**Dokumentvorlage,** Version vom 18.11.2025

# Dossier zur Nutzenbewertung gemäß § 35a SGB V

*Teplizumab (Teizeild®)*

Sanofi-Aventis Deutschland GmbH

## Modul 4A Anhang 4-G

*Erhalt der β-Zellfunktion, um das Fortschreiten von Typ-1-Diabetes in das Stadium 3 bei Kindern ab 8 Jahren, Jugendlichen und Erwachsenen mit Typ-1-Diabetes im Stadium 2 zu verzögern*

Medizinischer Nutzen und
medizinischer Zusatznutzen,
Patientengruppen mit therapeutisch
bedeutsamem Zusatznutzen

Stand: 13.02.2026

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## 1.1 Studie TN-10 – Subgruppenanalysen für die Time-to-Event-Analysen

### 1.1.1 Summary table of treatment-by-subgroup p-value for all Time-to-Event Analysis - ITT population

Tabelle 1-1: Summary table of treatment-by-subgroup p-value for all Time-to-Event Analysis - ITT population

| Efficacy endpoint | Subgroup | Overall treatment-by-subgroup p-value |
|---|---|---|
| Time to Diabetes Onset (Months) | Age (years) ( < 18 , >= 18 ) | 0.7988 |
| | Gender ( Female , Male ) | 0.2144 |
| | C-peptide level ( < Median , >= Median ) | 0.0789 |

Overall treatment-by-subgroup p-values derived using Cox regression model with discrete time intervals including intervention, strata (ages 8-17 with a confirmed abnormal OGTT/ages 8-17 with an abnormal OGTT that was not confirmed (expanded eligibility criteria)/ 18 or older with a confirmed abnormal OGTT), age (except for age subgroup), subgroup and treatment-by-subgroup interaction as covariates.

### 1.1.2 Time to Diabetes Onset up to 84 Months (Months) – Subgroup Analyses

Tabelle 1-2: Time to Diabetes Onset up to 84 Months (Months) – Per Age

| Time to Diabetes Onset (Months) | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| | Teplizumab (N=29) | Placebo (N=26) | Teplizumab (N=15) | Placebo (N=6) |
| Number of patients with event | 14 (48.3) | 18 (69.2) | 6 (40.0) | 5 (83.3) |
| Number of patients who are censored | 15 (51.7) | 8 (30.8) | 9 (60.0) | 1 (16.7) |
| 25% quantile time to first event (months) (95% CI)[a] | 21.16 (12.45 to 32.20) | 5.55 (3.22 to 12.42) | 43.27 (9.46 to NE) | 24.90 (3.75 to 31.41) |
| Median time to first event (months) (95% CI)[a] | 33.45 (25.86 to NE) | 17.68 (6.28 to 48.59) | NE (24.84 to NE) | 30.95 (3.75 to NE) |
| 75% quantile time to first event (months) (95% CI)[a] | 60.48 (60.42 to NE) | 55.20 (30.52 to NE) | NE (49.54 to NE) | 60.45 (24.90 to NE) |
| Unstratified Log-Rank test p-value[a] | 0.0337 | - | 0.1406 | - |
| Hazard Ratio (95% CI) vs. placebo[b] | 0.47 (0.23 to 0.96) | | 0.40 (0.12 to 1.31) | |
| p-value for Hazard Ratio[b] | 0.0385 | | 0.1284 | |
| Treatment-by-subgroup p-value[c] | | | | 0.7988 |

[a]derived from Kaplan-Meier estimates for each modality of subgroup.

[b]derived using two Cox regression models for each modality of subgroup with discrete time intervals including intervention and strata (ages 8-17 with a confirmed abnormal OGTT/ages 8-17 with an abnormal OGTT that was not confirmed (expanded eligibility criteria)/ 18 or older with a confirmed abnormal OGTT) as covariates.

[c]derived using Cox regression model with discrete time intervals including intervention, strata (ages 8-17 with a confirmed abnormal OGTT/ages 8-17 with an abnormal OGTT that was not confirmed (expanded eligibility criteria)/ 18 or older with a confirmed abnormal OGTT), age and treatment-by-subgroup interaction as covariates.

Note: Time is calculated from randomization to diabetes onset up to 84 months.

Tabelle 1-3: Time to Diabetes Onset up to 84 Months (Months) – Per Gender

| Time to Diabetes Onset (Months) | Gender | | | |
|---|---|---|---|---|
| | Male (N=42) | | Female (N=34) | |
| | Teplizumab (N=25) | Placebo (N=17) | Teplizumab (N=19) | Placebo (N=15) |
| Number of patients with event | 13 (52.0) | 11 (64.7) | 7 (36.8) | 12 (80.0) |
| Number of patients who are censored | 12 (48.0) | 6 (35.3) | 12 (63.2) | 3 (20.0) |
| 25% quantile time to first event (months) (95% CI)[a] | 25.86 (6.44 to 44.25) | 9.46 (2.73 to 30.49) | 24.84 (9.46 to 43.27) | 5.55 (3.22 to 17.68) |
| Median time to first event (months) (95% CI)[a] | 49.54 (25.86 to NE) | 30.52 (5.36 to 60.45) | 43.27 (24.84 to NE) | 19.06 (4.50 to 48.59) |
| 75% quantile time to first event (months) (95% CI)[a] | NE (49.54 to NE) | 60.45 (30.49 to NE) | NE (43.27 to NE) | 48.59 (19.06 to NE) |
| Unstratified Log-Rank test p-value[a] | 0.1407 | - | 0.0229 | - |
| Hazard Ratio (95% CI) vs. placebo[b] | 0.59 (0.26 to 1.35) | | 0.21 (0.07 to 0.66) | |
| p-value for Hazard Ratio[b] | 0.2123 | | 0.0073 | |
| Treatment-by-subgroup p-value[c] | | | | 0.2144 |

[a]derived from Kaplan-Meier estimates for each modality of subgroup.
[b]derived using two Cox regression models for each modality of subgroup with discrete time intervals including intervention, strata (ages 8-17 with a confirmed abnormal OGTT/ages 8-17 with an abnormal OGTT that was not confirmed (expanded eligibility criteria)/ 18 or older with a confirmed abnormal OGTT) and age as covariates.
[c]derived using Cox regression model with discrete time intervals including intervention, strata (ages 8-17 with a confirmed abnormal OGTT/ages 8-17 with an abnormal OGTT that was not confirmed (expanded eligibility criteria)/ 18 or older with a confirmed abnormal OGTT), age, subgroup and treatment-by-subgroup interaction as covariates.
Note: Time is calculated from randomization to diabetes onset up to 84 months.

Tabelle 1-4: Time to Diabetes Onset up to 84 Months (Months) – Per C-peptide level

| Time to Diabetes Onset (Months) | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| | Teplizumab (N=20) | Placebo (N=18) | Teplizumab (N=24) | Placebo (N=14) |
| Number of patients with event | 9 (45.0) | 15 (83.3) | 11 (45.8) | 8 (57.1) |
| Number of patients who are censored | 11 (55.0) | 3 (16.7) | 13 (54.2) | 6 (42.9) |
| 25% quantile time to first event (months) (95% CI)[a] | 25.86 (9.46 to 33.45) | 4.50 (2.73 to 11.79) | 21.78 (6.44 to 49.54) | 13.93 (4.01 to 48.59) |
| Median time to first event (months) (95% CI)[a] | 43.27 (25.86 to NE) | 12.42 (4.50 to 30.52) | 60.42 (24.84 to NE) | 48.59 (6.28 to NE) |
| 75% quantile time to first event (months) (95% CI)[a] | NE (33.45 to NE) | 30.52 (12.42 to NE) | NE (60.42 to NE) | NE (42.64 to NE) |
| Unstratified Log-Rank test p-value[a] | 0.0012 | - | 0.4369 | - |
| Hazard Ratio (95% CI) vs. placebo[b] | 0.24 (0.10 to 0.60) | | 0.72 (0.26 to 1.94) | |
| p-value for Hazard Ratio[b] | 0.0023 | | 0.5133 | |

| Time to Diabetes Onset (Months) | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| | Teplizumab (N=20) | Placebo (N=18) | Teplizumab (N=24) | Placebo (N=14) |
| Treatment-by-subgroup p-value[c] | | | | 0.0789 |

[a]derived from Kaplan-Meier estimates for each modality of subgroup.

[b]derived using two Cox regression models for each modality of subgroup with discrete time intervals including intervention, strata (ages 8-17 with a confirmed abnormal OGTT/ages 8-17 with an abnormal OGTT that was not confirmed (expanded eligibility criteria)/ 18 or older with a confirmed abnormal OGTT) and age as covariates.

[c]derived using Cox regression model with discrete time intervals including intervention, strata (ages 8-17 with a confirmed abnormal OGTT/ages 8-17 with an abnormal OGTT that was not confirmed (expanded eligibility criteria)/ 18 or older with a confirmed abnormal OGTT), age, subgroup and treatment-by-subgroup interaction as covariates.

Note: Time is calculated from randomization to diabetes onset up to 84 months.

## 1.2 Studie TN-10 – Subgruppenanalysen für die kontinuierlichen Analysen

### 1.2.1 Summary table of treatment-by-subgroup p-value for all subgroups - ITT population

Tabelle 1-5: Summary table of treatment-by-subgroup p-value for all subgroups - ITT population

| Efficacy endpoint | Subgroup | Overall treatment-by-subgroup at month 24 p-value |
|---|---|---|
| Mean C-peptide (nmol/L) AUC in 2-hour OGTT / Month 24 | Age (years) ( < 18 , >= 18 ) | 0.9572 |
| | Gender ( Female , Male ) | 0.1692 |
| | C-peptide level ( < Median , >= Median ) | 0.8899 |
| C-peptide (nmol/L) ln(AUC + 1) by treatment and time window from the 2-year model / Month 24 | Age (years) ( < 18 , >= 18 ) | 0.8301 |
| | Gender ( Female , Male ) | 0.1744 |
| | C-peptide level ( < Median , >= Median ) | 0.7061 |

Overall treatment-by-subgroup p-values derived from MMRM model with change from baseline up to month 24 as the response variable and corresponding baseline value, treatment group, subgroup, onset of diabetes, visit, baseline-by-visit interaction, Onset-of-diabetes-by-visit interaction, treatment-by-visit interaction, treatment-by-subgroup interaction and treatment-by-subgroup-by-visit interaction as covariates

### 1.2.2 Change from baseline in mean C-peptide AUC in 2-hour OGTT at month 24 (MMRM) – Subgroup Analyses

Tabelle 1-6: Change from baseline in mean C-peptide AUC in 2-hour OGTT at month 24 – Per Age

| | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| Mean C-peptide (nmol/L) AUC in 2-hour OGTT (MMRM) | Teplizumab (N=29) | Placebo (N=26) | Teplizumab (N=15) | Placebo (N=6) |
| Baseline | | | | |
| Number | 29 | 26 | 15 | 6 |
| Mean (SD) | 1.83 (0.78) | 1.84 (0.67) | 2.26 (0.92) | 2.10 (0.98) |
| Month 24 | | | | |
| Value | | | | |
| Number | 17 | 10 | 13 | 5 |
| Mean (SD) | 1.95 (0.79) | 1.94 (0.63) | 2.39 (0.98) | 1.89 (1.08) |
| Change from baseline | | | | |
| Number | 17 | 10 | 13 | 5 |
| Mean (SD) | 0.36 (0.49) | -0.07 (0.59) | 0.03 (0.88) | -0.28 (0.51) |
| LS Mean (SE)[a] | 0.15 (0.10) | -0.06 (0.13) | -0.05 (0.16) | -0.11 (0.27) |
| LS Mean Diff vs. Placebo (95% CI)[a] | -0.22 (-0.55 to 0.12) | | -0.07 (-0.73 to 0.60) | |
| P-value vs. Placebo[a] | 0.1972 | | 0.8339 | |
| Hedges'g vs. Placebo (95% CI) | -0.51 (-1.29 to 0.27) | - | -0.11 (-1.21 to 0.99) | - |
| Treatment-by-subgroup p-value[b] | | | | 0.9572 |

| | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| **Mean C-peptide (nmol/L) AUC in 2-hour OGTT (MMRM)** | **Teplizumab (N=29)** | **Placebo (N=26)** | **Teplizumab (N=15)** | **Placebo (N=6)** |

[a] Derived from two MMRM models for each modality of subgroup with change from baseline up to month 24 as the response variable and corresponding baseline value, treatment group, onset of diabetes, visit, baseline-by-visit interaction, Onset-of-diabetes-by-visit interaction and treatment-by-visit interaction as covariates.

[b] Derived from MMRM model with change from baseline up to month 24 as the response variable and corresponding baseline value, treatment group, subgroup, onset of diabetes, visit, baseline-by-visit interaction, Onset-of-diabetes-by-visit interaction, treatment-by-visit interaction, treatment-by-subgroup interaction and treatment-by-subgroup-by-visit interaction as covariates.
Note: No imputation was used for missing values.

Tabelle 1-7: Change from baseline in mean C-peptide AUC in 2-hour OGTT at month 24 – Per Gender

| | Gender | | | |
|---|---|---|---|---|
| | Male (N=42) | | Female (N=34) | |
| **Mean C-peptide (nmol/L) AUC in 2-hour OGTT (MMRM)** | **Teplizumab (N=25)** | **Placebo (N=17)** | **Teplizumab (N=19)** | **Placebo (N=15)** |
| Baseline | | | | |
| Number | 25 | 17 | 19 | 15 |
| Mean (SD) | 1.94 (0.83) | 1.74 (0.81) | 2.03 (0.89) | 2.06 (0.58) |
| Month 24 | | | | |
| Value | | | | |
| Number | 18 | 9 | 12 | 6 |
| Mean (SD) | 2.30 (1.04) | 1.96 (0.81) | 1.90 (0.55) | 1.87 (0.77) |
| Change from baseline | | | | |
| Number | 18 | 9 | 12 | 6 |
| Mean (SD) | 0.37 (0.60) | -0.08 (0.59) | -0.02 (0.78) | -0.22 (0.54) |
| LS Mean (SE)[a] | 0.33 (0.11) | -0.13 (0.15) | -0.21 (0.16) | -0.06 (0.21) |
| LS Mean Diff vs. Placebo (95% CI)[a] | -0.46 (-0.83 to -0.09) | | 0.15 (-0.38 to 0.68) | |
| P-value vs. Placebo[a] | 0.0153 | | 0.5613 | |
| Hedges'g vs. Placebo (95% CI) | -1.01 (-1.81 to -0.21) | - | 0.28 (-0.70 to 1.26) | - |
| Treatment-by-subgroup p-value[b] | | | | 0.1692 |

[a] Derived from two MMRM models for each modality of subgroup with change from baseline up to month 24 as the response variable and corresponding baseline value, treatment group, onset of diabetes, visit, baseline-by-visit interaction, Onset-of-diabetes-by-visit interaction and treatment-by-visit interaction as covariates.

[b] Derived from MMRM model with change from baseline up to month 24 as the response variable and corresponding baseline value, treatment group, subgroup, onset of diabetes, visit, baseline-by-visit interaction, Onset-of-diabetes-by-visit interaction, treatment-by-visit interaction, treatment-by-subgroup interaction and treatment-by-subgroup-by-visit interaction as covariates.
Note: No imputation was used for missing values.

Tabelle 1-8: Change from baseline in mean C-peptide AUC in 2-hour OGTT at month 24 – Per C-peptide level

| | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| **Mean C-peptide (nmol/L) AUC in 2-hour OGTT (MMRM)** | **Teplizumab (N=20)** | **Placebo (N=18)** | **Teplizumab (N=24)** | **Placebo (N=14)** |
| Baseline | | | | |
| Number | 20 | 18 | 24 | 14 |
| Mean (SD) | 1.38 (0.30) | 1.38 (0.34) | 2.48 (0.83) | 2.56 (0.50) |
| Month 24 | | | | |
| Value | | | | |
| Number | 14 | 6 | 16 | 9 |
| Mean (SD) | 1.57 (0.35) | 1.20 (0.25) | 2.64 (0.92) | 2.40 (0.59) |
| Change from baseline | | | | |
| Number | 14 | 6 | 16 | 9 |
| Mean (SD) | 0.23 (0.37) | -0.02 (0.41) | 0.20 (0.89) | -0.22 (0.65) |
| LS Mean (SE)[a] | 0.16 (0.08) | -0.07 (0.13) | 0.03 (0.17) | -0.23 (0.22) |
| LS Mean Diff vs. Placebo (95% CI)[a] | -0.23 (-0.53 to 0.07) | | -0.27 (-0.84 to 0.30) | |
| P-value vs. Placebo[a] | 0.1303 | | 0.3446 | |
| Hedges'g vs. Placebo (95% CI) | -0.76 (-1.75 to 0.24) | - | -0.39 (-1.22 to 0.44) | - |
| Treatment-by-subgroup p-value[b] | | | | 0.8899 |

[a] Derived from two MMRM models for each modality of subgroup with change from baseline up to month 24 as the response variable and corresponding baseline value, treatment group, onset of diabetes, visit, baseline-by-visit interaction, Onset-of-diabetes-by-visit interaction and treatment-by-visit interaction as covariates.

[b] Derived from MMRM model with change from baseline up to month 24 as the response variable and corresponding baseline value, treatment group, subgroup, onset of diabetes, visit, baseline-by-visit interaction, Onset-of-diabetes-by-visit interaction, treatment-by-visit interaction, treatment-by-subgroup interaction and treatment-by-subgroup-by-visit interaction as covariates.

Note: No imputation was used for missing values.

### 1.2.3 C-peptide ln(AUC + 1) by treatment and time window from the 2-year model at month 24 (MMRM) – Subgroup Analyses

Tabelle 1-9: C-peptide ln(AUC + 1) by treatment and time window from the 2-year model at month 24 – Per Age

| | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| **C-peptide (nmol/L) ln(AUC + 1) by treatment and time window from the 2-year model (MMRM)** | **Teplizumab (N=29)** | **Placebo (N=26)** | **Teplizumab (N=15)** | **Placebo (N=6)** |
| Baseline | | | | |
| Number | 29 | 26 | 15 | 6 |
| Mean (SD) | 1.01 (0.25) | 1.02 (0.24) | 1.15 (0.26) | 1.09 (0.29) |
| Month 24 | | | | |
| Value | | | | |

| | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| **C-peptide (nmol/L) ln(AUC + 1) by treatment and time window from the 2-year model (MMRM)** | **Teplizumab (N=29)** | **Placebo (N=26)** | **Teplizumab (N=15)** | **Placebo (N=6)** |
| Number | 17 | 10 | 13 | 5 |
| Mean (SD) | 1.05 (0.25) | 1.06 (0.21) | 1.18 (0.28) | 1.01 (0.37) |
| LS Mean (SE)[a] | 1.08 (0.03) | 1.00 (0.04) | 1.14 (0.05) | 1.10 (0.09) |
| LS Mean Diff vs. Placebo (95% CI)[a] | -0.08 (-0.18 to 0.03) | | -0.05 (-0.26 to 0.17) | |
| P-value vs. Placebo[a] | 0.1366 | | 0.6581 | |
| Hedges'g vs. Placebo (95% CI) | -0.59 (-1.37 to 0.19) | - | -0.24 (-1.35 to 0.88) | - |
| Change from baseline | | | | |
| Number | 17 | 10 | 13 | 5 |
| Mean (SD) | 0.12 (0.17) | -0.01 (0.20) | 0.00 (0.24) | -0.10 (0.15) |
| Treatment-by-subgroup p-value[b] | | | | 0.8301 |

[a] Derived from two MMRM models for each modality of subgroup with change from baseline up to month 24 as the response variable and corresponding baseline value, treatment group, onset of diabetes, visit, baseline-by-visit interaction, Onset-of-diabetes-by-visit interaction and treatment-by-visit interaction as covariates.

[b] Derived from MMRM model with change from baseline up to month 24 as the response variable and corresponding baseline value, treatment group, subgroup, onset of diabetes, visit, baseline-by-visit interaction, Onset-of-diabetes-by-visit interaction, treatment-by-visit interaction, treatment-by-subgroup interaction and treatment-by-subgroup-by-visit interaction as covariates.

Note: No imputation was used for missing values.

Tabelle 1-10: C-peptide ln(AUC + 1) by treatment and time window from the 2-year model at month 24 – Per Gender

| | Gender | | | |
|---|---|---|---|---|
| | Male (N=42) | | Female (N=34) | |
| **C-peptide (nmol/L) ln(AUC + 1) by treatment and time window from the 2-year model (MMRM)** | **Teplizumab (N=25)** | **Placebo (N=17)** | **Teplizumab (N=19)** | **Placebo (N=15)** |
| Baseline | | | | |
| Number | 25 | 17 | 19 | 15 |
| Mean (SD) | 1.04 (0.27) | 0.97 (0.28) | 1.07 (0.26) | 1.10 (0.20) |
| Month 24 | | | | |
| Value | | | | |
| Number | 18 | 9 | 12 | 6 |
| Mean (SD) | 1.15 (0.30) | 1.05 (0.28) | 1.05 (0.19) | 1.02 (0.26) |
| LS Mean (SE)[a] | 1.14 (0.03) | 1.00 (0.04) | 1.02 (0.05) | 1.06 (0.07) |
| LS Mean Diff vs. Placebo (95% CI)[a] | -0.15 (-0.26 to -0.03) | | 0.04 (-0.13 to 0.21) | |
| P-value vs. Placebo[a] | 0.0120 | | 0.6191 | |
| Hedges'g vs. Placebo (95% CI) | -1.05 (-1.85 to -0.25) | - | 0.24 (-0.74 to 1.22) | - |
| Change from baseline | | | | |
| Number | 18 | 9 | 12 | 6 |

| | Gender | | | |
|---|---|---|---|---|
| | Male (N=42) | | Female (N=34) | |
| **C-peptide (nmol/L) ln(AUC + 1) by treatment and time window from the 2-year model (MMRM)** | **Teplizumab (N=25)** | **Placebo (N=17)** | **Teplizumab (N=19)** | **Placebo (N=15)** |
| Mean (SD) | 0.12 (0.18) | -0.01 (0.19) | 0.00 (0.24) | -0.08 (0.18) |
| Treatment-by-subgroup p-value[b] | | | | 0.1744 |

[a] Derived from two MMRM models for each modality of subgroup with change from baseline up to month 24 as the response variable and corresponding baseline value, treatment group, onset of diabetes, visit, baseline-by-visit interaction, Onset-of-diabetes-by-visit interaction and treatment-by-visit interaction as covariates.
[b] Derived from MMRM model with change from baseline up to month 24 as the response variable and corresponding baseline value, treatment group, subgroup, onset of diabetes, visit, baseline-by-visit interaction, Onset-of-diabetes-by-visit interaction, treatment-by-visit interaction, treatment-by-subgroup interaction and treatment-by-subgroup-by-visit interaction as covariates.
Note: No imputation was used for missing values.

Tabelle 1-11: C-peptide ln(AUC + 1) by treatment and time window from the 2-year model at month 24 – Per C-peptide level

| | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| **C-peptide (nmol/L) ln(AUC + 1) by treatment and time window from the 2-year model (MMRM)** | **Teplizumab (N=20)** | **Placebo (N=18)** | **Teplizumab (N=24)** | **Placebo (N=14)** |
| Baseline | | | | |
| Number | 20 | 18 | 24 | 14 |
| Mean (SD) | 0.86 (0.14) | 0.86 (0.15) | 1.22 (0.22) | 1.26 (0.14) |
| Month 24 | | | | |
| Value | | | | |
| Number | 14 | 6 | 16 | 9 |
| Mean (SD) | 0.93 (0.13) | 0.78 (0.11) | 1.26 (0.26) | 1.21 (0.18) |
| LS Mean (SE)[a] | 0.91 (0.03) | 0.82 (0.05) | 1.24 (0.05) | 1.17 (0.07) |
| LS Mean Diff vs. Placebo (95% CI)[a] | -0.09 (-0.21 to 0.03) | | -0.07 (-0.24 to 0.10) | |
| P-value vs. Placebo[a] | 0.1258 | | 0.4043 | |
| Hedges'g vs. Placebo (95% CI) | -0.77 (-1.76 to 0.23) | - | -0.34 (-1.17 to 0.49) | - |
| Change from baseline | | | | |
| Number | 14 | 6 | 16 | 9 |
| Mean (SD) | 0.10 (0.15) | -0.00 (0.19) | 0.05 (0.25) | -0.06 (0.19) |
| Treatment-by-subgroup p-value[b] | | | | 0.7061 |

[a] Derived from two MMRM models for each modality of subgroup with change from baseline up to month 24 as the response variable and corresponding baseline value, treatment group, onset of diabetes, visit, baseline-by-visit interaction, Onset-of-diabetes-by-visit interaction and treatment-by-visit interaction as covariates.
[b] Derived from MMRM model with change from baseline up to month 24 as the response variable and corresponding baseline value, treatment group, subgroup, onset of diabetes, visit, baseline-by-visit interaction, Onset-of-diabetes-by-visit interaction, treatment-by-visit interaction, treatment-by-subgroup interaction and treatment-by-subgroup-by-visit interaction as covariates.
Note: No imputation was used for missing values.

# 2 Studie TN-10 – Sicherheit und Verträglichkeit – Safety Population

## 2.1 Studie TN-10 – Gesamtraten der UE – Subgruppenanalysen

### 2.1.1 Summary table of treatment-by-subgroup p-value for all subgroups

Tabelle 2-1:Summary table of treatment-by-subgroup p-value for all subgroups

| Safety endpoint | Subgroup | Overall treatment-by-subgroup p-value |
|---|---|---|
| Any TEAE | Age (years) ( < 18 , >= 18 ) | <.0001 |
| | Gender ( Female , Male ) | <.0001 |
| | C-peptide level ( < Median , >= Median ) | <.0001 |
| Any grade >= 3 TEAE | Age (years) ( < 18 , >= 18 ) | 0.9773 |
| | Gender ( Female , Male ) | 0.9782 |
| | C-peptide level ( < Median , >= Median ) | 0.5864 |

Overall treatment-by-subgroup p-values derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

### 2.1.2 Any TEAE – Subgroup Analyses

Tabelle 2-2: Any TEAE – Per Age

| | | Age (years) | | | |
|---|---|---|---|---|---|
| | | < 18 (N=55) | | >= 18 (N=21) | |
| Safety population<br>Any TEAE | | Teplizumab (N=29) | Placebo (N=26) | Teplizumab (N=15) | Placebo (N=6) |
| Any TEAE [n (%)] | | | | | |
| Patients with any events [n(%)] | | 28 (96.6) | 17 (65.4) | 15 (100) | 5 (83.3) |
| Patients without events [n(%)] | | 1 (3.4) | 9 (34.6) | 0 | 1 (16.7) |
| Odds Ratio (95% CI) vs Placebo[a] | | 4.55 (0.99 to 21.00) | - | 2.25 (0.11 to 46.95) | - |
| p-value for Odds Ratio[a] | | 0.0519 | | 0.5831 | |
| Risk Ratio (95% CI) vs Placebo[a] | | 1.13 (NE to NE) | - | 1.05 (NE to NE) | - |
| Reversed Risk ratio (95% CI) | | 0.88 (NE to NE) | - | 0.95 (NE to NE) | - |
| p-value for Risk Ratio[a] | | NE | | NE | |
| Risk Difference (95% CI) vs Placebo[a] | | 31.17 (11.26 to 51.08) | - | 16.67 (NE to NE) | - |
| p-value for Risk Difference[a] | | 0.0028 | | <0.0001 | |
| Treatment-by-subgroup p-value[b] | | | | | <.0001 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).
Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.
[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Tabelle 2-3: Any TEAE – Per Gender

| | Gender | | | |
|---|---|---|---|---|
| | Male (N=42) | | Female (N=34) | |
| **Safety population Any TEAE** | **Teplizumab (N=25)** | **Placebo (N=17)** | **Teplizumab (N=19)** | **Placebo (N=15)** |
| Any TEAE [n (%)] | | | | |
| Patients with any events [n(%)] | 25 (100) | 12 (70.6) | 18 (94.7) | 10 (66.7) |
| Patients without events [n(%)] | 0 | 5 (29.4) | 1 (5.3) | 5 (33.3) |
| Odds Ratio (95% CI) vs Placebo[a] | 4.18 (0.66 to 26.60) | - | 3.92 (0.57 to 26.70) | - |
| p-value for Odds Ratio[a] | 0.1260 | | 0.1571 | |
| Risk Ratio (95% CI) vs Placebo[a] | 1.11 (NE to NE) | - | 1.12 (NE to NE) | - |
| Reversed Risk ratio (95% CI) | 0.90 (NE to NE) | - | 0.89 (NE to NE) | - |
| p-value for Risk Ratio[a] | NE | | NE | |
| Risk Difference (95% CI) vs Placebo[a] | 29.41 (NE to NE) | - | 28.07 (1.17 to 54.97) | - |
| p-value for Risk Difference[a] | <0.0001 | | 0.0413 | |
| Treatment-by-subgroup p-value[b] | | | | <.0001 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).
Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.
[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Tabelle 2-4: Any TEAE – Per C-peptide level

| | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| **Safety population Any TEAE** | **Teplizumab (N=20)** | **Placebo (N=18)** | **Teplizumab (N=24)** | **Placebo (N=14)** |
| Any TEAE [n (%)] | | | | |
| Patients with any events [n(%)] | 20 (100) | 11 (61.1) | 23 (95.8) | 11 (78.6) |
| Patients without events [n(%)] | 0 | 7 (38.9) | 1 (4.2) | 3 (21.4) |
| Odds Ratio (95% CI) vs Placebo[a] | 6.63 (0.96 to 46.00) | - | 2.32 (0.33 to 16.24) | - |
| p-value for Odds Ratio[a] | 0.0553 | | 0.3878 | |
| Risk Ratio (95% CI) vs Placebo[a] | 1.17 (NE to NE) | - | 1.06 (NE to NE) | - |
| Reversed Risk ratio (95% CI) | 0.85 (NE to NE) | - | 0.94 (NE to NE) | - |
| p-value for Risk Ratio[a] | NE | | NE | |
| Risk Difference (95% CI) vs Placebo[a] | 38.89 (NE to NE) | - | 17.26 (-6.47 to 40.99) | - |
| p-value for Risk Difference[a] | <0.0001 | | 0.1488 | |

| | | C-peptide level | | | |
|---|---|---|---|---|---|
| | | < Median (N=38) | | >= Median (N=38) | |
| Safety population<br>Any TEAE | | Teplizumab (N=20) | Placebo (N=18) | Teplizumab (N=24) | Placebo (N=14) |
| Treatment-by-subgroup p-value[b] | | | | | <.0001 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).
Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.
[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

### 2.1.3 Any grade >=3 TEAE – Subgroup Analyses

Tabelle 2-5: Any grade >=3 TEAE – Per Age

| | | Age (years) | | | |
|---|---|---|---|---|---|
| | | < 18 (N=55) | | >= 18 (N=21) | |
| Safety population<br>Any grade | | Teplizumab (N=29) | Placebo (N=26) | Teplizumab (N=15) | Placebo (N=6) |
| Any grade >= 3 TEAE [n (%)] | | | | | |
| Patients with any events [n(%)] | | 13 (44.8) | 3 (11.5) | 13 (86.7) | 0 |
| Patients without events [n(%)] | | 16 (55.2) | 23 (88.5) | 2 (13.3) | 6 (100) |
| Odds Ratio (95% CI) vs Placebo[a] | | 5.05 (1.27 to 20.05) | - | 67.72 (2.06 to 2228.14) | - |
| p-value for Odds Ratio[a] | | 0.0223 | | 0.0206 | |
| Peto Odds Ratio (95% CI) vs Placebo[a] | | | | 33.12 (4.94 to 221.98) | - |
| Reversed Peto Odds Ratio (95% CI) | | | | 0.03 (0.00 to 0.20) | - |
| p-value for Peto Odds Ratio | | | | 0.0003 | |
| Risk Ratio (95% CI) vs Placebo[a] | | 2.28 (1.40 to 3.72) | - | 11.81 (0.81 to 172.16) | - |
| Reversed Risk ratio (95% CI) | | 0.44 (0.27 to 0.71) | - | 0.08 (0.01 to 1.23) | - |
| p-value for Risk Ratio[a] | | 0.0009 | | 0.0709 | |
| Risk Difference (95% CI) vs Placebo[a] | | 33.29 (10.91 to 55.67) | - | 86.67 (NE to NE) | - |
| p-value for Risk Difference[a] | | 0.0043 | | <0.0001 | |
| Treatment-by-subgroup p-value[b] | | | | | 0.9773 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).
Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.
[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Tabelle 2-6: Any grade >=3 TEAE – Per Gender

| | Gender | | | |
|---|---|---|---|---|
| | Male (N=42) | | Female (N=34) | |
| **Safety population Any grade** | **Teplizumab (N=25)** | **Placebo (N=17)** | **Teplizumab (N=19)** | **Placebo (N=15)** |
| Any grade >= 3 TEAE [n (%)] | | | | |
| Patients with any events [n(%)] | 14 (56.0) | 0 | 12 (63.2) | 3 (20.0) |
| Patients without events [n(%)] | 11 (44.0) | 17 (100) | 7 (36.8) | 12 (80.0) |
| Odds Ratio (95% CI) vs Placebo[a] | 15.24 (2.11 to 109.90) | - | 8.16 (1.54 to 43.14) | - |
| p-value for Odds Ratio[a] | 0.0081 | | 0.0151 | |
| Peto Odds Ratio (95% CI) vs Placebo[a] | 11.70 (3.22 to 42.58) | - | | |
| Reversed Peto Odds Ratio (95% CI) | 0.09 (0.02 to 0.31) | - | | |
| p-value for Peto Odds Ratio | 0.0002 | | | |
| Risk Ratio (95% CI) vs Placebo[a] | 20.08 (1.28 to 315.44) | - | 1.82 (1.19 to 2.80) | - |
| Reversed Risk ratio (95% CI) | 0.05 (0.00 to 0.78) | - | 0.55 (0.36 to 0.84) | - |
| p-value for Risk Ratio[a] | 0.0328 | | 0.0061 | |
| Risk Difference (95% CI) vs Placebo[a] | 56.00 (NE to NE) | - | 43.16 (12.32 to 73.99) | - |
| p-value for Risk Difference[a] | <0.0001 | | 0.0076 | |
| Treatment-by-subgroup p-value[b] | | | | 0.9782 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).
Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.
[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Tabelle 2-7: Any grade >=3 TEAE – Per C-peptide level

| | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| **Safety population Any grade** | **Teplizumab (N=20)** | **Placebo (N=18)** | **Teplizumab (N=24)** | **Placebo (N=14)** |
| Any grade >= 3 TEAE [n (%)] | | | | |
| Patients with any events [n(%)] | 10 (50.0) | 1 (5.6) | 16 (66.7) | 2 (14.3) |
| Patients without events [n(%)] | 10 (50.0) | 17 (94.4) | 8 (33.3) | 12 (85.7) |
| Odds Ratio (95% CI) vs Placebo[a] | 8.69 (1.42 to 53.29) | - | 12.78 (2.19 to 74.59) | - |
| p-value for Odds Ratio[a] | 0.0209 | | 0.0059 | |

| | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| **Safety population Any grade** | **Teplizumab (N=20)** | **Placebo (N=18)** | **Teplizumab (N=24)** | **Placebo (N=14)** |
| Risk Ratio (95% CI) vs Placebo[a] | 3.85 (1.65 to 8.97) | - | 2.33 (1.32 to 4.10) | - |
| Reversed Risk ratio (95% CI) | 0.26 (0.11 to 0.61) | - | 0.43 (0.24 to 0.76) | - |
| p-value for Risk Ratio[a] | 0.0018 | | 0.0034 | |
| Risk Difference (95% CI) vs Placebo[a] | 44.44 (19.26 to 69.62) | - | 52.38 (25.17 to 79.59) | - |
| p-value for Risk Difference[a] | 0.0010 | | 0.0004 | |
| Treatment-by-subgroup p-value[b] | | | | 0.5864 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

## 2.2 Studie TN-10 – Jegliche UE nach SOC und PT – Subgruppenanalysen

### 2.2.1 Summary table of treatment-by-subgroup p-value for all subgroups

Tabelle 2-8: Summary table of treatment-by-subgroup p-value for all subgroups

| Safety endpoint | Subgroup | Overall treatment-by-subgroup p-value |
|---|---|---|
| TEAE - PT=Lymphopenia | Age (years) ( < 18 , >= 18 ) | 0.9788 |
| | Gender ( Female , Male ) | 0.9861 |
| | C-peptide level ( < Median , >= Median ) | 0.9702 |
| TEAE - SOC=Blood and lymphatic system disorders | Age (years) ( < 18 , >= 18 ) | 0.9776 |
| | Gender ( Female , Male ) | 0.9724 |
| | C-peptide level ( < Median , >= Median ) | 0.3287 |
| TEAE - SOC=Infections and infestations | Age (years) ( < 18 , >= 18 ) | 0.7805 |
| | Gender ( Female , Male ) | 0.8679 |
| | C-peptide level ( < Median , >= Median ) | 0.3339 |
| TEAE - SOC=Skin and subcutaneous tissue disorders | Age (years) ( < 18 , >= 18 ) | 0.9812 |
| | Gender ( Female , Male ) | 0.7214 |
| | C-peptide level ( < Median , >= Median ) | 0.7067 |

Overall treatment-by-subgroup p-values derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

### 2.2.2 Any TEAE - PT=Lymphopenia – Subgroup Analyses

Tabelle 2-9: Any TEAE - PT=Lymphopenia – Per Age

| | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| **Safety population Lymphopenia** | **Teplizumab (N=29)** | **Placebo (N=26)** | **Teplizumab (N=15)** | **Placebo (N=6)** |
| Lymphopenia [n (%)] | | | | |
| Patients with any events [n(%)] | 19 (65.5) | 2 (7.7) | 13 (86.7) | 0 |
| Patients without events [n(%)] | 10 (34.5) | 24 (92.3) | 2 (13.3) | 6 (100) |
| Odds Ratio (95% CI) vs Placebo[a] | 16.65 (3.81 to 72.85) | - | 67.72 (2.06 to 2228.14) | - |
| p-value for Odds Ratio[a] | 0.0003 | | 0.0206 | |
| Peto Odds Ratio (95% CI) vs Placebo[a] | | | 33.12 (4.94 to 221.98) | - |
| Reversed Peto Odds Ratio (95% CI) | | | 0.03 (0.00 to 0.20) | - |
| p-value for Peto Odds Ratio | | | 0.0003 | |
| Risk Ratio (95% CI) vs Placebo[a] | 3.51 (1.93 to 6.36) | - | 11.81 (0.81 to 172.16) | - |
| Reversed Risk ratio (95% CI) | 0.28 (0.16 to 0.52) | - | 0.08 (0.01 to 1.23) | - |
| p-value for Risk Ratio[a] | <0.0001 | | 0.0709 | |
| Risk Difference (95% CI) vs Placebo[a] | 57.82 (37.25 to 78.40) | - | 86.67 (NE to NE) | - |
| p-value for Risk Difference[a] | <0.0001 | | <0.0001 | |

| | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| **Safety population Lymphopenia** | **Teplizumab (N=29)** | **Placebo (N=26)** | **Teplizumab (N=15)** | **Placebo (N=6)** |
| Treatment-by-subgroup p-value[b] | | | | 0.9788 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

## Tabelle 2-10: Any TEAE - PT=Lymphopenia – Per Gender

| | Gender | | | |
|---|---|---|---|---|
| | Male (N=42) | | Female (N=34) | |
| **Safety population Lymphopenia** | **Teplizumab (N=25)** | **Placebo (N=17)** | **Teplizumab (N=19)** | **Placebo (N=15)** |
| Lymphopenia [n (%)] | | | | |
| Patients with any events [n(%)] | 17 (68.0) | 1 (5.9) | 15 (78.9) | 1 (6.7) |
| Patients without events [n(%)] | 8 (32.0) | 16 (94.1) | 4 (21.1) | 14 (93.3) |
| Odds Ratio (95% CI) vs Placebo[a] | 20.52 (3.29 to 127.94) | - | 33.64 (4.28 to 264.07) | - |
| p-value for Odds Ratio[a] | 0.0018 | | 0.0015 | |
| Risk Ratio (95% CI) vs Placebo[a] | 4.20 (1.81 to 9.73) | - | 4.10 (1.75 to 9.59) | - |
| Reversed Risk ratio (95% CI) | 0.24 (0.10 to 0.55) | - | 0.24 (0.10 to 0.57) | - |
| p-value for Risk Ratio[a] | 0.0008 | | 0.0011 | |
| Risk Difference (95% CI) vs Placebo[a] | 62.12 (40.01 to 84.22) | - | 72.28 (49.15 to 95.41) | - |
| p-value for Risk Difference[a] | <0.0001 | | <0.0001 | |
| Treatment-by-subgroup p-value[b] | | | | 0.9861 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

Tabelle 2-11: Any TEAE - PT=Lymphopenia – Per C-peptide level

| | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| **Safety population Lymphopenia** | **Teplizumab (N=20)** | **Placebo (N=18)** | **Teplizumab (N=24)** | **Placebo (N=14)** |
| Lymphopenia [n (%)] | | | | |
| Patients with any events [n(%)] | 12 (60.0) | 2 (11.1) | 20 (83.3) | 0 |
| Patients without events [n(%)] | 8 (40.0) | 16 (88.9) | 4 (16.7) | 14 (100) |
| Odds Ratio (95% CI) vs Placebo[a] | 10.78 (1.98 to 58.82) | - | 57.58 (5.89 to 563.29) | - |
| p-value for Odds Ratio[a] | 0.0073 | | 0.0009 | |
| Peto Odds Ratio (95% CI) vs Placebo[a] | | | 25.91 (7.04 to 95.32) | - |
| Reversed Peto Odds Ratio (95% CI) | | | 0.04 (0.01 to 0.14) | - |
| p-value for Peto Odds Ratio | | | <0.0001 | |
| Risk Ratio (95% CI) vs Placebo[a] | 2.66 (1.47 to 4.80) | - | 24.60 (1.60 to 377.72) | - |
| Reversed Risk ratio (95% CI) | 0.38 (0.21 to 0.68) | - | 0.04 (0.00 to 0.62) | - |
| p-value for Risk Ratio[a] | 0.0012 | | 0.0216 | |
| Risk Difference (95% CI) vs Placebo[a] | 48.89 (22.07 to 75.71) | - | 83.33 (NE to NE) | - |
| p-value for Risk Difference[a] | 0.0007 | | <0.0001 | |
| Treatment-by-subgroup p-value[b] | | | | 0.9702 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

### 2.2.3 Any TEAE - SOC=Blood and lymphatic system disorders – Subgroup Analyses

Tabelle 2-12: Any TEAE - SOC=Blood and lymphatic system disorders – Per Age

| | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| **Safety population Blood and lymphatic system disorders** | **Teplizumab (N=29)** | **Placebo (N=26)** | **Teplizumab (N=15)** | **Placebo (N=6)** |
| Blood and lymphatic system disorders [n (%)] | | | | |
| Patients with any events [n(%)] | 20 (69.0) | 4 (15.4) | 13 (86.7) | 0 |
| Patients without events [n(%)] | 9 (31.0) | 22 (84.6) | 2 (13.3) | 6 (100) |
| Odds Ratio (95% CI) vs Placebo[a] | 13.55 (3.47 to 52.85) | - | 67.72 (2.06 to 2228.14) | - |
| p-value for Odds Ratio[a] | 0.0003 | | 0.0206 | |
| Peto Odds Ratio (95% CI) vs Placebo[a] | | | 33.12 (4.94 to 221.98) | - |
| Reversed Peto Odds Ratio (95% CI) | | | 0.03 (0.00 to 0.20) | - |
| p-value for Peto Odds Ratio | | | 0.0003 | |
| Risk Ratio (95% CI) vs Placebo[a] | 2.24 (1.52 to 3.31) | - | 11.81 (0.81 to 172.16) | - |
| Reversed Risk ratio (95% CI) | 0.45 (0.30 to 0.66) | - | 0.08 (0.01 to 1.23) | - |
| p-value for Risk Ratio[a] | <0.0001 | | 0.0709 | |
| Risk Difference (95% CI) vs Placebo[a] | 53.58 (31.26 to 75.90) | - | 86.67 (NE to NE) | - |
| p-value for Risk Difference[a] | <0.0001 | | <0.0001 | |
| Treatment-by-subgroup p-value[b] | | | | 0.9776 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

Tabelle 2-13: Any TEAE - SOC=Blood and lymphatic system disorders – Per Gender

| | Gender | | | |
|---|---|---|---|---|
| | Male (N=42) | | Female (N=34) | |
| **Safety population Blood and lymphatic system disorders** | **Teplizumab (N=25)** | **Placebo (N=17)** | **Teplizumab (N=19)** | **Placebo (N=15)** |
| Blood and lymphatic system disorders [n (%)] | | | | |
| Patients with any events [n(%)] | 18 (72.0) | 2 (11.8) | 15 (78.9) | 2 (13.3) |

| | Gender | | | |
|---|---|---|---|---|
| | Male (N=42) | | Female (N=34) | |
| **Safety population Blood and lymphatic system disorders** | **Teplizumab (N=25)** | **Placebo (N=17)** | **Teplizumab (N=19)** | **Placebo (N=15)** |
| Patients without events [n(%)] | 7 (28.0) | 15 (88.2) | 4 (21.1) | 13 (86.7) |
| Odds Ratio (95% CI) vs Placebo[a] | 18.72 (3.39 to 103.40) | - | 24.32 (3.62 to 163.40) | - |
| p-value for Odds Ratio[a] | 0.0013 | | 0.0018 | |
| Risk Ratio (95% CI) vs Placebo[a] | 2.73 (1.53 to 4.88) | - | 2.59 (1.46 to 4.59) | - |
| Reversed Risk ratio (95% CI) | 0.37 (0.20 to 0.65) | - | 0.39 (0.22 to 0.69) | - |
| p-value for Risk Ratio[a] | 0.0007 | | 0.0012 | |
| Risk Difference (95% CI) vs Placebo[a] | 60.24 (36.18 to 84.29) | - | 65.61 (39.49 to 91.74) | - |
| p-value for Risk Difference[a] | <0.0001 | | <0.0001 | |
| Treatment-by-subgroup p-value[b] | | | | 0.9724 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

## Tabelle 2-14: Any TEAE - SOC=Blood and lymphatic system disorders – Per C-peptide level

| | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| **Safety population Blood and lymphatic system disorders** | **Teplizumab (N=20)** | **Placebo (N=18)** | **Teplizumab (N=24)** | **Placebo (N=14)** |
| Blood and lymphatic system disorders [n (%)] | | | | |
| Patients with any events [n(%)] | 13 (65.0) | 3 (16.7) | 20 (83.3) | 1 (7.1) |
| Patients without events [n(%)] | 7 (35.0) | 15 (83.3) | 4 (16.7) | 13 (92.9) |
| Odds Ratio (95% CI) vs Placebo[a] | 10.49 (2.10 to 52.56) | - | 40.68 (5.20 to 318.17) | - |
| p-value for Odds Ratio[a] | 0.0054 | | 0.0008 | |
| Risk Ratio (95% CI) vs Placebo[a] | 2.08 (1.33 to 3.25) | - | 3.99 (1.71 to 9.31) | - |
| Reversed Risk ratio (95% CI) | 0.48 (0.31 to 0.75) | - | 0.25 (0.11 to 0.58) | - |
| p-value for Risk Ratio[a] | 0.0014 | | 0.0014 | |
| Risk Difference (95% CI) vs Placebo[a] | 48.33 (20.31 to 76.36) | - | 76.19 (55.38 to 97.00) | - |
| p-value for Risk Difference[a] | 0.0013 | | <0.0001 | |

| | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| **Safety population Blood and lymphatic system disorders** | **Teplizumab (N=20)** | **Placebo (N=18)** | **Teplizumab (N=24)** | **Placebo (N=14)** |
| Treatment-by-subgroup p-value[b] | | | | 0.3287 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

## 2.2.4 Any TEAE - SOC=Infections and infestations – Subgroup Analyses

Tabelle 2-15: Any TEAE - SOC=Infections and infestations – Per Age

| | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| **Safety population Infections and infestations** | **Teplizumab (N=29)** | **Placebo (N=26)** | **Teplizumab (N=15)** | **Placebo (N=6)** |
| Infections and infestations [n (%)] | | | | |
| Patients with any events [n(%)] | 12 (41.4) | 6 (23.1) | 11 (73.3) | 2 (33.3) |
| Patients without events [n(%)] | 17 (58.6) | 20 (76.9) | 4 (26.7) | 4 (66.7) |
| Odds Ratio (95% CI) vs Placebo[a] | 2.44 (0.71 to 8.30) | - | 7.00 (0.75 to 65.67) | - |
| p-value for Odds Ratio[a] | 0.1513 | | 0.0848 | |
| Risk Ratio (95% CI) vs Placebo[a] | 1.39 (1.02 to 1.89) | - | 1.42 (0.93 to 2.16) | - |
| Reversed Risk ratio (95% CI) | 0.72 (0.53 to 0.99) | - | 0.71 (0.46 to 1.08) | - |
| p-value for Risk Ratio[a] | 0.0399 | | 0.1053 | |
| Risk Difference (95% CI) vs Placebo[a] | 18.30 (-6.42 to 43.02) | - | 40.00 (-6.84 to 86.84) | - |
| p-value for Risk Difference[a] | 0.1435 | | 0.0898 | |
| Treatment-by-subgroup p-value[b] | | | | 0.7805 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

## Tabelle 2-16: Any TEAE - SOC=Infections and infestations – Per Gender

| | Gender | | | |
|---|---|---|---|---|
| | Male (N=42) | | Female (N=34) | |
| **Safety population Infections and infestations** | **Teplizumab (N=25)** | **Placebo (N=17)** | **Teplizumab (N=19)** | **Placebo (N=15)** |
| Infections and infestations [n (%)] | | | | |
| Patients with any events [n(%)] | 13 (52.0) | 4 (23.5) | 10 (52.6) | 4 (26.7) |
| Patients without events [n(%)] | 12 (48.0) | 13 (76.5) | 9 (47.4) | 11 (73.3) |
| Odds Ratio (95% CI) vs Placebo[a] | 3.99 (0.95 to 16.85) | - | 3.54 (0.76 to 16.54) | - |
| p-value for Odds Ratio[a] | 0.0590 | | 0.1052 | |
| Risk Ratio (95% CI) vs Placebo[a] | 1.52 (1.06 to 2.17) | - | 1.42 (1.00 to 2.00) | - |
| Reversed Risk ratio (95% CI) | 0.66 (0.46 to 0.94) | - | 0.71 (0.50 to 1.00) | - |
| p-value for Risk Ratio[a] | 0.0215 | | 0.0489 | |
| Risk Difference (95% CI) vs Placebo[a] | 28.47 (-0.51 to 57.46) | - | 25.96 (-6.98 to 58.91) | - |
| p-value for Risk Difference[a] | 0.0540 | | 0.1182 | |
| Treatment-by-subgroup p-value[b] | | | | 0.8679 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

## Tabelle 2-17: Any TEAE - SOC=Infections and infestations – Per C-peptide level

| | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| **Safety population Infections and infestations** | **Teplizumab (N=20)** | **Placebo (N=18)** | **Teplizumab (N=24)** | **Placebo (N=14)** |
| Infections and infestations [n (%)] | | | | |
| Patients with any events [n(%)] | 10 (50.0) | 3 (16.7) | 13 (54.2) | 5 (35.7) |
| Patients without events [n(%)] | 10 (50.0) | 15 (83.3) | 11 (45.8) | 9 (64.3) |
| Odds Ratio (95% CI) vs Placebo[a] | 5.06 (1.05 to 24.44) | - | 2.45 (0.59 to 10.15) | - |
| p-value for Odds Ratio[a] | 0.0440 | | 0.2080 | |
| Risk Ratio (95% CI) vs Placebo[a] | 1.87 (1.18 to 2.96) | - | 1.22 (0.93 to 1.58) | - |
| Reversed Risk ratio (95% CI) | 0.54 (0.34 to 0.85) | - | 0.82 (0.63 to 1.07) | - |
| p-value for Risk Ratio[a] | 0.0078 | | 0.1451 | |

| | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| **Safety population Infections and infestations** | **Teplizumab (N=20)** | **Placebo (N=18)** | **Teplizumab (N=24)** | **Placebo (N=14)** |
| Risk Difference (95% CI) vs Placebo[a] | 33.33 (4.50 to 62.17) | - | 18.45 (-14.71 to 51.62) | - |
| p-value for Risk Difference[a] | 0.0247 | | 0.2666 | |
| Treatment-by-subgroup p-value[b] | | | | 0.3339 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

### 2.2.5 Any TEAE - SOC=Skin and subcutaneous tissue disorders – Subgroup Analyses

Tabelle 2-18: Any TEAE - SOC=Skin and subcutaneous tissue disorders – Per Age

| | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| **Safety population Skin and subcutaneous tissue disorders** | **Teplizumab (N=29)** | **Placebo (N=26)** | **Teplizumab (N=15)** | **Placebo (N=6)** |
| Skin and subcutaneous tissue disorders [n (%)] | | | | |
| Patients with any events [n(%)] | 14 (48.3) | 3 (11.5) | 6 (40.0) | 0 |
| Patients without events [n(%)] | 15 (51.7) | 23 (88.5) | 9 (60.0) | 6 (100) |
| Odds Ratio (95% CI) vs Placebo[a] | 5.97 (1.51 to 23.64) | - | 7.00 (0.25 to 195.02) | - |
| p-value for Odds Ratio[a] | 0.0119 | | 0.2360 | |
| Peto Odds Ratio (95% CI) vs Placebo[a] | | | 6.47 (0.84 to 49.99) | - |
| Reversed Peto Odds Ratio (95% CI) | | | 0.15 (0.02 to 1.19) | - |
| p-value for Peto Odds Ratio | | | 0.0736 | |
| Risk Ratio (95% CI) vs Placebo[a] | 2.36 (1.46 to 3.83) | - | 5.69 (0.37 to 87.72) | - |
| Reversed Risk ratio (95% CI) | 0.42 (0.26 to 0.69) | - | 0.18 (0.01 to 2.71) | - |
| p-value for Risk Ratio[a] | 0.0005 | | 0.2130 | |
| Risk Difference (95% CI) vs Placebo[a] | 36.74 (14.28 to 59.19) | - | 40.00 (NE to NE) | - |
| p-value for Risk Difference[a] | 0.0018 | | <0.0001 | |
| Treatment-by-subgroup p-value[b] | | | | 0.9812 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

| | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| **Safety population** | **Teplizumab** | **Placebo** | **Teplizumab** | **Placebo** |
| **Skin and subcutaneous tissue disorders** | **(N=29)** | **(N=26)** | **(N=15)** | **(N=6)** |

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

## Tabelle 2-19: Any TEAE - SOC=Skin and subcutaneous tissue disorders – Per Gender

| | Gender | | | |
|---|---|---|---|---|
| | Male (N=42) | | Female (N=34) | |
| **Safety population** | **Teplizumab** | **Placebo** | **Teplizumab** | **Placebo** |
| **Skin and subcutaneous tissue disorders** | **(N=25)** | **(N=17)** | **(N=19)** | **(N=15)** |
| Skin and subcutaneous tissue disorders [n (%)] | | | | |
| Patients with any events [n(%)] | 12 (48.0) | 2 (11.8) | 8 (42.1) | 1 (6.7) |
| Patients without events [n(%)] | 13 (52.0) | 15 (88.2) | 11 (57.9) | 14 (93.3) |
| Odds Ratio (95% CI) vs Placebo[a] | 5.83 (1.12 to 30.28) | - | 5.61 (0.80 to 39.06) | - |
| p-value for Odds Ratio[a] | 0.0367 | | 0.0799 | |
| Risk Ratio (95% CI) vs Placebo[a] | 2.33 (1.29 to 4.20) | - | 3.18 (1.34 to 7.57) | - |
| Reversed Risk ratio (95% CI) | 0.43 (0.24 to 0.78) | - | 0.31 (0.13 to 0.75) | - |
| p-value for Risk Ratio[a] | 0.0052 | | 0.0088 | |
| Risk Difference (95% CI) vs Placebo[a] | 36.24 (10.60 to 61.87) | - | 35.44 (8.90 to 61.98) | - |
| p-value for Risk Difference[a] | 0.0068 | | 0.0105 | |
| Treatment-by-subgroup p-value[b] | | | | 0.7214 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

Tabelle 2-20: Any TEAE - SOC=Skin and subcutaneous tissue disorders – Per C-peptide level

| | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| **Safety population**<br>**Skin and subcutaneous tissue disorders** | **Teplizumab (N=20)** | **Placebo (N=18)** | **Teplizumab (N=24)** | **Placebo (N=14)** |
| Skin and subcutaneous tissue disorders [n (%)] | | | | |
| Patients with any events [n(%)] | 9 (45.0) | 2 (11.1) | 11 (45.8) | 1 (7.1) |
| Patients without events [n(%)] | 11 (55.0) | 16 (88.9) | 13 (54.2) | 13 (92.9) |
| Odds Ratio (95% CI) vs Placebo[a] | 5.20 (0.96 to 28.05) | - | 6.57 (0.96 to 44.70) | - |
| p-value for Odds Ratio[a] | 0.0550 | | 0.0543 | |
| Risk Ratio (95% CI) vs Placebo[a] | 2.35 (1.28 to 4.30) | - | 3.17 (1.35 to 7.48) | - |
| Reversed Risk ratio (95% CI) | 0.43 (0.23 to 0.78) | - | 0.32 (0.13 to 0.74) | - |
| p-value for Risk Ratio[a] | 0.0056 | | 0.0083 | |
| Risk Difference (95% CI) vs Placebo[a] | 33.89 (6.78 to 60.99) | - | 38.69 (13.78 to 63.60) | - |
| p-value for Risk Difference[a] | 0.0157 | | 0.0033 | |
| Treatment-by-subgroup p-value[b] | | | | 0.7067 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

## 2.3 Studie TN-10 – Schwere UE (CTCAE-Grad ≥ 3) nach SOC und PT – Subgruppenanalysen

### 2.3.1 Summary table of treatment-by-subgroup p-value for all subgroups

Tabelle 2-21: Summary table of treatment-by-subgroup p-value for all subgroups

| Safety endpoint | Subgroup | Overall treatment-by-subgroup p-value |
|---|---|---|
| Grade 3 TEAE - PT=Lymphopenia | Age (years) ( < 18 , >= 18 ) | 0.9993 |
| | Gender ( Female , Male ) | 0.9998 |
| | C-peptide level ( < Median , >= Median ) | 0.9999 |
| Grade 3 TEAE - SOC=Blood and lymphatic system disorders | Age (years) ( < 18 , >= 18 ) | 0.9993 |
| | Gender ( Female , Male ) | 0.9998 |
| | C-peptide level ( < Median , >= Median ) | 0.9999 |

Overall treatment-by-subgroup p-values derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

### 2.3.2 Grade ≥ 3 TEAE – PT= Lymphopenia – Subgroup Analyses

Tabelle 2-22: Grade ≥ 3 TEAE – PT= Lymphopenia – Per Age

| | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| **Safety population Lymphopenia** | **Teplizumab (N=29)** | **Placebo (N=26)** | **Teplizumab (N=15)** | **Placebo (N=6)** |
| Lymphopenia [n (%)] | | | | |
| Patients with any events [n(%)] | 10 (34.5) | 0 | 11 (73.3) | 0 |
| Patients without events [n(%)] | 19 (65.5) | 26 (100) | 4 (26.7) | 6 (100) |
| Odds Ratio (95% CI) vs Placebo[a] | 5.35 (1.03 to 27.85) | - | 35.41 (1.21 to 1039.27) | - |
| p-value for Odds Ratio[a] | 0.0464 | | 0.0396 | |
| Peto Odds Ratio (95% CI) vs Placebo[a] | 9.74 (2.50 to 37.93) | - | 16.44 (2.59 to 104.58) | - |
| Reversed Peto Odds Ratio (95% CI) | 0.10 (0.03 to 0.40) | - | 0.06 (0.01 to 0.39) | - |
| p-value for Peto Odds Ratio | 0.0010 | | 0.0030 | |
| Risk Ratio (95% CI) vs Placebo[a] | 18.90 (1.16 to 307.40) | - | 10.06 (0.68 to 148.02) | - |
| Reversed Risk ratio (95% CI) | 0.05 (0.00 to 0.86) | - | 0.10 (0.01 to 1.46) | - |
| p-value for Risk Ratio[a] | 0.0389 | | 0.0923 | |
| Risk Difference (95% CI) vs Placebo[a] | 34.48 (NE to NE) | - | 73.33 (NE to NE) | - |
| p-value for Risk Difference[a] | <0.0001 | | <0.0001 | |
| Treatment-by-subgroup p-value[b] | | | | 0.9993 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

| | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| **Safety population Lymphopenia** | **Teplizumab (N=29)** | **Placebo (N=26)** | **Teplizumab (N=15)** | **Placebo (N=6)** |

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

## Tabelle 2-23: Grade ≥ 3 TEAE – PT= Lymphopenia – Per Gender

| | Gender | | | |
|---|---|---|---|---|
| | Male (N=42) | | Female (N=34) | |
| **Safety population Lymphopenia** | **Teplizumab (N=25)** | **Placebo (N=17)** | **Teplizumab (N=19)** | **Placebo (N=15)** |
| Lymphopenia [n (%)] | | | | |
| Patients with any events [n(%)] | 11 (44.0) | 0 | 10 (52.6) | 0 |
| Patients without events [n(%)] | 14 (56.0) | 17 (100) | 9 (47.4) | 15 (100) |
| Odds Ratio (95% CI) vs Placebo[a] | 8.50 (1.18 to 61.31) | - | 12.94 (1.51 to 110.53) | - |
| p-value for Odds Ratio[a] | 0.0345 | | 0.0209 | |
| Peto Odds Ratio (95% CI) vs Placebo[a] | 9.23 (2.31 to 36.84) | - | 11.71 (2.71 to 50.61) | - |
| Reversed Peto Odds Ratio (95% CI) | 0.11 (0.03 to 0.43) | - | 0.09 (0.02 to 0.37) | - |
| p-value for Peto Odds Ratio | 0.0017 | | 0.0010 | |
| Risk Ratio (95% CI) vs Placebo[a] | 15.92 (1.00 to 253.33) | - | 16.80 (1.06 to 265.39) | - |
| Reversed Risk ratio (95% CI) | 0.06 (0.00 to 1.00) | - | 0.06 (0.00 to 0.94) | - |
| p-value for Risk Ratio[a] | 0.0499 | | 0.0451 | |
| Risk Difference (95% CI) vs Placebo[a] | 44.00 (NE to NE) | - | 52.63 (NE to NE) | - |
| p-value for Risk Difference[a] | <0.0001 | | <0.0001 | |
| Treatment-by-subgroup p-value[b] | | | | 0.9998 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

Tabelle 2-24: Grade ≥ 3 TEAE – PT= Lymphopenia – Per C-peptide level

| | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| **Safety population Lymphopenia** | **Teplizumab (N=20)** | **Placebo (N=18)** | **Teplizumab (N=24)** | **Placebo (N=14)** |
| Lymphopenia [n (%)] | | | | |
| Patients with any events [n(%)] | 9 (45.0) | 0 | 12 (50.0) | 0 |
| Patients without events [n(%)] | 11 (55.0) | 18 (100) | 12 (50.0) | 14 (100) |
| Odds Ratio (95% CI) vs Placebo[a] | 8.92 (1.23 to 64.51) | - | 11.38 (1.32 to 98.16) | - |
| p-value for Odds Ratio[a] | 0.0311 | | 0.0280 | |
| Peto Odds Ratio (95% CI) vs Placebo[a] | 11.29 (2.58 to 49.51) | - | 9.52 (2.35 to 38.57) | - |
| Reversed Peto Odds Ratio (95% CI) | 0.09 (0.02 to 0.39) | - | 0.11 (0.03 to 0.43) | - |
| p-value for Peto Odds Ratio | 0.0013 | | 0.0016 | |
| Risk Ratio (95% CI) vs Placebo[a] | 17.19 (1.07 to 275.79) | - | 15.00 (0.96 to 235.41) | - |
| Reversed Risk ratio (95% CI) | 0.06 (0.00 to 0.93) | - | 0.07 (0.00 to 1.05) | - |
| p-value for Risk Ratio[a] | 0.0446 | | 0.0539 | |
| Risk Difference (95% CI) vs Placebo[a] | 45.00 (NE to NE) | - | 50.00 (NE to NE) | - |
| p-value for Risk Difference[a] | <0.0001 | | <0.0001 | |
| Treatment-by-subgroup p-value[b] | | | | 0.9999 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

### 2.3.3 Grade ≥ 3 TEAE – SOC=Blood and lymphatic system disorders – Subgroup Analyses

Tabelle 2-25: Grade ≥ 3 TEAE – SOC=Blood and lymphatic system disorders – Per Age

| | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| **Safety population Blood and lymphatic system disorders** | **Teplizumab (N=29)** | **Placebo (N=26)** | **Teplizumab (N=15)** | **Placebo (N=6)** |
| Blood and lymphatic system disorders [n (%)] | | | | |
| Patients with any events [n(%)] | 10 (34.5) | 0 | 11 (73.3) | 0 |
| Patients without events [n(%)] | 19 (65.5) | 26 (100) | 4 (26.7) | 6 (100) |

| | Age (years) | | | |
|---|---|---|---|---|
| | < 18 (N=55) | | >= 18 (N=21) | |
| **Safety population Blood and lymphatic system disorders** | **Teplizumab (N=29)** | **Placebo (N=26)** | **Teplizumab (N=15)** | **Placebo (N=6)** |
| Odds Ratio (95% CI) vs Placebo[a] | 5.35 (1.03 to 27.85) | - | 35.41 (1.21 to 1039.27) | - |
| p-value for Odds Ratio[a] | 0.0464 | | 0.0396 | |
| Peto Odds Ratio (95% CI) vs Placebo[a] | 9.74 (2.50 to 37.93) | - | 16.44 (2.59 to 104.58) | - |
| Reversed Peto Odds Ratio (95% CI) | 0.10 (0.03 to 0.40) | - | 0.06 (0.01 to 0.39) | - |
| p-value for Peto Odds Ratio | 0.0010 | | 0.0030 | |
| Risk Ratio (95% CI) vs Placebo[a] | 18.90 (1.16 to 307.40) | - | 10.06 (0.68 to 148.02) | - |
| Reversed Risk ratio (95% CI) | 0.05 (0.00 to 0.86) | - | 0.10 (0.01 to 1.46) | - |
| p-value for Risk Ratio[a] | 0.0389 | | 0.0923 | |
| Risk Difference (95% CI) vs Placebo[a] | 34.48 (NE to NE) | - | 73.33 (NE to NE) | - |
| p-value for Risk Difference[a] | <0.0001 | | <0.0001 | |
| Treatment-by-subgroup p-value[b] | | | | 0.9993 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

## Tabelle 2-26: Grade ≥ 3 TEAE – SOC=Blood and lymphatic system disorders – Per Gender

| | Gender | | | |
|---|---|---|---|---|
| | Male (N=42) | | Female (N=34) | |
| **Safety population Blood and lymphatic system disorders** | **Teplizumab (N=25)** | **Placebo (N=17)** | **Teplizumab (N=19)** | **Placebo (N=15)** |
| Blood and lymphatic system disorders [n (%)] | | | | |
| Patients with any events [n(%)] | 11 (44.0) | 0 | 10 (52.6) | 0 |
| Patients without events [n(%)] | 14 (56.0) | 17 (100) | 9 (47.4) | 15 (100) |
| Odds Ratio (95% CI) vs Placebo[a] | 8.50 (1.18 to 61.31) | - | 12.94 (1.51 to 110.53) | - |
| p-value for Odds Ratio[a] | 0.0345 | | 0.0209 | |
| Peto Odds Ratio (95% CI) vs Placebo[a] | 9.23 (2.31 to 36.84) | - | 11.71 (2.71 to 50.61) | - |
| Reversed Peto Odds Ratio (95% CI) | 0.11 (0.03 to 0.43) | - | 0.09 (0.02 to 0.37) | - |
| p-value for Peto Odds Ratio | 0.0017 | | 0.0010 | |

| | Gender | | | |
|---|---|---|---|---|
| | Male (N=42) | | Female (N=34) | |
| **Safety population Blood and lymphatic system disorders** | **Teplizumab (N=25)** | **Placebo (N=17)** | **Teplizumab (N=19)** | **Placebo (N=15)** |
| Risk Ratio (95% CI) vs Placebo[a] | 15.92 (1.00 to 253.33) | - | 16.80 (1.06 to 265.39) | - |
| Reversed Risk ratio (95% CI) | 0.06 (0.00 to 1.00) | - | 0.06 (0.00 to 0.94) | - |
| p-value for Risk Ratio[a] | 0.0499 | | 0.0451 | |
| Risk Difference (95% CI) vs Placebo[a] | 44.00 (NE to NE) | - | 52.63 (NE to NE) | - |
| p-value for Risk Difference[a] | <0.0001 | | <0.0001 | |
| Treatment-by-subgroup p-value[b] | | | | 0.9998 |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.

## Tabelle 2-27: Grade ≥ 3 TEAE – SOC=Blood and lymphatic system disorders – Per C-peptide levels

| | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| **Safety population Blood and lymphatic system disorders** | **Teplizumab (N=20)** | **Placebo (N=18)** | **Teplizumab (N=24)** | **Placebo (N=14)** |
| Blood and lymphatic system disorders [n (%)] | | | | |
| Patients with any events [n(%)] | 9 (45.0) | 0 | 12 (50.0) | 0 |
| Patients without events [n(%)] | 11 (55.0) | 18 (100) | 12 (50.0) | 14 (100) |
| Odds Ratio (95% CI) vs Placebo[a] | 8.92 (1.23 to 64.51) | - | 11.38 (1.32 to 98.16) | - |
| p-value for Odds Ratio[a] | 0.0311 | | 0.0280 | |
| Peto Odds Ratio (95% CI) vs Placebo[a] | 11.29 (2.58 to 49.51) | - | 9.52 (2.35 to 38.57) | - |
| Reversed Peto Odds Ratio (95% CI) | 0.09 (0.02 to 0.39) | - | 0.11 (0.03 to 0.43) | - |
| p-value for Peto Odds Ratio | 0.0013 | | 0.0016 | |
| Risk Ratio (95% CI) vs Placebo[a] | 17.19 (1.07 to 275.79) | - | 15.00 (0.96 to 235.41) | - |
| Reversed Risk ratio (95% CI) | 0.06 (0.00 to 0.93) | - | 0.07 (0.00 to 1.05) | - |
| p-value for Risk Ratio[a] | 0.0446 | | 0.0539 | |
| Risk Difference (95% CI) vs Placebo[a] | 45.00 (NE to NE) | - | 50.00 (NE to NE) | - |
| p-value for Risk Difference[a] | <0.0001 | | <0.0001 | |
| Treatment-by-subgroup p-value[b] | | | | 0.9999 |

| | C-peptide level | | | |
|---|---|---|---|---|
| | < Median (N=38) | | >= Median (N=38) | |
| **Safety population** | **Teplizumab** | **Placebo** | **Teplizumab** | **Placebo** |
| **Blood and lymphatic system disorders** | **(N=20)** | **(N=18)** | **(N=24)** | **(N=14)** |

[a] Odds Ratio, Risk ratio, Risk Difference and related p-values are estimated by using a logistic regression with treatment effect for each modality of subgroup. For zero cells, Risk ratio and related p-value is estimated after zero cells correction applied (+0.5 for all cells in 2 x 2 table).

Peto OR calculation is based on Yusuf S et al. (Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71) and its p-value is derived using a normal approximation for each modality of subgroup.

[b] derived by using a generalized linear mixed model including treatment, subgroup, and treatment-by-subgroup interaction as covariate.

Note: system organ classes (SOCs) and preferred terms are based on MedDRA version 23.0.