 34.6]
Relationship with person with type 1 diabetes mellitus, n (%)		
Sibling	30 (68)	19 (59)
Offspring	7 (16)	6 (19)
Parent	7 (16)	6 (19)
Sibling and another first-degree relative	3 (7)	3 (9)
Second-degree relative	5 (11)	7 (22)
Third-degree relative or further removed	1 (2)	2 (6)
Autoantibodies		
GAD65A, n (%)		
Positive	40 (91)	28 (88)
Negative	4 (9)	4 (13)
mIAA, n (%)		
Positive	19 (43)	11 (34)
Negative	25 (57)	21 (66)
IA-2A, n (%)		
Positive	26 (59)	24 (75)
Negative	18 (41)	8 (25)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: teplizumab vs. placebo (multipage table)

Study **Characteristic** **Category**	**teplizumab** **N=44**	**placebo** **N=32**
ICA, n (%)		
Positive	29 (66)	28 (88)
Negative	15 (34)	4 (13)
ZnT8A, n (%)		
Positive	32 (73)	24 (75)
Negative	12 (27)	8 (25)
Number of positive antibodies, n (%)		
1	1 (2)[a]	0
2	12 (27)	7 (22)
3	11 (25)	5 (16)
4	12 (27)	14 (44)
5	8 (18)	6 (19)
Glucose level from an OGTT[b] [mg/dL], mean (SD)	162.5 (22.3)	155.3 (22.9)
HbA1c [%], mean (SD)	5.2 (0.3)	5.2 (0.3)
Treatment discontinuation, n (%)	1 (2)	2 (6)
Study discontinuation, n (%)	3 (7)	3 (9)

a. According to the company's information, one patient had one definitive autoantibody detected, whilst the confirmation of the second autoantibody was inconclusive, but borderline between positive and negative. This patient was enrolled in the study at the discretion of the investigator.
b. This is the mean value of the plasma glucose levels recorded during the 2-hour OGTT (fasting glucose and measurements taken at 30, 60, 90 and 120 minutes).

BMI: body mass index; GAD65A: glutamic acid decarboxylase-65 antibodies; HbA1c: glycated haemoglobin; IA-2A: insulinoma-associated antigen-2 autoantibodies; ICA: islet cell autoantibodies; M: male; max: maximum; mIAA: micro-insulin autoantibodies; Min: minimum; mean; n: number of patients in the category; N: number of randomised patients; OGTT: oral glucose tolerance test; RCT: randomised controlled trial; standard deviation; w: female; ZnT8A: zinc transporter 8 antibodies

The characteristics of the patients were not consistently balanced between the 2 treatment arms of the TN-10 study. The median age was 14 versus 13 years. In the intervention arm, the proportion of patients <18 years (66%) was lower than in the comparator arm (81%). The patient population was almost exclusively of Caucasian family origin, and the proportion of boys and men was marginally higher than the proportion of girls and women. The mean body weight was similar in both treatment arms (58 kg versus 57 kg), but the median differed, at 52 kg in the intervention arm versus 61 kg in the comparator arm.

There were also differences in the family relationship with the person with clinically manifest type 1 diabetes mellitus. In the intervention arm, 68% of patients had siblings with type 1

diabetes mellitus, compared with 59% in the comparator arm. In the intervention arm, 11% of patients were included on the basis because they had a second-degree relative; in the comparator arm, the figure was 22%. It should be noted that several relatives may have had type 1 diabetes mellitus.

With regard to the autoantibodies used for inclusion in the study, 43% versus 34% were positive for mIAA. For the IA-2A, 59% versus 75% were positive. For the ICA, 66% versus 88% were positive. The proportions were roughly equal for GAD65 and ZnT8 antibodies. In total, 25% versus 16% were positive for 3 antibodies, and 27% versus 44% were positive for 4 antibodies. In one patient, the result of the second antibody test was inconclusive. The mean glucose level after OGTT was 162.5 mg/dL in the intervention arm, which was higher than the 155.3 mg/dL recorded in the comparator arm. The HbA1c value of 5.2% was the same in both arms. During the study, 1 versus 2 patients discontinued treatment; 3 patients in each of the 2 treatment arms discontinued the study.

Table 10 shows the treatment duration of the patients and the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: teplizumab vs. placebo

Study **Duration of the study phase** **Outcome category /** **outcome**	**teplizumab** **N=44**	**placebo** **N=32**
TN-10		
Treatment duration	ND[a]	
Observation period [months]		
Overall survival[b]		
Median [Q1; Q3]	27.5 [ND; ND]	17.8 [ND; ND]
Morbidity		
Onset of type 1 diabetes mellitus		
Median [Q1; Q3]	29.2 [ND; ND][c]	19.7 [ND; ND][c]
Health-related quality of life	No data on health-related quality of life were recorded.	
Side effects		
Median [Q1; Q3]	27.5 [ND; ND]	17.8 [ND; ND]

a. The planned course of treatment was 14 days, with one infusion per day. In the intervention arm, 41 (93.3%) patients received 14 infusions, 2 (4.5%) patients received 13 infusions and 1 (2.3%) patient received 12 infusions. In the comparator arm, 28 (87.5%) patients received 14 infusions, 2 (6.3%) patients received 13 infusions, 1 (3.1%) patient received 11 infusions and 1 (3.1%) patient received 8 infusions.
b. Time from randomisation to reaching the primary outcome or last contact.
c. This figure is taken from the study documents, which are based on the analysis 'time to diabetes diagnosis'. The data on side effects and all-cause mortality are taken from the analysis of 'time to the first of 2 positive OGTTs'. It is unclear why the median follow-up period differs between the analyses.

N: number of analysed patients; ND: no data; OGTT: oral glucose tolerance test; Q1: first quartile; Q3: third quartile; RCT: randomised controlled trial

The planned treatment duration was 14 days in both treatment arms. Due to treatment discontinuations, 41 (93.3%) patients in the intervention arm and 28 (87.5%) in the comparator arm were treated for 14 days.

The observation periods for the outcomes of all-cause mortality and side effects differed between the treatment arms, as these outcomes were only recorded until the primary outcome was reached. Progression to stage 3 occurred earlier in the comparator arm. The median observation period for all outcomes was 27.5 months in the intervention arm. In the comparator arm, the median observation period was 17.8 months.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: teplizumab 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			
TN-10	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomised controlled trial							

The risk of bias across outcomes was rated as low for TN-10.

Transferability of the study results to the German health care context

The company stated that the study was conducted exclusively in the United States and that the majority of patients were of Caucasian family origin. It added that the median age of 14 years and the sex ratio – which was almost balanced but showed a slight predominance of male patients – were similar to those of patients in the DPV registry for children and adolescents with type 1 diabetes mellitus in Germany, Austria and Switzerland [16]. Furthermore, the subgroup analyses showed no effect modifications by family origin, age and sex in the study, according to the company.

In addition, the company referred to the analyses of the Fr1da study on the early detection of type 1 diabetes mellitus, according to which results from the study population with a family history of the condition were transferable to the general German health care population, i.e. including those without a family history [12]. Thus, the company overall presumed the study 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. For information on the transferability of the study results to the entire therapeutic indication, see the Section ‘Restriction of the study population to individuals with stage 2 type 1 diabetes mellitus and a family history of the condition’ in this chapter.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - Onset of type 1 diabetes mellitus
- Health-related quality of life
- Side effects
  - Severe adverse events (AEs), operationalised as Common Terminology Criteria for Adverse Events [CTCAE] grade ≥3
  - Discontinuation due to AEs
  - Infections, operationalised as infections and infestations (System Organ Class [SOC], AEs and serious adverse events [SAEs])
  - 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 A).

Table 12 shows for which outcomes data were available in the included study.

Table 12: Matrix of outcomes – RCT, direct comparison: teplizumab vs. placebo

Study	Outcomes								
	All-cause mortality[a]	Onset of type 1 diabetes mellitus	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Infections[c]	Serious infections[c]	Other specific AEs
TN-10	Yes	Yes	No[e]	No[d]	Yes	Yes	No[d]	No[d]	No[f]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalised as CTCAE grade ≥3.
c. All AEs of the SOC 'infections and infestations' are used for the recording of infections, and all SAEs of this SOC for the recording of serious infections.
d. No suitable data available; see body of text for reasons.
e. Outcomes in this category were not recorded.
f. No suitable analyses on AEs available, a choice of further specific AEs, specific severe AEs and specific SAEs is therefore impossible.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; PT: Preferred Term; RCT: randomised controlled trial; SAE: serious adverse event; SOC: System Organ Class

Notes on outcomes

Onset of type 1 diabetes mellitus

Operationalisation

The primary outcome of the TN-10 study was the onset of type 1 diabetes mellitus (stage 3), operationalised as the time to diagnosis of clinically manifest type 1 diabetes mellitus. The outcome was defined as the reaching of one of the following 4 criteria:

- Unequivocal hyperglycaemia with acute metabolic decompensation (diabetic ketoacidosis)
- Clinical symptoms of type 1 diabetes mellitus (polyuria, polydipsia and unexplained weight loss) and a casual (i.e. without regard to time since the last meal) plasma glucose concentration of ≥200 mg/dL (11.1 mmol/L)
- Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L); 'fasting' was defined as no caloric intake for at least 8 hours
- 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L); the test was to be performed using a glucose load containing the equivalent of 1.75 g/kg body weight to a maximum of 75 g anhydrous glucose dissolved in water

If the diagnosis was based on glucose testing (criteria 2 to 4 in the list above), these criteria had to be met on 2 occasions as close together as possible, but no less than one day part. It was recommended that at least one testing occasion involve an OGTT.

After enrolment in the study, OGTT was conducted at 3 and 6 months, and then every 6 months. In addition, random glucose values were measured at 3 month intervals in which no OGTT was scheduled. If these random measurements showed glucose >200 mg/dL or if patients had symptoms (blurred vision, polyuria, polydipsia, unexplained weight loss), fasting glucose levels were measured or an OGTT was conducted.

Clinically manifest type 1 diabetes mellitus was present if the required glucose values were determined in a TrialNet laboratory as part of an OGTT. Patients diagnosed by diabetes symptoms and casual glucose >200 mg/dL or by other criteria than the above were adjudicated by the TrialNet Diabetes Adjudication committee, according to the SAP. It was also possible to make a diagnosis based on other criteria, which were not further specified.

The company provided analyses exclusively for the outcome 'onset of type 1 diabetes mellitus'. The company did not present the results for the individual criteria.

Assessment of the primary outcome

The onset of type 1 diabetes mellitus was assessed as being patient-relevant. It should be noted that, in accordance with the therapeutic indication, the new intervention teplizumab cannot prevent the onset of a clinically manifest stage of type 1 diabetes mellitus (stage 3), but can only delay it. This therefore raises the question of what a particular delay in the progression of the disease means for patients.

Delaying the progression of the disease to stage 3 could lead to an improved long-term prognosis, thereby also delaying the onset of late complications. Although the company described this in Module 4 A, it did not provide any data on the extent to which a particular delay influences the occurrence of late complications. Furthermore, delaying the progression of the disease could have further advantages for patients, such as delaying the onset of symptoms (e.g. fatigue) and temporarily improving their quality of life (e.g. by avoiding insulin therapy or making dietary changes). However, effects on these outcomes can and should be recorded directly. In particular, this is the only way to take into account any potential negative effects of teplizumab on quality of life (including the impact of side effects).

Regardless of these general considerations, the criteria for reaching the primary outcome are discussed below.

The criteria set out for determining the onset of type 1 diabetes mellitus via a glucose test are in line with the S3 guidelines. Alternatively, however, the diagnosis can also be made on the

basis of an HbA1c value of ≥6.5 [1,2]. In principle, the criterion 'unequivocal hyperglycaemia with acute metabolic decompensation (diabetic ketoacidosis)' contained in the primary outcome is, in itself, clinically relevant to patients, as diabetic ketoacidosis is potentially life-threatening [1] and is classified as severity grade 4 according to the CTCAE criteria. As the study generally ended for a patient who reached the primary outcome – the onset of type 1 diabetes mellitus – cases of diabetic ketoacidosis were not required to be further recorded. It was therefore assumed that, if this outcome were considered in isolation, no suitable data would be available due to incomplete recording.

With regard to the criteria 'clinical symptoms of type 1 diabetes mellitus (polyuria, polydipsia and unexplained weight loss)' and 'a casual plasma glucose concentration of ≥200 mg/dL (11.1 mmol/L)', it was unclear what the temporal relationship was between these symptoms and casual measurement of an elevated plasma glucose concentration. In accordance with the study design, patients had interim contact with study personnel for formal enquiry about the symptoms of blurred vision, polyuria, polydipsia and unintended weight loss. However, it was unclear at what intervals this contact took place and how soon after an enquiry, in case of the existence of symptoms, a plasma glucose measurement was conducted, which – upon reaching or exceeding a threshold value of 200 mg/dL (and following further confirmation by a glucose test) – led to a diagnosis of manifest type 1 diabetes mellitus. Furthermore, it was also unclear whether patients were instructed to report to the study personnel if they experienced symptoms characteristic of hyperglycaemia, and whether their glucose levels were subsequently measured. For the same reason as in the case of diabetic ketoacidosis, it was assumed that symptomatic hyperglycaemia could not be considered as an independent outcome.

There was also some uncertainty regarding the diagnosis of clinically manifest type 1 diabetes mellitus. The case report form (CRF) contained 2 versions of a form for documenting the onset of type 1 diabetes mellitus. Compared with the old form ('Diabetes Onset Form (Old)'), the new form ('Diabetes Onset Form') also included the HbA1c value as a diagnostic criterion.

The diagnostic criteria in the new form were the following:

- 2 consecutive OGTT clinical alerts
- Diabetic ketoacidosis or unequivocally symptomatic (defined as severe/persistent polyuria, polydipsia, and/or significant unexplained weight loss) AND one diabetic lab value (defined as fasting glucose ≥126 mg/dL OR HbA1c ≥6.5%).
- One OGTT clinical alert and one other diabetic lab value (defined as fasting glucose ≥126 mg/dL OR HbA1c ≥6.5%)
- Fasting glucose ≥126 mg/dL AND HbA1c ≥6.5%

- Diagnosis made by criteria other than those listed above

Although the HbA1c value was also recorded in the old documentation form, it was not listed there amongst the diagnostic criteria. To record the onset of type 1 diabetes mellitus – and thus the primary outcome – existing symptoms in the new form were linked either to the fasting plasma glucose level or to the HbA1c value, analogous to the prespecified operationalisation (see above). As an OGTT is more sensitive than a random plasma glucose value for detecting elevated plasma glucose levels, and as the HbA1c value is highly specific for the diagnosis of stage 3 [15], this combination would also be suitable for detecting symptomatic hyperglycaemia. In the new form, the diagnosis of type 1 diabetes mellitus was also linked to a fasting plasma glucose level of ≥126 mg/dL and the simultaneous presence of an HbA1c value of ≥6.5%. It was not clear from the study documentation provided whether the new form was used, and if so, from when; nor was it clear how many patients were consequently diagnosed with manifest type 1 diabetes mellitus on the basis of criteria other than those listed in the prespecified operationalisation. It also remained unclear whether, and if so, in how many patients, manifest type 1 diabetes mellitus was diagnosed on the basis of criteria other than the predefined ones or those set out in the new form ('Diagnosis made by criteria other than listed above'), and which criteria were used in such cases.

In the given situation, the uncertainties described above regarding the diagnosis had no consequences for the assessment.

C-peptide

For the C-peptide outcome, the company used the change in the C-peptide area under the curve (AUC) following a 2-hour OGTT from baseline to Month 24 for the benefit assessment. In clinical studies, the C-peptide level is used as a marker of endogenous insulin production, as C-peptide is produced in equal amounts to insulin when proinsulin is converted to insulin [17,18]. As a laboratory parameter, the C-peptide level is not in itself patient-relevant. Although the company implied that the C-peptide is a surrogate marker for residual endogenous insulin production, which is associated with other outcomes (including severe hypoglycaemia, diabetic ketoacidosis, retinopathy and microangiopathy [19-26]), it did not provide any surrogate validation. In Module 4 A, the company cited various publications [19-28]; however, these did not constitute validation studies based on RCTs in the sense of a correlation analysis between a treatment effect on a surrogate outcome and a treatment effect on a patient-relevant outcome. Instead, the various publications included analyses of risk reduction based on cohort studies. Surrogate validation via cohort studies is, in principle, a viable alternative to correlation-based methods in specific situations and has previously been accepted by IQWiG for the therapeutic indication of hepatitis C [29]. However, there was no information retrieval (e.g. in the form of focused information retrieval) that sufficiently ensured the completeness of the evidence base. Furthermore, the studies presented, which

involved patients with stage 3 type 1 diabetes mellitus who are also insulin-dependent, relate to a different population from that covered by the therapeutic indication at hand. On the basis of the available information, it was therefore not possible to perform an assessment of the C-peptide level as a surrogate outcome. The outcome C-peptide was therefore not used for the benefit assessment. Regardless of this, the results for C-peptide presented by the company in Module 4 A showed no statistically significant effect at the primary analysis timepoint after 24 months.

Outcomes in the category of side effects

In the TN-10 study, AEs were recorded from baseline until the onset of type 1 diabetes mellitus or until the end of the study. As a result, there were notable differences in the observation periods due to the more frequent and earlier onset of type 1 diabetes mellitus in the comparator arm (see Table 10). The company presented analyses of relative risk (RR) for the outcomes in the side effects category. Apart from the outcome 'discontinuation due to AEs', this was not appropriate, as a meaningful interpretation of the RR is generally not possible in case of different observation periods. The treatment lasted approximately 14 days in both study arms (see Table 10); therefore, discontinuations due to AEs could only occur during this period. No analyses based on time-to-event analyses were available for AEs of any severity, severe AEs or SAEs. The analysis provided on AEs, severe AEs and SAEs was therefore not suitable for selecting specific AEs, specific severe AEs and specific SAEs based on the frequencies.

However, given the available data, the analysis for severe AEs was nevertheless interpretable due to the size of the effect for the RR (RR [95% confidence interval (95% CI)]: 6.30 [2.05; 19.38]; p = 0.001), see Table 14), and was used in the benefit assessment. Furthermore, an analysis of all patients with AEs up to 28 days after the end of the 14-day treatment with the study medication showed that most AEs occurred within this period (intervention arm: 42 out of 43 patients with AEs; comparator arm: 12 out of 22 patients with AEs). No data on severe AEs were available for the analysis period up to 28 days after the end of treatment with the study medication; however, in the comparator arm, severe AEs occurred in only 3 patients in total.

It should be noted that, in the infections outcome (operationalised via the SOC 'infections and infestations'), there was a suggestion of disadvantages of teplizumab. Furthermore, the specific AEs of skin and subcutaneous tissue disorders [SOC, AEs] and blood and lymphatic system disorders [SOC, AEs, severe AEs] showed greater harm of major extent of teplizumab in comparison with the ACT, based on the presented effect measure RR.

I 4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: teplizumab vs. placebo

Study	Study level	Outcomes								
		All-cause mortality[a]	Onset of type 1 diabetes mellitus	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Infections[c]	Serious infections[c]	Other specific AEs
TN-10	L	H[d]	L	–[f]	–[e]	H[d]	L	–[e]	–[e]	–[g]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalised as CTCAE grade ≥3.
c. All AEs of the SOC 'infections and infestations' are used for the recording of infections, and all SAEs of the SOC 'infections and infestations' are used for the recording of serious infections.
d. Incomplete observations for potentially informative reasons.
e. No suitable data available; see Section I 4.1 for the reasoning.
f. Outcomes in this category were not recorded.
g. No suitable analyses on AEs available, a choice of specific AEs is therefore impossible.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; PT: Preferred Term; RCT: randomised controlled trial; SAE: serious adverse event; SOC: System Organ Class

The risk of bias was rated as high for the results for the outcomes all-cause mortality and severe AEs. This was due to incomplete observations for potentially informative reasons with different observation periods. The risk of bias for the outcomes of onset of type 1 diabetes mellitus and discontinuation due to AEs was rated as low. No data or no suitable data were available for the remaining outcomes, so the risk of bias was not assessed.

Summary assessment of the certainty of conclusions

The TN-10 study enrolled patients with stage 2 type 1 diabetes mellitus. As already described in Section I 3.2, there were deviations from the guideline recommendations regarding the diagnosis of stage 2 type 1 diabetes mellitus at the time of enrolment, based on abnormal glucose tolerance. In addition, there were deviations in the dosage of teplizumab in the TN-10 study compared with the authorised commercial product. It was unclear how the deviations in enrolment and dosage affected the results of the study. The certainty of conclusions of the study results for the given research question was therefore reduced overall. Based on the available information from the TN-10 study, at most hints, e.g. of an added benefit, could be derived for all outcomes presented.

I 4.3 Results

Table 14 and Table 15 summarise the results of the comparison of teplizumab with placebo in patients with stage 2 type 1 diabetes mellitus. Where necessary, calculations conducted by

the Institute are provided in addition to the data from the company's dossier. The Kaplan-Meier curves on the time-to-event analyses are presented in I Appendix B of the full dossier assessment, and the tables on common AEs, common severe AEs and common SAEs can be found in I Appendix C of the full dossier assessment.

Table 14: Results (mortality, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: teplizumab vs. placebo

Study	**teplizumab**		**placebo**		**teplizumab vs. placebo**
Outcome category **outcome**	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
TN-10					
Mortality					
All-cause mortality	44	0 (0)	32	0 (0)	–
Health-related quality of life	No suitable data available				
Side effects					
AEs (supplementary information)	44	43 (97.7)	32	22 (68.8)	–
SAEs	No suitable data available[c]				
Severe AEs[d]	44	26 (59.1)	32	3 (9.4)	6.30 [2.05; 19.38]; 0.001
Discontinuation due to AEs	44	1 (2.3)	32	2 (6.3)	0.36 [0.03; 3.99]; 0.408
Infections[e] (AEs)	No suitable data available[c]				
Serious infections[e] (SAEs)	No suitable data available[c]				

a. According to the company, the results were derived from a logistic regression model.
b. The results on all-cause mortality are based on the data on fatal AEs.
c. See Section I 4.1 of this dossier assessment for the reasoning.
d. Operationalised as CTCAE grade ≥3.
e. Operationalised as infections and infestations (SOC).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; 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

Table 15: Results (morbidity, time to event) – RCT, direct comparison: teplizumab vs. placebo

Study Outcome category outcome	teplizumab N	teplizumab Median time to event in months [95% CI] Patients with event n (%)	placebo N	placebo Median time to event in months [95% CI] Patients with event n (%)	teplizumab vs. placebo HR [95% CI]; p-value[a]
TN-10					
Morbidity					
Onset of type 1 diabetes mellitus at Month 84[b]	44	49.5 [32.2; NC] 20 (45.5)	32	24.9 [9.5; 48.6] 23 (71.9)	0.41 [0.22; 0.78]; 0.007

a. Cox proportional hazards model, stratified by age and OGTT confirmation status (age <18 years with confirmed abnormal OGTT vs. age <18 years with unconfirmed abnormal OGTT vs. age ≥ 18 years with confirmed abnormal OGTT).

b. The diagnosis was made on the basis of one of the following criteria: unequivocal hyperglycaemia with acute metabolic decompensation (diabetic ketoacidosis), clinical symptoms of type 1 diabetes mellitus (polyuria, polydipsia and unexplained weight loss) and a casual (i.e. without regard to time since the last meal) plasma glucose concentration of ≥200 mg/dL (11.1 mmol/L), fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), or 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L); results for the individual criteria are not available; see Section I 4.1.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; RCT: randomised controlled trial

Based on the available information, at most hints, e.g. of an added benefit, could be determined for all outcomes (see Section I 4.2).

Mortality

No deaths occurred in the TN-10 study. There is no hint of an added benefit of teplizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Onset of type 1 diabetes mellitus

For the outcome ‘onset of type 1 diabetes mellitus’, the analysis of the time to onset of type 1 diabetes mellitus showed a statistically significant advantage of teplizumab compared with placebo. The median delay in the onset of type 1 diabetes mellitus was 2 years. The observation period was too short to investigate whether teplizumab can completely prevent the onset of type 1 diabetes mellitus. In addition, it was unclear to what extent the observed delay has a positive effect on the long-term course of the disease (particularly the occurrence of micro- and macrovascular late complications). The effects of the delay on health-related quality of life and symptoms were not recorded.

There is no hint of an added benefit of teplizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

Data for the category of health-related quality of life were not recorded. There is no hint of an added benefit of teplizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

Severe AEs

A statistically significant difference between treatment groups to the disadvantage of teplizumab was found for the outcome of severe AEs. There is a hint of greater harm of teplizumab in comparison with watchful waiting.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm of teplizumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Infections (AEs), serious infections (SAEs)

No suitable data were available for the outcomes of infections (AEs) and serious infections (SAEs) (see Section I 4.1 for reasoning). In each case, there is no hint of greater or lesser harm of teplizumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account in this benefit assessment:

- Age (<18 years versus ≥18 years)
- Sex (female versus male)

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.

Using the methods described above, the available subgroup analyses did not reveal any effect modifications.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [3].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 16).

Table 16: Extent of added benefit at outcome level: teplizumab vs. watchful waiting

Outcome category **outcome**	**teplizumab vs. placebo** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality	0 vs. 0 RR: –	Lesser benefit not proven / added benefit not proven
Morbidity		
Onset of type 1 diabetes mellitus	49.5 vs. 24.9 HR: 0.41 [0.22; 0.78]; p = 0.007	Lesser benefit not proven / added benefit not proven[c]
Health-related quality of life	Outcomes from this category were not recorded	
Side effects		
SAEs	No suitable data[d]	Greater/lesser harm not proven
Severe AEs	59.1% vs. 9.4% RR: 6.30 [2.05; 19.38]; RR: 0.16 [0.05; 0.49][e] p = 0.001 Probability: hint	Outcome category: serious/severe side effects CI_u <0.75, risk ≥5% Greater harm, extent: major
Discontinuation due to AEs	2.3% vs. 6.3% RR: 0.36 [0.03; 3.99]; p = 0.408	Greater/lesser harm not proven
Infections (AE)	No suitable data[d]	Greater/lesser harm not proven
Serious infections (SAE)	No suitable data[d]	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. See Section I 4.3 of this dossier assessment for the reasoning.
d. See Section I 4.1 of the present dossier assessment for the reasoning.
e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; RR: relative risk; SAE: serious adverse event

I 5.2 Overall conclusion on added benefit

Table 17 summarises the results taken into account for the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of teplizumab in comparison with watchful waiting

Positive effects	Negative effects
–	Serious/severe side effects ▪ Severe AEs: hint of greater harm – extent: major
It is unclear to what extent the delay shown in the outcome of onset of type 1 diabetes mellitus has a positive effect on the long-term course of the disease (particularly the occurrence of micro- and macrovascular late complications). Furthermore, the effects of the delay on health-related quality of life and symptoms were not recorded. No suitable data were available for the outcomes SAEs, infections and serious infections, or for further specific AEs.	
AE: adverse event; SAE: serious adverse event	

In this benefit assessment, based on the TN-10 study, it was only possible to draw conclusions on patients who have a family history of type 1 diabetes mellitus (see Section I 3.2). No data were available for patients with no family history of the condition.

Overall, there is a negative effect in the category of serious/severe side effects for patients with stage 2 type 1 diabetes mellitus and with a family history of the condition. There is a hint of greater harm with major extent. The outcomes in the side effects category could not be fully taken into account due to the analyses presented in Module 4 A regarding the RR in the presence of different observation periods; however, disadvantages regarding specific AEs were suggested (see Section I 4.1). For the outcome ‘onset of type 1 diabetes mellitus’, there was a statistically significant advantage of teplizumab in comparison with watchful waiting, with a median delay in onset of 2 years. However, it is unclear to what extent this delay has a positive effect on the long-term course of the disease (particularly the occurrence of micro- and macrovascular late complications). The effects of the delay on health-related quality of life and symptoms were not recorded.

As there is some uncertainty regarding the effects of teplizumab on morbidity and health-related quality of life due to missing data, the negative effect observed in the side effects category is not sufficient, in the given situation, to justify a conclusion that there is a lesser benefit.

In summary, there is no hint of an added benefit of teplizumab in comparison with the ACT for adult and paediatric patients 8 years of age and older, with a family history, with stage 2 type 1 diabetes mellitus, to delay the onset of stage 3. An added benefit is therefore not proven for this patient group.

For adult and paediatric patients 8 years of age and older, without a family history, with stage 2 type 1 diabetes mellitus, the TN-10 study provided no data to assess the added benefit of teplizumab in comparison with the ACT. An added benefit is therefore not proven for this patient group.

Table 18: Teplizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult and paediatric patients 8 years of age and older with stage 2 type 1 diabetes mellitus[b], to delay the onset of stage 3	Watchful waiting	▪ For patients with a family history: added benefit not proven (based on the results of the relevant study[c]) ▪ For patients without a family history: added benefit not proven (no relevant study[d])

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the criteria apply to people who do not (yet) have clinically manifest type 1 diabetes mellitus, but who have persistent autoantibodies in conjunction with a fasting plasma glucose level of between 100 and 125 mg/dL or an HbA1c level of between 5.7% and 6.4%. In accordance with current guidelines, these people are classified as having stage 2 type 1 diabetes mellitus. People with stage 1 and 2 type 1 diabetes mellitus are assumed to not be insulin-dependent.
c. TheTN-10 study only included patients from the age of 8 to a maximum of 49.5 years. It remains unclear whether the observed effects can be transferred to patients older than 49.5 years.
d. The research question of teplizumab in comparison with watchful waiting in patients without a family history was not investigated in the TN-10 study.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HbA1c: glycated haemoglobin

The assessment described above differs from that of the company, which – irrespective of family history – derived an indication of considerable added benefit for all patients in the given therapeutic indication based on the outcome onset of type 1 diabetes mellitus.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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