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

Addendum to Project A26-11
(dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

1 Background

On 23 June 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A26-11 (Teplizumab – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprised the assessment of the analyses submitted by the pharmaceutical company (hereinafter referred to as 'the company') in the commenting procedure [2], taking into account the information provided in the dossier [3]:

- Safety and tolerability data based on time-to-event analyses
- Data on adverse events (AEs), serious adverse events (SAEs) and severe AEs by System Organ Class (SOC) and Preferred Term (PT) (in particular, PT lymphopenia; patients with infections in the presence of lymphopenia)

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

Benefit assessment A26-11 [1] described that 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, and that this resulted in notable differences in the observation periods due to the more frequent and earlier onset of stage 3 type 1 diabetes mellitus in the comparator arm. In the dossier, the company only 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. Due to differences in observation periods, the analyses provided on AEs, severe AEs and SAEs were not suitable for selecting specific AEs, specific severe AEs and specific SAEs based on the frequencies.

In its comments [2], the company provided time-to-event analyses for various outcomes in the side effects category. In addition, the company provided further analyses on lymphopenia. The assessment of the data subsequently submitted is provided below.

2.1 Time-to-event analyses

The time-to-event analyses subsequently submitted for AEs, SAEs and severe AEs were used. In dossier assessment A26-11, the severe AEs based on the RR were taken into account due to the effect size. In principle, however, given the situation with different observation periods, the hazard ratio (HR) represents the appropriate effect measure, as described above.

The time-to-event analyses subsequently submitted for outcomes in the category of side effects by SOC and PT were incomplete, as – with the exception of the SOC infections and infestations (SAEs) – the company only provided analyses for those outcomes that were used in the dossier for the derivation of the extent of the added benefit. Furthermore, the results of time-to-event analyses are not suitable for assessment in cases where there are 0 events in a study arm, and no appropriate method for estimating the HR (such as the Firth correction [4]) has been applied. In this assessment, where no time-to-event analyses were available or where these were unsuitable, RRs were used as a stopgap measure. This is because, compared with benefit assessment A26-11, the risks associated with the use of RRs were weighted differently in this addendum. The data situation in the TN-10 study was characterised by the fact that there were either very large effects or no effects at all in the RR. Consequently, it was now assumed that any large effects in the RR would also be evident in the HR. Furthermore, it was now assumed that the risk of overlooking effects in the HR would be low if there were no effects in the RR. In principle, however, time-to-event analyses are still preferable. The specific AEs, specific severe AEs and specific SAEs identified on the basis of their frequencies were skin and subcutaneous tissue disorders (SOC, AEs) and severe lymphopenia (PT, severe AEs [operationalised as Common Terminology Criteria for Adverse Events [CTCAE] grade ≥3]) (see Table 1).

2.2 Further analyses of lymphopenia

The TN-10 study provided a hint of greater harm of major extent for teplizumab versus watchful waiting for severe AEs based on the RR. Lymphopenia was the most common severe AE. In its comments [2], the company provided information on recovery status and the duration of the AE for the outcome of lymphopenia (AEs). In the TN-10 study, lymphopenia of any severity (AEs) occurred in 32 patients (72.7%) in the intervention arm versus 2 patients (6.3%) in the control arm . These were predominantly severe cases of lymphopenia (CTCAE grade ≥3); see Table 1. In total, 2 lymphopenia events were observed in one patient in the intervention arm, for which no final data were recorded. For the remaining patients, complete resolution or resolving lymphopenia was documented. In its comments, the company explained that this outcome is a transient side effect and that the lymphocyte count usually returns to normal within a few days. In the TN-10 study, the median duration was 9 and 8 days respectively. The company also referred to the pooled safety dataset on teplizumab presented in the EPAR, comprising 1008 patients [5], the Protégé study referred to in the EPAR involving people with stage 3 type 1 diabetes mellitus [5], as well as an observational study involving people with stage 2 type 1 diabetes mellitus [6], to illustrate the reversible nature of lymphopenia events. For patients, however, what is particularly important is whether a patient-relevant event occurs at all. The duration of the event is of secondary importance.

The company further explained that there was no association between the occurrence of lymphopenia and infections. To support this, it cited the PROTECT study involving people with stage 3 type 1 diabetes mellitus. In addition, it provided details of the TN-10 study, in which 2 (6.3%) patients in the teplizumab arm developed infections whilst experiencing lymphopenia. Given the available data, with a small sample size in the TN-10 study, it was not possible to draw any definitive conclusions regarding a potential association between lymphopenia and infections.

2.3 Results on added benefit

2.3.1 Risk of bias

The risk of bias in the subsequently submitted results for the outcomes AEs, severe AEs and SAEs was rated as high. This was due to incomplete observations for potentially informative reasons with different observation periods.

2.3.2 Results

Table 1 summarises the results for the outcomes of mortality, health-related quality of life and side effects. The Kaplan-Meier curves for the time-to-event analyses are presented in Appendix A.

Table 1: Results (mortality, health-related quality of life, side effects, 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					
Mortality					
All-cause mortality[b]	44	NA 0 (0)	32	NA 0 (0)	–
Health-related quality of life	No suitable data available				
Side effects					
AEs (supplementary information)	44	ND 43 (97.7)	32	ND 22 (68.8)	–
SAEs	44	61.1 [61.1; NC] 7 (15.9)	32	NA 1 (3.1)	4.76 [0.57; 39.76]; 0.112
Severe AEs[c]	44	0.7 [0.1; NC] 26 (59.1)	32	NA [26.0; NC] 3 (9.4)	8.24 [2.48; 27.36]; <0.001
Discontinuation due to AEs	44	– 1 (2.3)	32	– 2 (6.3)	RR[d]: 0.36 [0.03; 3.99]; 0.408
Infections[e] (AEs)	44	27.2 [15.8; 42.5] 23 (52.3)	32	25.3 [16.9; NC] 8 (25.0)	1.43 [0.63; 3.24]; 0.390
Infections[e] (SAEs)	44	61.1 [61.1; NC] 4 (9.1)	32	NA 0 (0)	RR[f]: 6.66 [0.37; 118.40]; 0.092
Skin and subcutaneous tissue disorders (SOC, AEs)	44	57.8 [0.5; NC] 20 (45.5)	32	NA [44.8; NC] 3 (9.4)	6.52 [1.92; 22.09]; <0.001
Lymphopenia (PT, severe AEs[c])	44	NA [0.1; NC] 21 (47.7)	32	NA 0 (0)	RR[f]: 31.53 [1.98; 502.04]; <0.001

a. Effect and CI: Cox proportional hazards model; p-value: unstratified log-rank test.
b. The results on all-cause mortality are based on the data on fatal AEs.
c. Operationalised as CTCAE grade ≥3 (CTCAE version 3).
d. According to the company, the results were derived from a logistic regression model.
e. Operationalised as infections and infestations (SOC).
f. Used as a substitute in the absence of time-to-event analyses (see Section 2.1 for reasons); Institute's calculation of RR, 95% CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [7]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

Only the results for the side effects outcome category are described below. For a result description for the other outcomes, see dossier assessment A26-11.

For the reasons described in dossier assessment A26-11, at most hints, e.g. of greater harm, could be determined for all outcomes presented here.

Side effects

SAEs

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

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 statistically significant difference was found between treatment groups for either of the outcomes of infections (AEs) and serious infections (SAEs). 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 for either of these outcomes.

Skin and subcutaneous tissue disorders (AEs)

A statistically significant difference between treatment groups to the disadvantage of teplizumab was found for the outcome of skin and subcutaneous tissue disorders (AEs). There is a hint of greater harm of teplizumab in comparison with watchful waiting.

Lymphopenia (severe AEs)

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

2.4 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 dossier assessment A26-11 and in Section 2.3 (see Table 2).

Table 2: Extent of added benefit at outcome level: teplizumab vs. watchful waiting (multipage table)

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	61.1 vs. NA HR: 4.76 [0.57; 39.76]; p=0.112	Greater/lesser harm not proven
Severe AEs	0.7 vs. NA HR: 8.24 [2.48; 27.36]; HR: 0.12 [0.04; 0.40][d]; 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)	27.2 vs. 25.3 HR: 1.43 [0.63; 3.24]; p=0.390	Greater/lesser harm not proven
infections (SUE)	61.1 vs. NA RR[e]: 6.66 [0.37; 118.40]; p=0.092	Greater/lesser harm not proven
Skin and subcutaneous tissue disorders (AEs)	57.8 vs. NA HR: 6.52 [1.92; 22.09]; HR: 0.15 [0.05; 0.52][d]; p<0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications CI_u<0.80 Greater harm, extent: considerable

Table 2: Extent of added benefit at outcome level: teplizumab vs. watchful waiting (multipage table)

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]**
Lymphopenia (severe AE)	NA vs. NA RR[e]: 31.53 [1.98; 502.04]; RR[e]: 0.03 [0.002; 0.51][d] p<0.001 Probability: hint	Outcome category: serious/severe side effects CI_u <0.75, risk ≥5% Greater harm, extent: major
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. For justification see Section I 4.3 of dossier assessment A26-11 [1]. d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit. e. Used as a substitute in the absence of time-to-event analyses (for justification see Section 2.1). AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; HR: hazard ratio; RR: relative risk; SAE: serious adverse event		

Table 3 summarises the results included in the overall conclusion on the extent of the added benefit.

Table 3: 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 ▪ Lymphopenia (severe AE): hint of greater harm – extent: major
	Non-serious/non-severe side effects ▪ Skin and subcutaneous tissue disorders (AE): hint of greater harm – extent: considerable
It is unclear to what extent the delay shown in the outcome of onset of type 1 diabetes mellitus has an effect on health-related quality of life and morbidity, as no data were available for these outcome categories. Furthermore, it is unclear to what extent it has a positive effect on the long-term course of the disease (particularly the occurrence of micro- and macrovascular late complications).	
AE: adverse event	

2.5 Summary

As described in the dossier assessment, 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. It is unclear, however, whether 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), because no relevant data were recorded. This should be considered, particularly in the context of the administration of a new treatment, which is given to treatment-naive patients and which is associated with side effects. Recording quality of life would be the only way to take into account any potential negative effects of teplizumab on quality of life (including the impact of side effects). It was noted during the oral hearing [8] that the onset of diabetes is associated with a deterioration in quality of life. However, no data are available on how the quality of life develops in patients diagnosed at stage 2 and progressing to stage 3 – particularly under treatment with teplizumab.

Furthermore, it was discussed in the oral hearing [8] to what extent complications such as diabetic ketoacidosis might be prevented by the administration of teplizumab. Acute complications such as diabetic ketoacidosis and severe hyperglycaemic and hypoglycaemic episodes are generally considered very relevant; however, the TN-10 study did not provide any relevant results on diabetic ketoacidosis or hyperglycaemic and hypoglycaemic episodes. This was because the recording for each patient generally ended as soon as the primary outcome, the onset of type 1 diabetes mellitus, was reached. Acute complications were then no longer systematically recorded. During the oral hearing, the company stated that no diabetic ketoacidosis had occurred by the end of the recording.

Irrespective of this, it is generally necessary to distinguish potential screening effects, such as a reduced incidence of diabetic ketoacidosis upon disease manifestation, from the question of the added benefit of teplizumab. Accordingly, the population in both arms of the relevant study had already been diagnosed at stage 2.

It is also still unclear to what extent the delay shown in the transition from stage 2 to stage 3 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). During the commenting procedure, reference was made to publications describing that the onset of type 1 diabetes in young adulthood is associated with a lower long-term risk of complications compared with onset in childhood. However, there is still a lack of data to show that a median delay of approximately 2 years translates into an improved long-term course of the disease.

Greater harm of major/considerable extent was now also derived for the PT lymphopenia, in addition to severe AEs, in the outcome category of serious/severe side effects, and for skin and subcutaneous tissue disorders in the outcome category of non-serious/non-severe side effects. As there is some uncertainty regarding the effects of teplizumab on morbidity and health-related quality of life due to missing data, the negative effects observed in the side effects category was not sufficient, in the given situation, to justify a conclusion that there is a lesser benefit.

Thus the data subsequently submitted by the company in the commenting procedure did not alter the conclusion on the added benefit of teplizumab drawn in dossier assessment A26-11.

The following Table 4 shows the result of the benefit assessment of teplizumab, taking into account dossier assessment A26-11 and this addendum.

Table 4: 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 G-BA decides on the added benefit.

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

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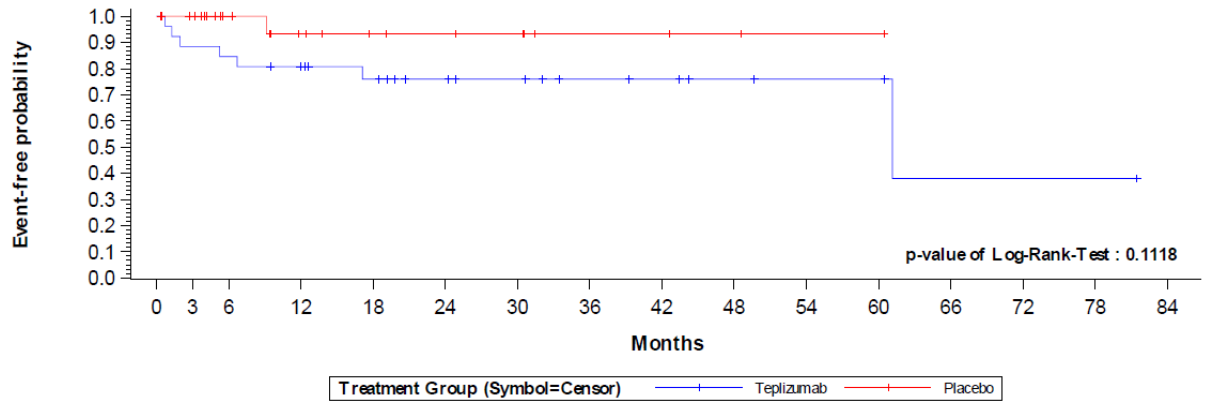
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Appendix A Kaplan-Meier curves on results of the TN-10 study



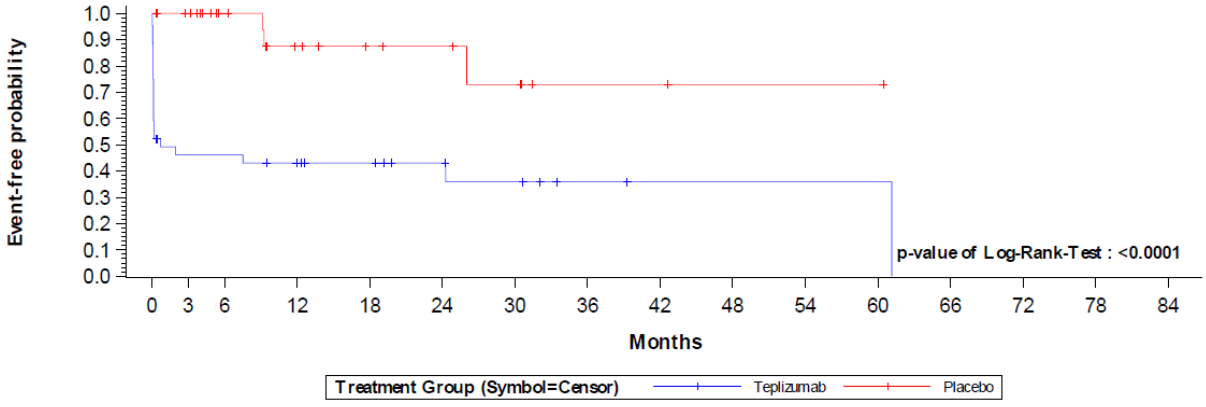
Number at Risk

Teplizumab	44	23	22	19	16	12	10	7	6	4	3	3	1	1	1	0
Placebo	32	23	16	11	8	7	6	3	3	2	1	1	0	0	0	0

Censored (%)

Teplizumab	0	40.9	40.9	45.5	50	59.1	63.6	70.5	72.7	77.3	79.5	79.5	81.8	81.8	81.8	84.1
Placebo	0	28.1	50	62.5	71.9	75	78.1	87.5	87.5	90.6	93.8	93.8	96.9	96.9	96.9	96.9

Figure 1: Kaplan-Meier curves for the outcome SAEs in the TN-10 study



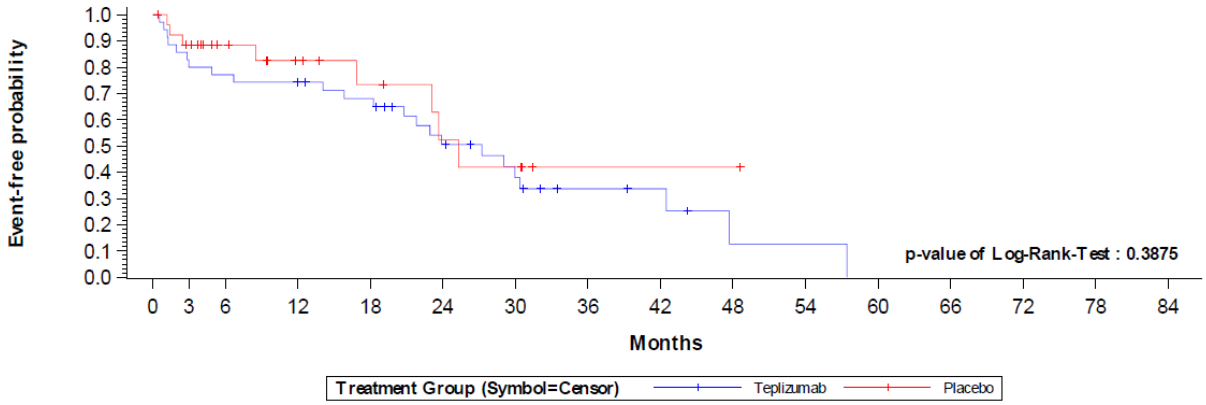
Number at Risk

Teplizumab	44	15	15	12	10	7	5	2	1	1	1	1	0	0	0	0
Placebo	32	24	17	11	8	7	5	2	2	1	1	1	0	0	0	0

Censored (%)

Teplizumab	0	13.6	13.6	18.2	22.7	29.5	31.8	38.6	40.9	40.9	40.9	40.9	40.9	40.9	40.9	40.9
Placebo	0	25	46.9	59.4	68.8	71.9	75	84.4	84.4	87.5	87.5	87.5	90.6	90.6	90.6	90.6

Figure 2: Kaplan-Meier curves for the outcome severe AEs in the TN-10 study



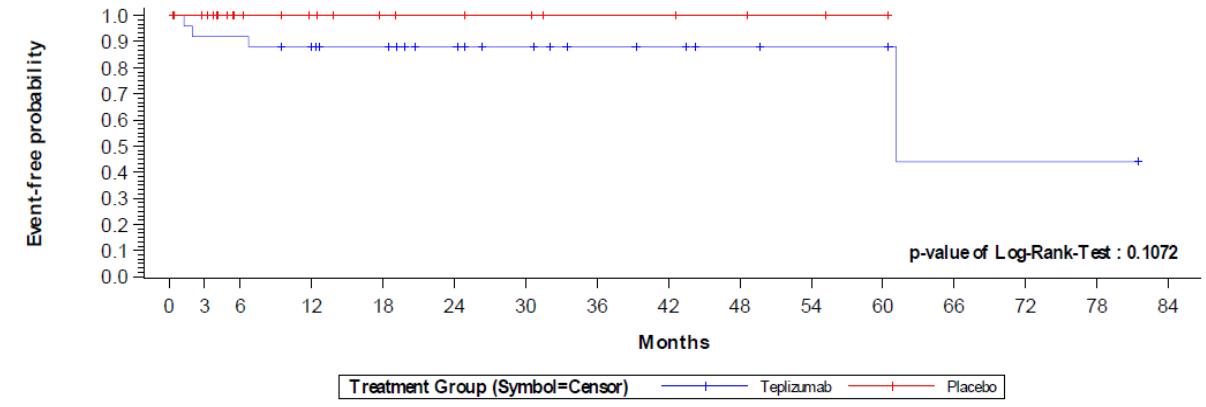
Number at Risk

Teplizumab	44	28	27	25	22	14	9	5	4	1	1	0	0	0	0	0
Placebo	32	22	16	11	8	5	4	1	1	1	0	0	0	0	0	0

Censored (%)

Teplizumab	0	20.5	20.5	22.7	25	31.8	36.4	43.2	45.5	47.7	47.7	47.7	47.7	47.7	47.7	47.7
Placebo	0	21.9	40.6	53.1	59.4	62.5	62.5	71.9	71.9	71.9	75	75	75	75	75	75

Figure 3: Kaplan-Meier curves for the outcome infections and infestations (SOC, AEs) in the TN-10 study



Number at Risk

Teplizumab	44	23	23	20	18	14	11	8	7	5	4	4	1	1	1	0
Placebo	32	23	16	12	9	8	7	4	4	3	2	1	0	0	0	0

Censored (%)

Teplizumab	0	43.2	43.2	47.7	52.3	61.4	68.2	75	77.3	81.8	84.1	84.1	88.6	88.6	88.6	90.9
Placebo	0	28.1	50	62.5	71.9	75	78.1	87.5	87.5	90.6	93.8	96.9	100	100	100	100

Figure 4: Kaplan-Meier curves for the outcome infections and infestations (SOC, SAEs) in the TN-10 study

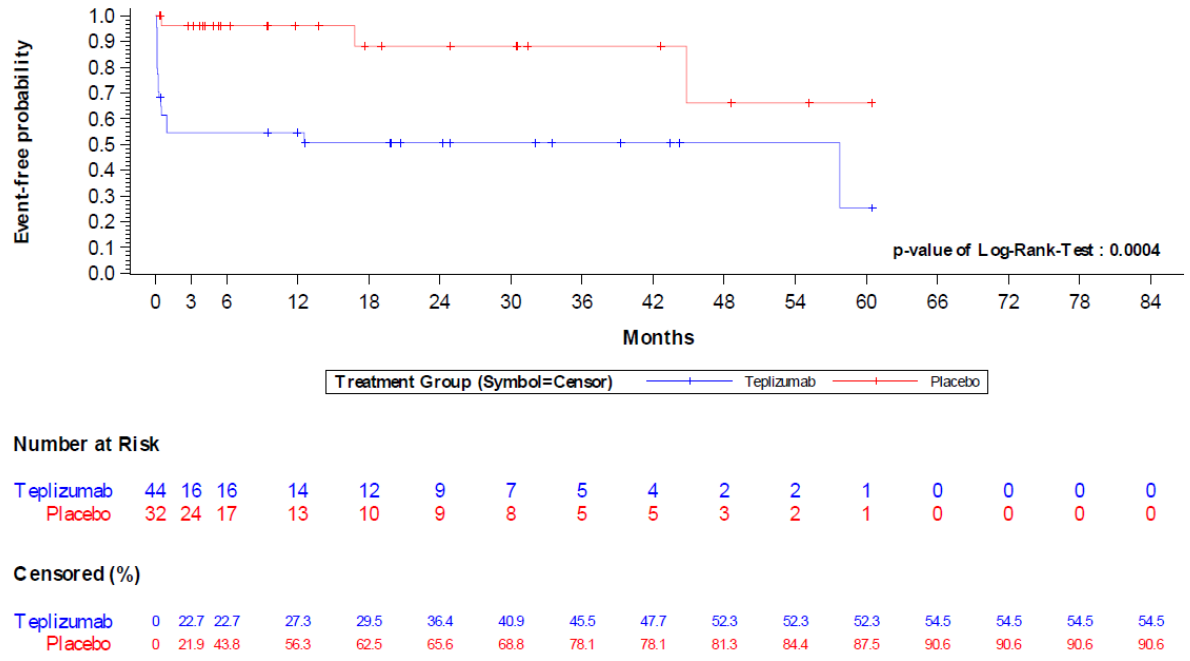


Figure 5: Kaplan-Meier curves for the outcome skin and subcutaneous tissue disorders (SOC, AEs) in the TN-10 study

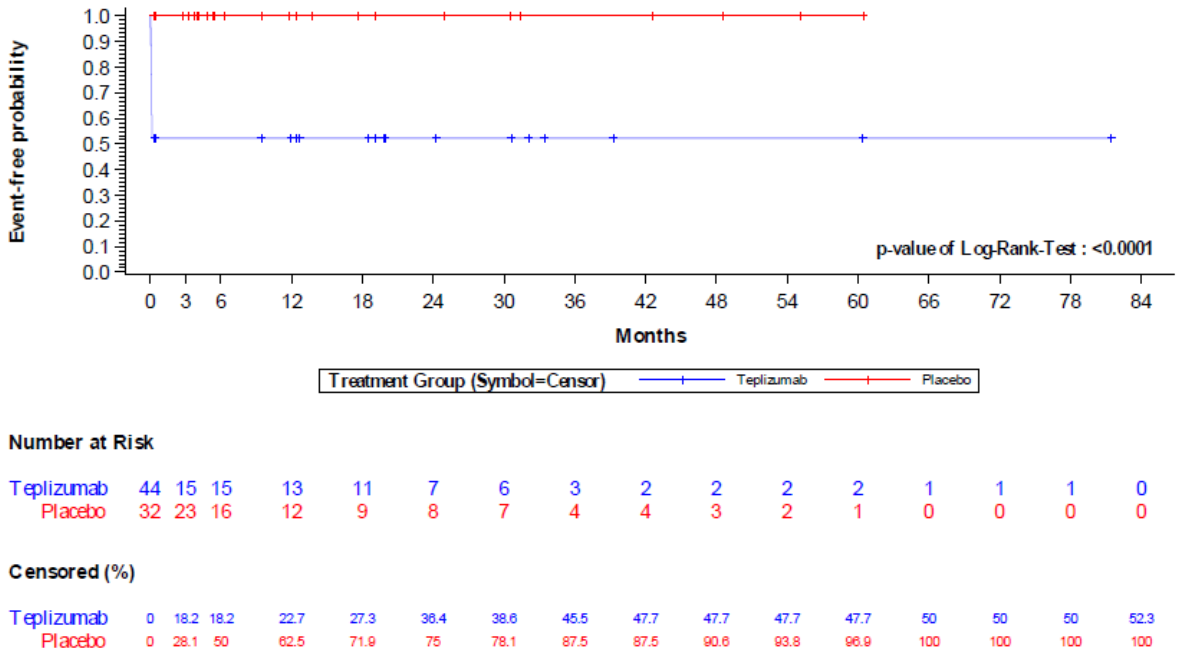


Figure 6: Kaplan-Meier curves for the outcome lymphopenia (PT, severe AEs) in the TN-10 study