TEPLIZUMAB FOR THE DELAY OF CLINICAL TYPE 1 DIABETES IN AT-RISK INDIVIDUALS

ERRATA FOR SPONSOR BRIEFING DOCUMENT

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

MEETING DATE: 27 MAY 2021

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

1. The indication was revised to remove "progression" throughout the document (pages 1, 10, 11, 12, 14, 21, 23, 24, 29, 34, 36, 92, 93) to align with the Agency's recommendation.

Original text:

Teplizumab for the delay of progression to clinical type 1 diabetes (T1D) in at-risk patients.

Revised text:

Teplizumab for the delay of clinical type 1 diabetes in at-risk individuals.

2. The number of patients who withdrew consent was incorrectly reported in the Executive summary on page 13 and in Section 6.1.2.1.

Executive Summary:

Original text:

Of the remaining 3 patients, 2 withdrew consent (~~1 teplizumab, 1 placebo~~) and 1 was lost to follow-up (placebo); these 3 patients were censored from the primary analysis.

Revised text:

Of the remaining 3 patients, 2 withdrew consent (**teplizumab**) and 1 was lost to follow-up (placebo); these 3 patients were censored from the primary analysis.

Section 6.1.2.1:

Original text:

The other 3 premature study discontinuations were due to lost to follow-up (1 placebo) and withdrawal of consent (~~1 placebo and 1 teplizumab~~).

Revised text:

The other 3 premature study discontinuations were due to lost to follow-up (1 placebo) and withdrawal of consent (**2 teplizumab)**.

3. In Section 6.1.2.4, Table 6, the first row header was changed from "Glucose AUC in OGTT" to "Glucose, random." In addition, the normal range for C-peptide levels was corrected.

Original table:

Table 6: TN-10: Baseline T1D-Related Clinical Characteristics (ITT Population)

	Teplizumab N=44	Placebo N=32	Normal Range
Glucose ~~**AUC in OGTT**~~, mg/dL			<180 mg/dL
mean (SD)	162.5 (22.29)	155.3 (22.94)	
median (min, max)	164.6 (115, 207)	154.4 (103, 200)	
Glucose, fasting, mg/dL			<100 mg/dL
mean (SD)	97.4	109.5	
median (min, max)	94.5 (70, 168)	101 (79, 198)	
C-peptide AUC in OGTT, nmol/L			~~**0.5 to 2.0 nmol/L**~~
mean (SD)	1.98 (0.85)	1.89 (0.72)	
median (min, max)	1.77 (0.6, 4.4)	1.73 (0.7, 3.8)	
HbA1c, %			<5.7%
mean (SD)	5.16 (0.33)	5.21 (0.26)	
median (min, max)	5.2 (4.6, 6.1)	5.3 (4.3, 5.6)	

Abbreviations: AUC=area under the concentration-time curve, HbA1c=hemoglobin A1c, ITT=intent-to-treat, OGTT=oral glucose tolerance test, SD=standard deviation

Revised table:

Table 6: TN-10: Baseline T1D-Related Clinical Characteristics (ITT Population)

	Teplizumab N=44	Placebo N=32	Normal Range
Glucose, **random**, mg/dL			<180 mg/dL
mean (SD)	162.5 (22.29)	155.3 (22.94)	
median (min, max)	164.6 (115, 207)	154.4 (103, 200)	
Glucose, fasting mg/dL			<100 mg/dL
mean (SD)	97.4	109.5	
median (min, max)	94.5 (70, 168)	96.5 (45, 120)	
C-peptide AUC in OGTT, nmol/L			**1.2 to 3.3 nmol/L***
mean (SD)	1.98 (0.85)	1.89 (0.72)	
median (min, max)	1.77 (0.6, 4.4)	1.73 (0.7, 3.8)	
HbA1c, %			<5.7%
mean (SD)	5.16 (0.33)	5.21 (0.26)	
median (min, max)	5.2 (4.6, 6.1)	5.3 (4.3, 5.6)	

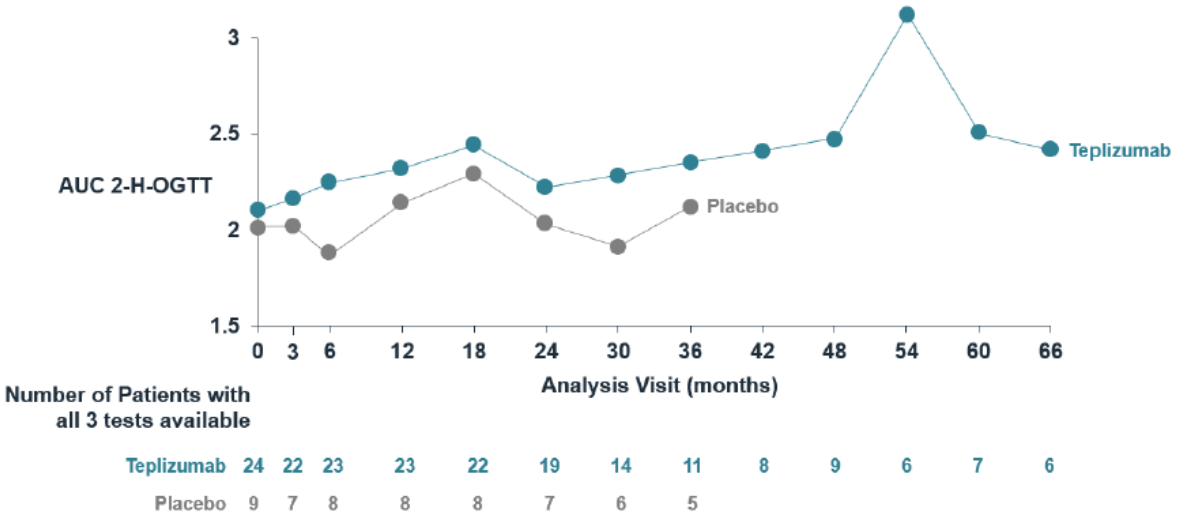
Abbreviations: AUC=area under the concentration-time curve, HbA1c=hemoglobin A1c, ITT=intent-to-treat, OGTT=oral glucose tolerance test, SD=standard deviation

*K. Herold, TrialNet data.

4. Figure 16 was revised to change "Number of Patients with all 3 tests available" to "Number of Patients Available".

Original figure:

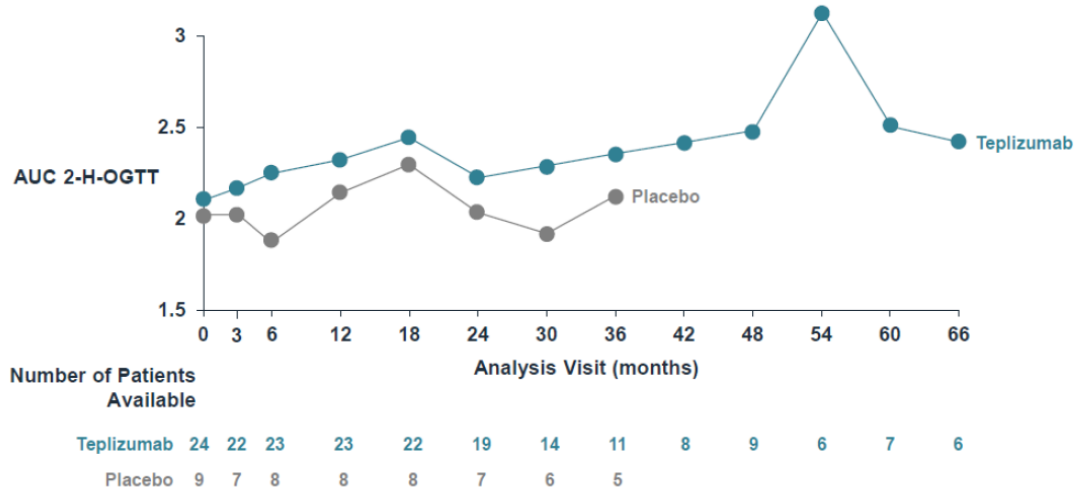
Figure 16: TN-10: C-Peptide AUCs (nmol/L) in Patients without T1D



Abbreviations: AUC=area under the concentration-time curve, T1D=type 1 diabetes, 2-H-OGTT= 2-hour oral glucose tolerance test

Revised figure:

Figure 16: TN-10: C-Peptide AUCs (nmol/L) in Patients without T1D

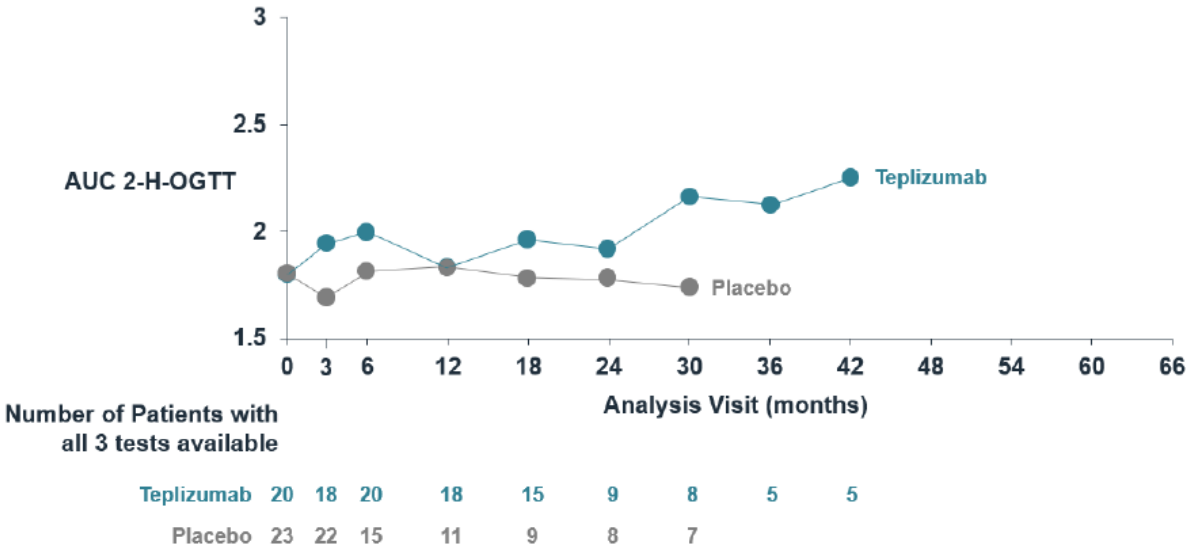


Abbreviations: AUC=area under the concentration-time curve, T1D=type 1 diabetes, 2-H-OGTT= 2-hour oral glucose tolerance test

5. Figure 17 was revised to change ""Number of Patients with all 3 tests available" to "Number of Patients Available".

Original figure:

Figure 17: TN-10: C-Peptide AUCs (nmol/L) in Patients with T1D



Abbreviations: AUC=area under the concentration-time curve, T1D=type 1 diabetes, 2-H-OGTT= 2-hour oral glucose tolerance test

Revised figure:

Figure 17: TN-10: C-Peptide AUCs (nmol/L) in Patients with T1D

Abbreviations: AUC=area under the concentration-time curve, T1D=type 1 diabetes, 2-H-OGTT= 2-hour oral glucose tolerance test

6. In Table 14, the p-value for the control-based sensitivity analysis of the 1-year follow up data was incorrect. The original and revised tables are presented below.

Original table:

Table 1: Supportive Studies: Predicted Mean Difference Between Teplizumab and Control in the Change from Baseline in C-peptide ln(AUC+1) (nmol/L) at 1-Year Follow-up

	Change from Baseline (nmol/L)		Difference in Change from Baseline (nmol/L)		
	Teplizumab LSM (SE)	Control LSM (SE)	LSM (SE)	95% CI	p-value
Observed data	-0.0569 (0.01386)	-0.1380 (0.01513)	0.0811 (0.02042)	0.041, 0.121	<0.0001
Imputed data	-0.0537 (0.01339)	-0.1433 (0.0149)	0.0896 (0.02026)	0.050, 0.129	<0.0001
Sensitivity: Control-based	-0.0626 (0.0152)	-0.1466 (0.01758)	0.0840 (0.02094)	0.043, 0.125	~~0.0001~~

Note: C-peptide AUC data at 1-year follow-up were obtained from all 5 studies: Protégé, Encore, Study 1, AbATE, and Delay.Abbreviations: AUC=area under the concentration-time curve, CI=confidence interval, LSM=least squares mean, SE=standard error.

Revised table:

Table 2: Supportive Studies: Predicted Mean Difference Between Teplizumab and Control in the Change from Baseline in C-peptide ln(AUC+1) (nmol/L) at 1-Year Follow-up

	Change from Baseline (nmol/L)		Difference in Change from Baseline (nmol/L)		
	Teplizumab LSM (SE)	Control LSM (SE)	LSM (SE)	95% CI	p-value
Observed data	-0.0569 (0.01386)	-0.1380 (0.01513)	0.0811 (0.02042)	0.041, 0.121	<0.0001
Imputed data	-0.0537 (0.01339)	-0.1433 (0.0149)	0.0896 (0.02026)	0.050, 0.129	<0.0001
Sensitivity: Control-based	-0.0626 (0.0152)	-0.1466 (0.01758)	0.0840 (0.02094)	0.043, 0.125	**<0.0001**

Note: C-peptide AUC data at 1-year follow-up were obtained from all 5 studies: Protégé, Encore, Study 1, AbATE, and Delay.Abbreviations: AUC=area under the concentration-time curve, CI=confidence interval, LSM=least squares mean, SE=standard error.

7. In Table 15, the p-value for the control-based sensitivity analysis of the 1-year follow up data was incorrect. The original and revised tables are presented below.

Original table:

Table 3: Supportive Studies: Predicted Mean Difference Between Teplizumab and Control in the Change from Baseline in C-peptide ln(AUC+1) (nmol/L) at 2-Years Follow-up

	Change from Baseline (nmol/L)		Difference in Change from Baseline (nmol/L)		
	Teplizumab LSM (SE)	Control LSM (SE)	LSM (SE)	95% CI	p-value
Observed data	-0.1334 (0.0168)	-0.2516 (0.02158)	0.1182 (0.02710)	0.065, 0.172	<0.0001
Imputed data	-0.1434 (0.0169)	-0.2476 (0.0211)	0.1042 (0.02660)	0.052, 0.156	<0.0001
Sensitivity: Control-based	-0.1471 (0.018)	-0.254 (0.023)	0.1069 (0.02793)	0.052, 0.162	~~<0.0001~~

Note: C-peptide AUC data at 2-year follow-up were obtained from 3 studies that had 2-year data: Protégé, Study 1, and AbATE. Abbreviations: AUC=area under the concentration-time curve, CI=confidence interval, LSM=least squares mean, SE=standard error.

Revised table:

Table 4: Supportive Studies: Predicted Mean Difference Between Teplizumab and Control in the Change from Baseline in C-peptide ln(AUC+1) (nmol/L) at 2-Years Follow-up

	Change from Baseline (nmol/L)		Difference in Change from Baseline (nmol/L)		
	Teplizumab LSM (SE)	Control LSM (SE)	LSM (SE)	95% CI	p-value
Observed data	-0.1334 (0.0168)	-0.2516 (0.02158)	0.1182 (0.02710)	0.065, 0.172	<0.0001
Imputed data	-0.1434 (0.0169)	-0.2476 (0.0211)	0.1042 (0.02660)	0.052, 0.156	<0.0001
Sensitivity: Control-based	-0.1471 (0.018)	-0.254 (0.023)	0.1069 (0.02793)	0.052, 0.162	**0.0001**

Note: C-peptide AUC data at 2-year follow-up were obtained from 3 studies that had 2-year data: Protégé, Study 1, and AbATE. Abbreviations: AUC=area under the concentration-time curve, CI=confidence interval, LSM=least squares mean, SE=standard error.

8. The first paragraph of Section 7.8 was revised to delete the patient ID.

Original Text:

In the 5 studies included in the pooled analysis, one case of metastatic melanoma (~~Protégé~~ (b) (6)) was reported. This was a case of metastatic melanoma in a pre-existing lesion that was not diagnosed until after entering the study in a subject who had a history of dysplastic nevi. The subject underwent excision of the lesion and was in full remission 2 years post-excision, and there has been no recurrence of metastatic malignant melanoma (see Appendix 10.3).

Revised Text:

In the 5 studies included in the pooled analysis, one case of metastatic melanoma was reported **in the Protégé study**. This was a case of metastatic melanoma in a pre-existing lesion that was not diagnosed until after entering the study in a patient who had a history of dysplastic nevi. The subject underwent excision of the lesion and was in full remission 2 years post-excision, and there has been no recurrence of metastatic malignant melanoma (see Appendix 10.3).

9. Clarification on Section 5.2.3 Biocomparability Study to Support Commercial Drug Product

The biocomparability study had two pre-specified primary endpoints: Cmax and AUC0-inf. The Sponsor notes that AUC0-inf could not be reliably determined according to pre-specified standard criteria, and was not included in the body of the study report. Individual values were provided, but only 9 out of 51 and 2 out of 49 subjects in the test and reference groups, respectively, had reliable values.

By contrast, partial AUCs were reliably calculated to evaluate teplizumab exposure, which revealed that the exposure in the test product group, relative to the reference product, was 79.2% at 24 hours, or AUC0-24, in the Sponsor's view a relevant time frame for a daily IV infusion product.