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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	BLA 761183
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Submission Date	17 Feb 2022
Submission Type	Resubmission 351(a), Priority review
Brand Name	Tzield
Generic Name	Teplizumab
Dosage Form and Strength	Solution and 1 mg/mL
Route of Administration	Intravenous infusion
Proposed Indication	Delay of clinical type 1 diabetes in at-risk individuals
Applicant	Provention Bio, Inc.
Associated IND	102629 and 100262
OCP Review Team	Harisudhan Thanukrishnan Ph.D., Elyes Dahmane Ph.D., Justin Earp Ph.D., Jayabharathi Vaidyanathan Ph.D., Hao Zhu Ph.D.
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1. EXECUTIVE SUMMARY

Teplizumab-mzwv (Tzield, called teplizumab in this review) is a first-in-class humanized anti-CD3 monoclonal antibody proposed to delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D.

The initial Biologics Licensing Application (BLA) was received on November 2, 2020, and the original clinical pharmacology review for this BLA is available in DARRTS, dated April 30, 2021. At the end of the first review cycle, recommendations were issued in a Complete Response (CR) action letter dated July 2, 2021. The main deficiency identified by OCP in the CR letter pertained to the lack of demonstration of comparability between the to-be-marketed drug product (AGC Biologics product) and the drug product used in clinical trials including the TN-10 study (Eli Lilly product). The AGC Biologics product had about 50% lower AUCinf as compared to the Eli Lilly product in the single dose comparability study.

In response to the CR (this submission), Provention Bio submitted results from the pharmacokinetic (PK) sub study of the ongoing PROTECT study in which new-onset T1D patients (8-17 years of age) received either placebo or one of the teplizumab products (Eli Lilly (N=138) or AGC Biologics (N=33)) during the 12-day regimen of Course 1. Sparse PK samples were obtained from subjects, and a population PK model was used to predict the primary PK parameters for teplizumab corresponding to the 12-day dosing, which was used for further assessment of PK comparability between the products. The clinical pharmacology review of this resubmission is focused on (a) evaluating if the results from the PROTECT PK sub study are adequate to address the main deficiency identified in the CR and are supportive of the PK comparability between the two teplizumab products and (b) evaluating if the proposed dosing recommendation for the to-be-marketed AGC product is appropriate.

The to-be-marketed product (AGC Biologics) is estimated to result in a 27% lower total exposure (AUCinf) than the clinical trial product (Eli Lilly) after the 12-day dosing regimen in the PROTECT study based on the population PK analysis. PK comparability was not considered established between the products, as the point estimates for AUC_{last} and AUC_{inf} were 0.74 and 0.78, respectively and the 90% confidence intervals fell outside of the standard 0.8-1.25 margin, despite the similar C_{max} (point estimate was 0.85).

From an analytical perspective, except for minor structural differences such as in the [redacted] profile [redacted] % for Eli Lilly and [redacted]% for AGC Biologics), the OBP review did not identify any major known analytical differences that could have accounted for the PK differences. Their review concludes that the products were analytically comparable. Results of the CD3 receptor occupancy which were obtained in a subset of patients in the PROTECT PK/PD sub study were suggestive of comparable target engagement response between the products

and were aligned with the observed analytical comparability between the products. However, the relationship between CD3 occupancy and efficacy is unclear and the relationship between the observed PK difference and its potential effect on efficacy is unknown. Therefore, exposure matching between teplizumab products was proposed to address the residual uncertainties about differences in clinical effect. The OCP team recommended that the Applicant propose an alternative 14-day regimen with a higher cumulative dose for the to-be-marketed product with the aim of matching the exposure between the clinical trial product (Eli Lilly) and to-be-marketed product (AGC). The proposed adjusted dosing regimen for the AGC product sought to match the total exposure (AUC_{inf}), peak concentration ($C_{max\ after\ the\ last\ dose}$) as well as trough concentrations after the last dose ($C_{trough\ after\ the\ last\ dose}$) in comparison to the clinical trial product during the 14-day regimen.

Overall, the OCP team has reviewed the information from the PROTECT PK sub study including the acceptability of the updated population PK modelling in describing and predicting the PK from teplizumab products, conclusions regarding the analytical comparability, the available supporting information on CD3 receptor occupancy, and applied the totality of evidence approach in providing the final recommendations for the approval of the to-be-marketed product with a modified dosing regimen.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the BLA 761183 and recommend approval of a single 14-day course of teplizumab for delaying the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D. The recommended dosing regimen is daily intravenous infusions as follows:

Day 1	65 µg/m^2
Day 2	125 µg/m^2
Day 3	250 µg/m^2
Day 4	500 µg/m^2
Days 5-14	1030 µg/m^2

1.2 Post-Marketing Requirements and Commitments

No post-marketing requirements or commitments are needed from clinical pharmacology perspective.

1.3 Outstanding Issues

Two different teplizumab products were given at the same dose and resulted in similar C_{max} but demonstrated differences in clearance in both the single dose healthy volunteer study and the PROTECT sub-study. Both the Eli Lilly and AGC Biologics drug substance batches were manufactured from identical cell lines (working cell banks derived from the same master cell

bank) using substantially similar manufacturing processes and were reported to be analytically comparable. The root-cause analysis by Applicant was unable to provide a rationale for the difference in clearance between the drug products.

1.4 Summary of Labeling Recommendations

General labeling recommendations were provided to improve the clarity and relevance of clinical pharmacology information conveyed to the healthcare provider. In addition, the following labeling edits were recommended for inclusion in the final package insert.

- Section 2.2- The Applicant proposed dosing regimen was recommended to be updated with the revised dosing regimen (outlined in Section 1.1) based on exposure matching. [redacted] (b) (4) was removed to avoid confusion
- Section 12.1- Mechanism of action clarified by replacing [redacted] (b) (4) with "delays T1D"
- Section 12.2- Included a statement "exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of teplizumab-mzwv have not been fully characterized"

2. Background and Regulatory History

Teplizumab (PRV-031) is a 150 kiloDalton (kDa) humanized immunoglobin G1 (IgG1) monoclonal antibody (mAb) that specifically recognizes the CD3ε chain of the T-cell receptor complex on human T cells. The initial drug substance (DS) was manufactured by MacroGenics from 2005-2008, which continued in partnership with Eli Lilly for another year and later, the DS was solely manufactured by Eli Lilly until 2011. After 2018, the Applicant updated manufacturing process to a new facility operated by AGC Biologics. In addition to analytical comparability assessments, the Applicant conducted a double-blind, single, low-dose pharmacokinetics (PK) bridging study in healthy subjects (Study PRV-031-004) with teplizumab clinical material (Eli Lilly) and the planned commercial drug product (AGC Biologics).

The results of study PRV-031-004 failed to show PK comparability between the PRV-031 product used in TN-10 and the planned commercial product. Study PRV-031-004 revealed differences in the total area under the time-concentration curve extrapolated to infinity (AUC_{0-inf}) between the two products, with the planned commercial product providing a 51.5% lower AUC_{0-inf} (geometric mean ratio [90%CI] = 48.5% [43.6 - 54.1]), despite a comparable C_{max} after a single intravenous infusion dose of 207 μg/m^2. The submission received a complete response (CR) due to lack of a comparability demonstration between the to-be-marketed product and the clinical product. As PK serves as the primary endpoint for demonstration of comparability between the two products (as there was demonstrated analytical comparability), the Applicant

was asked to establish PK comparability appropriately between the intended commercial product and the clinical trial product or provide other data that adequately justify why PK comparability is not necessary. The applicant provided additional PK and PD data from the ongoing PROTECT study along with a newly proposed dosing regimen that included higher doses of the AGC product in order to match the exposures resulting from the Eli Lilly product.

2.1 Summary of prior clinical pharmacology assessment for the original BLA

The general pharmacology and pharmacokinetic characteristics of teplizumab were summarized in Section 3.2 in the Clinical pharmacology review for the original BLA (Refer to the clinical pharmacology review documented in DARRTS dated 4/30/2021).

Highlights of previous assessments are provided below:

- Applicant proposed a body surface area (BSA) based single 14-day course of teplizumab administered as a daily IV infusion over 30 minutes. Less than 10% of the total dose is given on the first 4 days of ramp-up as a precaution to avoid adverse reactions, e.g., cytokine release syndrome. Exposure to teplizumab after BSA-based regimen was found to be independent of age and body weight.
- The average accumulation ratio for AUC between Day 5 and Day 14 (the first and the last day with the full dose administration) is predicted to be 3.4. Steady state is not expected to be achieved at the end of dosing on Day 14.
- No therapeutic individualization is warranted for teplizumab based on intrinsic or extrinsic factors. Teplizumab is expected to be catabolized into smaller peptides.
- The single 14-day course administering a total of 9 mg/m^2 teplizumab dose was the only dosing regimen that was evaluated in the pivotal study (TN-10), which also was the single pivotal study that evaluated teplizumab for the proposed indication- delay in subjects at-risk for type 1 diabetes. The proposed dosing regimen is supported by delayed time to Stage 3 (clinical T1D) in the TN-10 study, as the median times to T1D was significantly delayed in teplizumab treated subjects (48.4 vs 24.4 months in the placebo) which resulted in lower annualized rates of clinical T1D development (14.9% vs 35.9% per year for the teplizumab and placebo groups, respectively).
- A single dose PK study (PRV-031-004) did not support the comparability of the commercial to-be-marketed drug product (AGC Biologics) with the clinical trial product (Eli Lilly).

2.2 Regulatory interactions prior to Resubmission

The key regulatory interactions with Applicant are summarized below:

- July 27, 2021- Applicant submitted an amendment for the ongoing PROTECT (PRV-031-001) study including the proposed protocol for the PK/PD sub study and the statistical analysis plan to provide the complete response and resubmission for the BLA.
- August 06, 2021- Advice letter was issued with recommendation for the pre-specification of the population pharmacokinetic model and analysis plan prior to the unblinding of the results for PK/PD sub study
- September 03, 2021- Feedback was provided on the pharmacometric modeling plan to estimate the PK parameters and statistical analysis plan
- Nov 18, 2021- Feedback was provided on the Stage 1 of the POPPK modeling and considerations for the Stage 2 of the model to estimate the PK parameters using sparse data from PROTECT study
- January 25, 2022- Feedback was provided on the clinical pharmacology data package for the BLA 761183 resubmission.
- February 17, 2022- BLA resubmission with PK, PD and immunogenicity data from the PROTECT sub study to compare both the teplizumab products following a 12-day dosing regimen in T1D patients
- June 10, 2022- Midcycle communication was sent to Applicant stating the need for an alternative dosing regimen to meet the pharmacokinetic equivalence criterion between the products.
- June 29, 2022- Applicant was notified of a major amendment due to revised analyses with updated ADA data and an extension in PDUFA goal date by 3 months to Nov 17, 2022.

2.3 Summary of clinical pharmacology assessment for the BLA Resubmission

The PROTECT PK/PD sub study was the focus of this resubmission. Based on the review of the PK comparability data from the PROTECT PK/PD sub study, the to-be-marketed product (AGC Biologics) was estimated to result in around 27% lower total exposure (AUC_{inf}) than the clinical trial product (Eli Lilly) after the 12-day dosing regimen. Though the PK comparison using AUC_{last} and AUC_{inf} fell outside of the standard 0.8-1.25 margin, it was observed that the point estimates for the comparisons (0.74 and 0.78, respectively) were closer to the lower cut off value of 0.8, following the clinically relevant multiple dose regimen that was employed in the PROTECT study, as compared with a single dose.

To further understand if the PK difference was due to any underlying quality related changes/issues, the Office of Biotechnology products (OBP) was consulted about the results from the analytical assessments for both the products (structural and functional comparability). As per OBP review of this original submission and resubmission, the available data was not indicative of any quality differences that could lead to the PK differences and OBP concluded that the products were analytically comparable. OBP acknowledged minor structural

differences in the (b) (4) profile ((b) (4) % for Eli Lilly and (b) (4) % for AGC Biologics), which however was not considered as a potential driver of the PK difference based on available literature and OBP experience.

The review team is of the opinion that immunogenicity of teplizumab was unlikely to play any role in its clearance (or in the difference in clearance between the products), given that the appearance of anti-drug antibodies (ADA) is delayed beyond the time during which difference in serum concentrations of teplizumab was observed, both in the single dose and the PK/PD sub study. The cross-disciplinary review teams including OBP (Quality review in DAARTS dated 14 May 2021 and 19 Oct 2022) and OCP acknowledge that no identifiable reasons are available for explaining the PK difference between the teplizumab products observed in both studies.

Prior to resubmission, the Applicant was also encouraged to obtain possible in vivo (or PD) markers that may be useful for evaluation as orthogonal markers to the PK and could facilitate the comprehensive assessment of the comparability between the products. The OCP review team also considered exploratory markers that were obtained in the PK/PD study such as the CD3 receptor occupancy of teplizumab and the post-dosing decline in lymphocyte counts, as supportive information for the in vivo comparability assessment. The CD3 receptor occupancy (binding) for teplizumab is a measure of its target engagement on T cells. The binding results in the sub study was characterized by an increase in the CD3 occupancy by teplizumab, in parallel to the higher serum concentrations of teplizumab achieved after the repeated dosing. This data was reassuring for the utility of CD3 binding as a supporting PD marker for assessment of comparability, as CD3 binding is upstream in the proposed mechanism of action for teplizumab and is apparently sensitive to changes in the serum levels of the biologic. Both the products showed similar receptor occupancy when examined on different days of the regimen. In the consolidated scatter plot analysis (Figure 6), the relationship of CD3 occupancy vs concentrations, spanning a broad range of teplizumab concentrations, was similar between the two teplizumab products. Though not a primary PD marker of interest, the overall profile in the decline and recovery in lymphocyte counts was also superimposable for both the products.

It is acknowledged that there is uncertainty with respect to the relationship of the PD markers to long-term drug effect or clinical outcome. However, based on what is known about the mechanism of action of teplizumab, the markers, especially CD3 binding may be able to provide supportive evidence as orthogonal tests for the functional bio comparability and given that, the data was suggestive of a similarity in target engagement response between the products.

The OCP team recommended that the Applicant should propose an alternative 14-day regimen for the to-be-marketed product and thereby match the PK between the clinical and to-be-marketed products. This recommendation to match the PK between the products by using dose adjustment was based on careful considerations to the following aspects:

a. Analytical comparability was confirmed between the two products. The residual uncertainty in the PK difference could be addressed with a dose adjustment.
b. Feasibility for predicting a dose for adjustment. The population PK model was considered reliable to describe the PK and simulate the doses for exposure-matching of teplizumab and the clearance of teplizumab is likely not saturated.
c. Evidence for a comparable *in-vitro* as well as *in-vivo* target engagement between the products was available via CD3 receptor occupancy data from the PROTECT sub-study, in support of the analytical comparability results.

Furthermore, based on the population PK analysis characterizing the PK of teplizumab products from the different studies, the AGC product has a saturable binding to target CD3 receptors but no target-mediated elimination through intracellular internalization, suggesting that the AGC product has linear non-specific elimination. Therefore, the increase in AGC product dosage is not expected to saturate the elimination of teplizumab.

3. Clinical Pharmacology Questions

3.1 Do the results from the PROTECT sub study support PK comparability between the teplizumab products?

PK comparability was not observed between the teplizumab products in the PROTECT sub-study as per the standard bioequivalence (BE) criterion (0.8-1.25).

The reviewer's evaluation of the PK comparability between the AGC product and the Lilly product in the PROTECT sub-study found that the AGC product had 27% and 22% lower AUCinf and Ctrough (after last dose) than the Lilly product, respectively.

Table 1 summarizes the point estimates for the GLSMs, ratio of GLSMs and 90% CI for the PK parameters that were predicted using population pharmacokinetic model (popPK) in the patients that received AGC biologics or Eli Lilly products. The PK parameters were not predictable for one participant in each group due to lack of adequate post-dose sampling time points for the popPK analysis.

Table 1. Comparison of the Observed and Model-Predicted PK Exposure Metrics from PROTECT Sub-Study, under the Planned PROTECT Study Regimen and Duration of Infusion

Predicted (Otherwise mentioned) PK exposure metrics	**Reviewer's evaluation**		
	AGC [n=32] GM [a] (%CV)	**Lilly [n=137] GM (%CV)**	**GMR (90% CI) [a]**
Cmax after last dose (ng/mL)	745 (12%)	872 (13%)	0.854 (0.821 - 0.89)
AUC(0-Tlast) [b] (ng*day/mL)	2797 (19%)	3598 (19%)	0.777 (0.732 - 0.826)
AUCinf [c] (ng*day/mL)	4528 (22%)	6176 (25%)	0.733 (0.678 - 0.792)
Observed Cmin before last dose (Day 12) [number of observations] [d]	287 (45%) [n=26]	368 (38%) [n=120]	0.78 (0.682 - 0.893)
Cmin before last dose (Day 12)	251 (30%)	373 (29%)	0.674 (0.614 - 0.740)
Cmin after last dose (Day 13)	265 (30%)	400 (30%)	0.664 (0.604 - 0.730)

[a] GM: geometric mean, GMR (90%CI): geometric mean ratio (90% confidence interval), derived from Student's t-test (with Levene Test for equality of variances) on natural log-transformed PK exposure metrics.

[b] AUC(0-Tlast): Tlast represents 24 hours after the last planned dose (Dose 12), calculated using the trapezoidal linear-up and log-down method.

[c] AUCinf: calculated using the trapezoidal linear-up and log-down method.

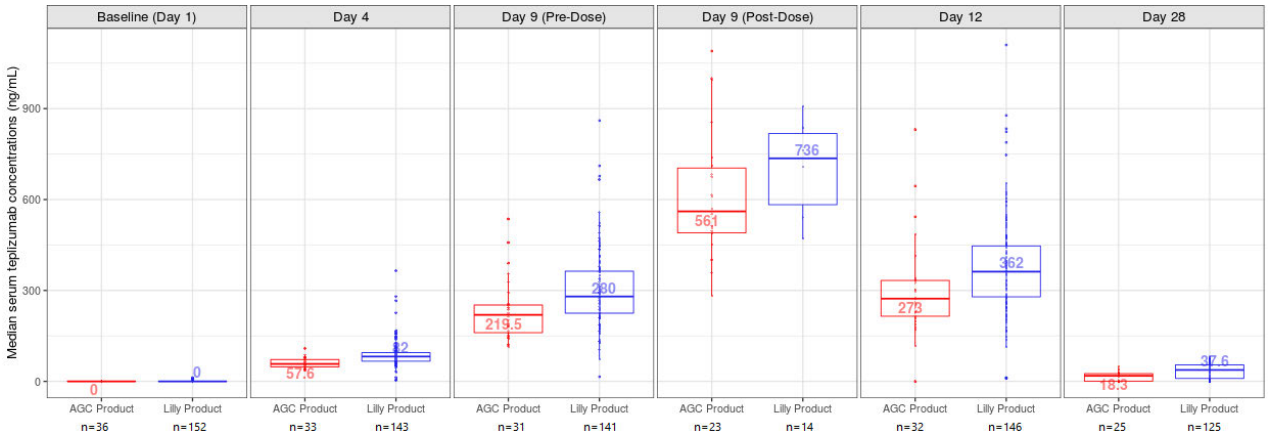
[d] Observed Cmin before last dose (Day 12) in patients who received all their 11 doses.

Source: FDA reviewer

The $AUC_{0\text{-}Day13}$ for teplizumab was also lower for the AGC product, albeit the difference was closer to the lower bioequivalence limit of 80%, when compared to the observed difference in the previous single dose study. As observed earlier in the single dose healthy volunteer study, there was no difference in predicted C_{max} after the last intravenous dose on Day 12.

A comparison of the observed trough concentrations between the two products, corresponding to the sparse sampling times is shown in Figure 1. The average teplizumab serum concentrations were lower for the AGC arm at all the observed time points.

Figure 1. Comparison of observed serum concentrations of teplizumab by product in PROTECT sub study

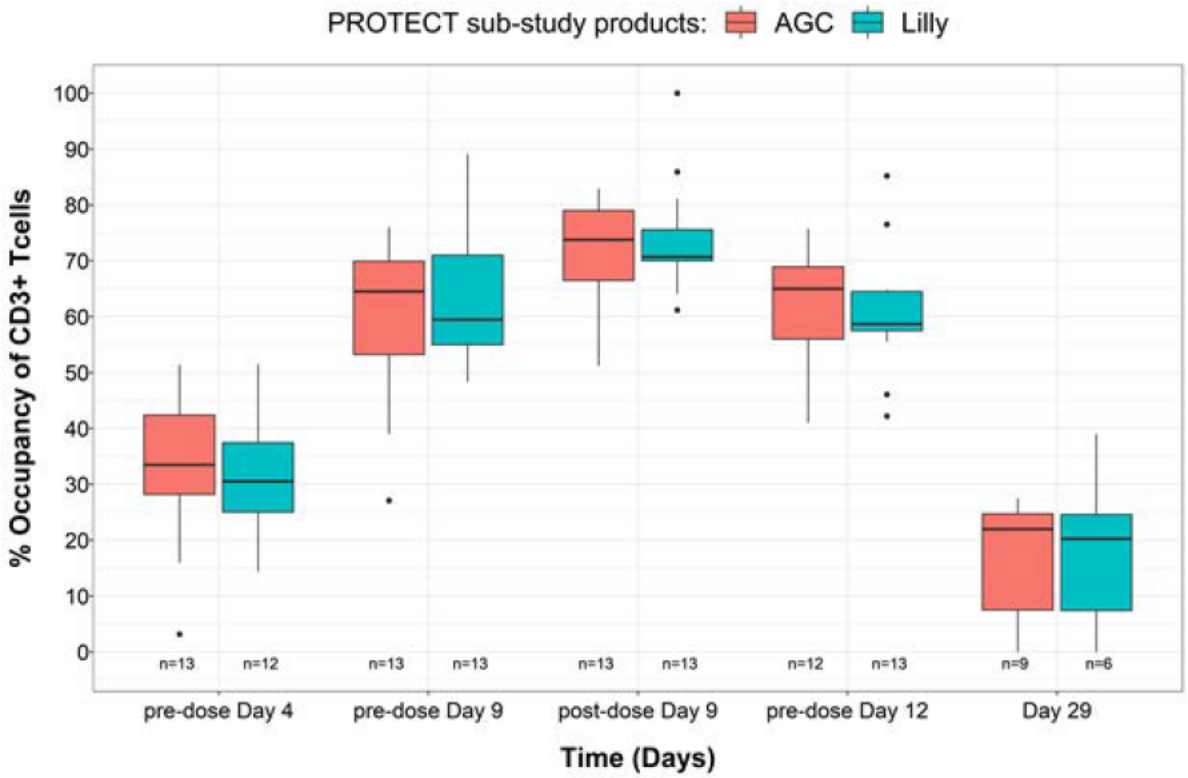


#Observations include samples in patients with missing doses and not completing the 12-day regimen; Values that were below the lower limit of quantification were replaced by zero

Source: FDA reviewer

The results for comparison of the CD3 receptor occupancy (coating) by teplizumab products is shown in Figure 2. The results were obtained from a subset of the population that provided PK samples in the PK/PD sub study and corresponds to the North American sites only. The CD3 coating at pre-dose on Day 4 (following the ramp-up doses and one full dose of 850 µg/m^2) was almost one half of the coating at pre-dose on Day 9 (following the ramp-up doses and six full doses of 850 µg/m^2). Subsequent value for CD3 obtained at pre-dose on Day 12 was almost comparable to values on Day 9, indicating a baseline threshold that was achieved for the CD3 coating within a dosing interval.

Figure 2. Teplizumab Occupancy (%) on CD3+ T Cells by Product in the PROTECT sub study



Note: the last planned sampling day for CD3+ occupancy assessment was variable and was restricted to sampling times ranging for Day 29 to Day 30 for adequate comparison.
Source: FDA reviewer (based on the lasted combined PD dataset pkpdnonmemprotect17feb22.xpt)

The CD3 coating by teplizumab at around 45 minutes following the end of infusion on Day 9 was higher by around 10% on an average, compared to the CD3 coating at pre-dose baseline on Days 9 or 12, while the corresponding serum concentrations of teplizumab were around 2-2.5-fold higher than the pre-dose baseline concentration. This was indicative of a less sensitive change in the CD3 coating in response to changes in the serum concentrations within a dosing interval following a repeat daily dosing. Overall, the CD3 coating by teplizumab was found to be comparable between the two products.

A similar trend of comparable coating for both products was also observed when the receptor occupancy for the T-cell subsets, CD4 and CD8 were examined. Despite the PK differences, the CD3 receptor occupancy that was explored in parallel provided support for the comparability in the in vivo target binding between the two products. Neither the clinical relevance of the lower exposure of teplizumab nor the CD3 occupancy are clearly established as neither of them were available to be evaluated against the delay of T1D in the target population. However, addressing and correcting the PK difference by increasing the proposed dose would help to lower the residual uncertainty that exists in the relationship between PD markers and long-term clinical outcome.

3.2 Is an alternative dosing regimen necessary and appropriate for the AGC Biologics product?

Through population PK simulations, the Applicant evaluated 3 alternative dosing regimens for the AGC product (Table 2), with regimen A being the Applicant's preferred regimen in order to match the exposure from the Lilly product (under the reference 14-day regimen). In comparison to the dosing regimens (A, B and C) proposed by the Applicant, an alternate regimen proposed by the review team (regimen D: 65 – 125 – 250 – 500 – (1030 x 10 days) µg/m2) was considered most appropriate for the AGC product

Table 2 summarizes the alternative dosing regimens proposed by the Applicant to match exposures between the AGC product and Lilly product.

Table 2. Applicant's Proposed Alternative Regimens A, B and C for the AGC product

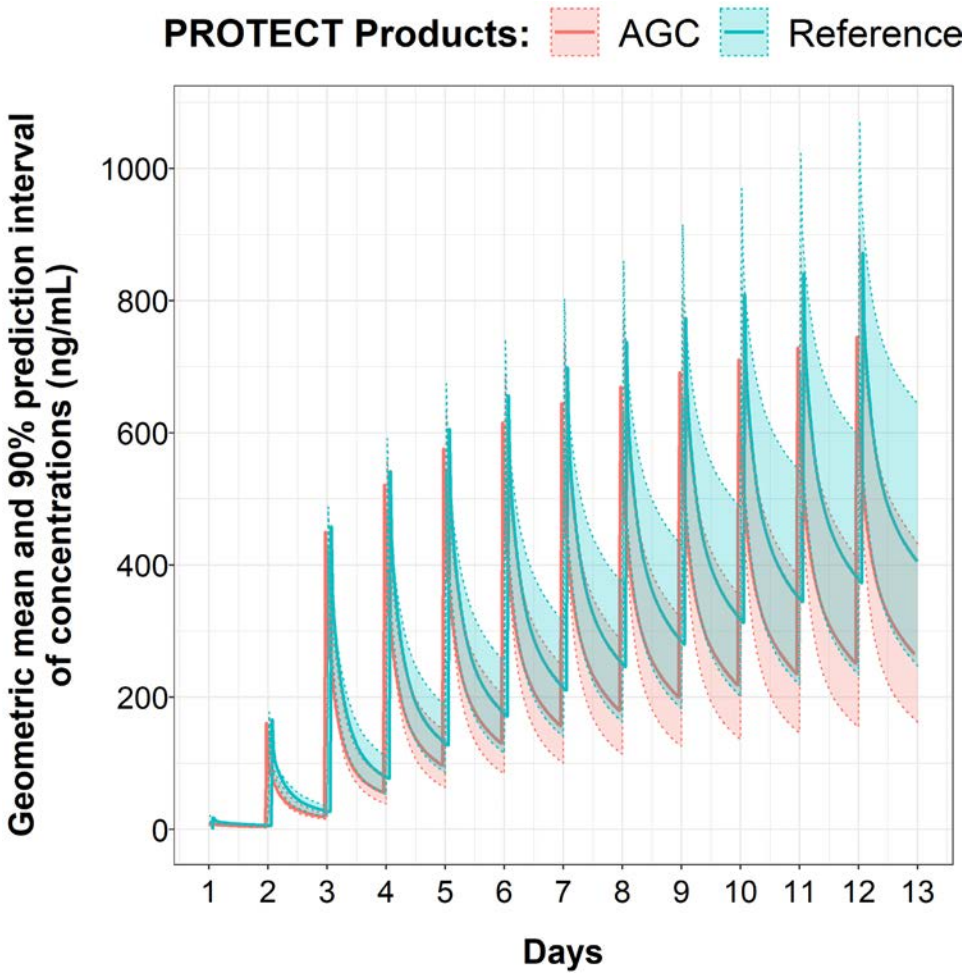
	Daily dose (µg/m²)					Cumulative dose (µg/m²) [Relative increase from reference]
	Day 1	Day 2	Day 3	Day 4	Days 5-14	
Reference TN-10 trial regimen Herold 14-day (Lilly)	51	103	207	413	826	9,034 [reference]
AGC Regimen A	(b) (4)					(b) (4) [21%]
AGC Regimen B						[24%]
AGC Regimen C						[35%]

Source: Adapted from Applicant's BLA Resubmission Topics (m1), Table 3 , page 6.

Reviewer's assessment of the proposed alternative dosing regimens for the AGC product and for the need a dosing adjustment for the AGC product

Figure 3 shows the model-predicted PK profiles for the AGC product (red) and the Lilly product (blue), under the PROTECT study 12-day dosing regimen. Teplizumab geometric mean concentrations from the AGC product (red) are located at the lower bound of the 90%PI (90% prediction interval) of all concentrations (i.e., distribution representing the between-subject variability) from the Lilly product (blue shaded area).

Figure 3. Model-Predicted PK Profiles of the AGC Product and the Lilly Product (Reference) in the PROTECT Sub-Study



The solid red and blue lines are the geometric means of teplizumab concentrations from the AGC product and Lilly product, respectively. The colored shaded areas are the distributions (90% prediction intervals [90%PIs]) of teplizumab concentrations for the AGC product (red) and the Lilly product (blue). The dotted lines delimiting the shaded areas are the upper and lower bounds of the 90%PIs. The PK profiles are generated from the individual (conditional) PK simulations (i.e., using the PK model estimated individual PK parameters of each patient enrolled in the PROTECT sub-study and rich PK sampling for simulation of individual teplizumab concentrations over time).
Source: FDA reviewer

Table 3 shows the FDA reviewer's evaluation of the proposed alternative regimens A, B or C for the AGC products using the FDA reviewer's PK model for simulations. The PK comparability results for exposure matching using conditional (individual) PK simulations are in concordance with the population (average) simulations findings. The proposed alternative regimens B and C meet the PK comparability criteria for AUCinf, Cmax (after last dose), Ctrough before last dose (Ctrough13), and Ctrough after last dose (Ctrough14). Even though the GMR point estimate or

the lower bound of the 90%CI of the GMR is close to 80%, the applicant's preferred regimen A does not meet the strict PK comparability criteria for Ctrough14, when considering either the conditional or the average PK simulations.

Table 3. Comparison of the Predicted PK Exposure Metrics between the Alternative Regimens (for AGC product) and the Reference 14-Day Regimen (for Lilly product)

	GMR (90% CI) [a]				**Passes PK comparability**
	AUCinf [b]	**Cmax (After last dose)**	**Ctrough13 (Before last dose)**	**Ctrough14 (After last dose)** *Not reported by Applicant*	
Conditional simulations (using PROTECT sub-study patients' PK parameters)					
Regimen A	0.910 (0.842 – 0.984)	1.065 (1.022 - 1.109)	0.872 (*0.795* - 0.958)	0.856 (*0.779* - 0.942)	Not Ctrough14
Regimen B	0.94 (0.869 - 1.016)	1.101 (1.057 - 1.147)	0.906 (0.826 - 0.995)	0.889 (0.808 - 0.978)	Yes
Regimen C	1.03 (0.952 - 1.113)	1.089 (1.045 - 1.134)	0.926 (0.843 - 1.016)	0.898 (0.816 - 0.988)	Yes
Population (average) simulations [c] *(using typical PK parameters under same ADA conditions)*					
Regimen A	0.904 (0.899 - 0.91)	1.034 (1.031 - 1.037)	0.815 (0.809 - 0.821)	*0.799 (0.793* - 0.805)	Not Ctrough14
Regimen B	0.928 (0.922 - 0.934)	1.066 (1.063 - 1.069)	0.841 (0.835 - 0.847)	0.824 (0.818 - 0.83)	Yes
Regimen C	1.021 (1.015 - 1.027)	1.055 (1.052 - 1.058)	0.861 (0.855 - 0.867)	0.834 (0.828 - 0.841)	Yes

[a] GMR (90%CI): geometric mean ratio (90% confidence interval), derived from Student's t-test (with Levene Test for equality of variances) on natural log-transformed of PK exposure metrics.

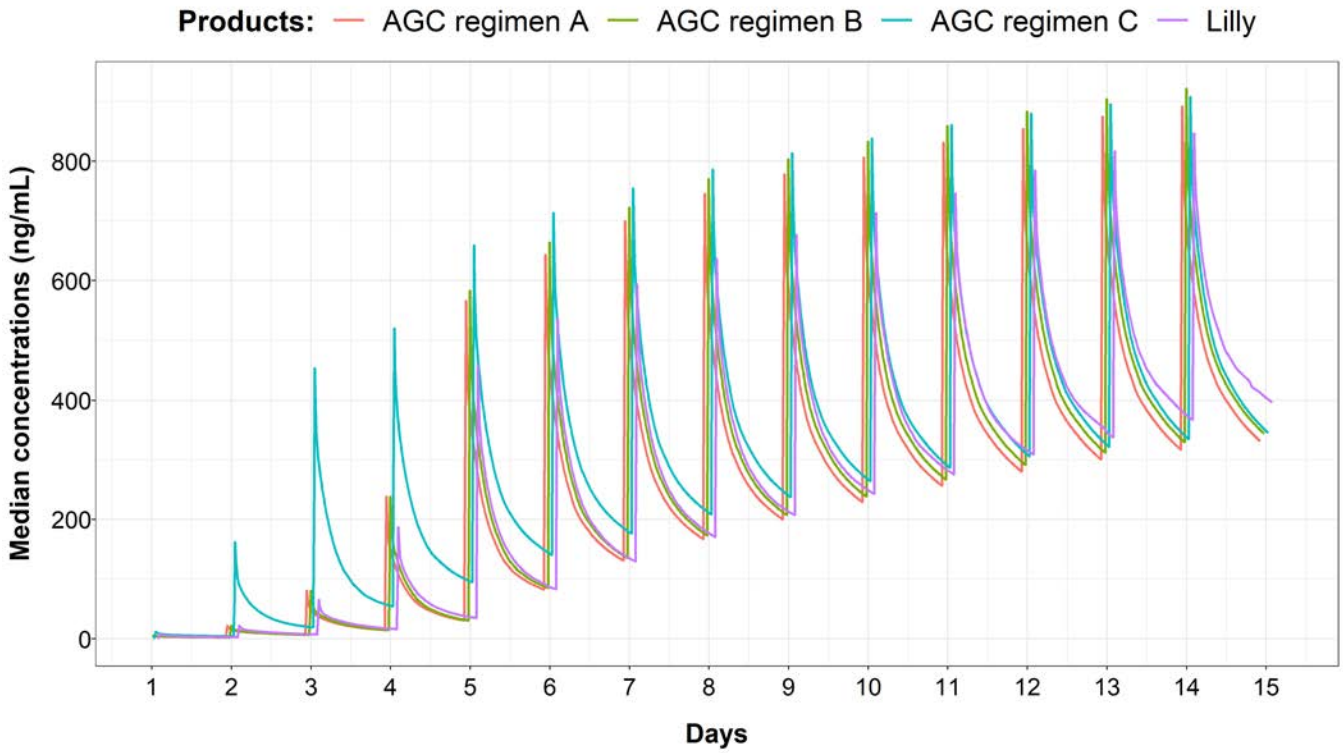
[b] AUCinf: calculated using the trapezoidal linear-up and log-down method.

[c] Average or population simulations: Monte-Carlo simulations (500 replicates of the PROTECT sub-study dataset, with subjects' BSA and weight and no ADA titers) were performed to calculate the uncertainty (90%CI) of the GMR, using Student's t-test (with Levene Test for equality of variances) on natural log-transformed median PK exposure metrics calculated from each replicate (500 replicates).

Figure 4 shows the model-predicted median PK profiles from the AGC product under the proposed 3 alternative 14- day regimen and from the Lilly product (reference) under the reference (Herold, i.e., TN-10 study) 14-day regimen. Regimen C does not provide additional advantages compared to Regimen B in term of matching the Lilly product reference exposure. In fact, the GMR and their 90%CI for AUCinf, Cmax (after last dose) and Ctrough14 are numerically very close (Table 3, Figure 4). However, regimen C is associated with unnecessarily higher exposure and Cmax values between Day 2 to 4 compared regimen B (Figure 4), as regimen C doses are 3.4 to 1.7-fold the doses in regimen B between Day 2 to 4 (Table 2).

Regimen B was considered the most appropriate regimen for the AGC product in order to match the overall exposure to the Lilly product under the reference (Herold) regimen. However, on Day 1 of regimen B, the dose of (b) (4) µg/m^2 was found not optimal to meet the PK comparability criteria for Cmax (after first dose) and AUC[0-24h], with a GMR (90%CI) of 0.796 (0.777 - 0.815) and 0.818 (0.795 - 0.843), respectively. On Day 1 of regimen B, a dose of (b) (4) µg/m^2 instead of (b) (4) µg/m^2 allows to meet the PK comparability criteria for Cmax and AUC[0-24h] based on conditional PK simulations, with a GMR (90%CI) of 0.879 (0.855 - 0.905) and 0.893 (0.868 - 0.92), respectively (Table 4).

Figure 4. Model-Predicted PK Profiles of the AGC Product (Alternative Regimens) and the Lilly Product (Reference Regimen)



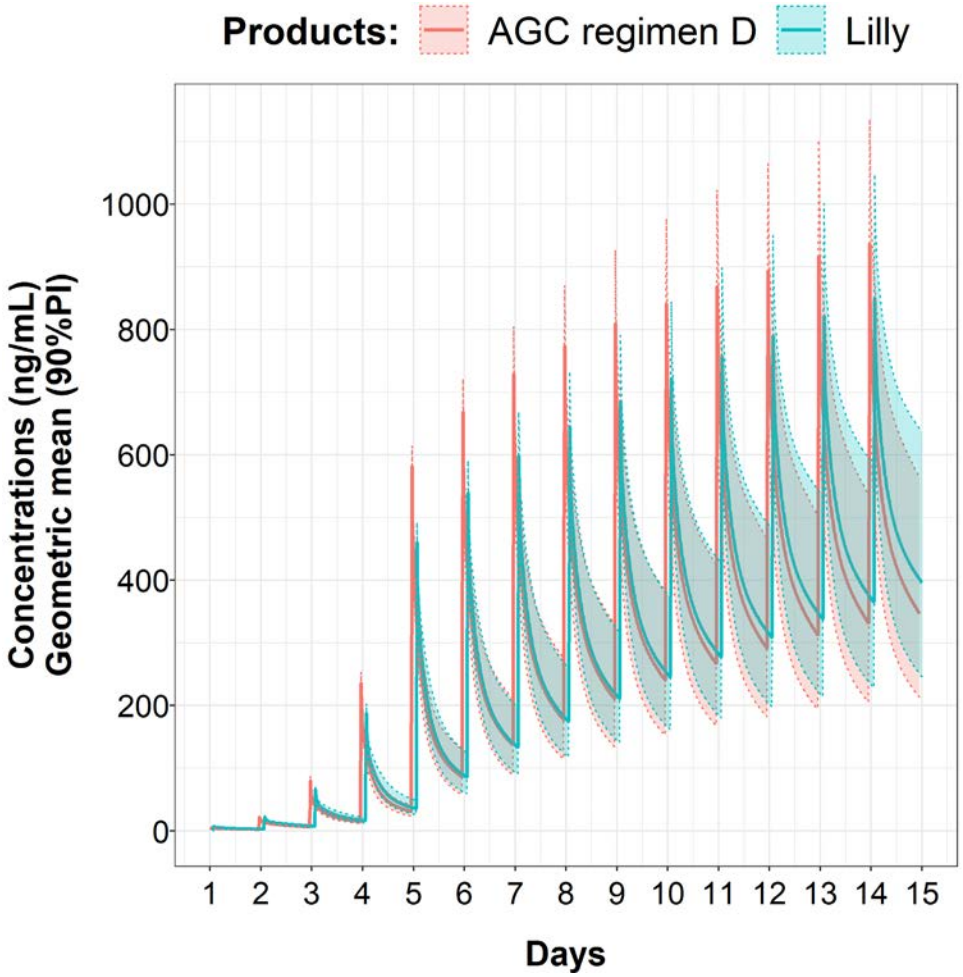
Reference 14-day regimen (daily dose): 51 – 103 – 207 – 413 – (825 x 10 days) µg/m2.
Regimen A (daily dose): (b) (4)
Regimen B (daily dose):
Regimen C (daily dose):
Source: FDA reviewer

The modified regimen B (regimen D), with the daily dosing of 65 – 125 – 250 – 500 – (1030 x 10 days) µg/m2 is considered the optimal regimen for exposure matching with the Lilly product (under the reference 14-day regimen). Figure 5 (A and B) shows the model-predicted PK profiles for the AGC product (red) and the Lilly product (blue), under the regimen D and the reference

(Herold or TN-10 study) 14-day regimen, respectively. The average and the variability in teplizumab product are overlapping during the 14-day treatment.

Figure 5. Model-Predicted PK Profiles of the AGC Product (Regimen D) and the Lilly Product (Reference Regimen), on Arithmetic scale (A) and semi-logarithmic scale (B).

(A)

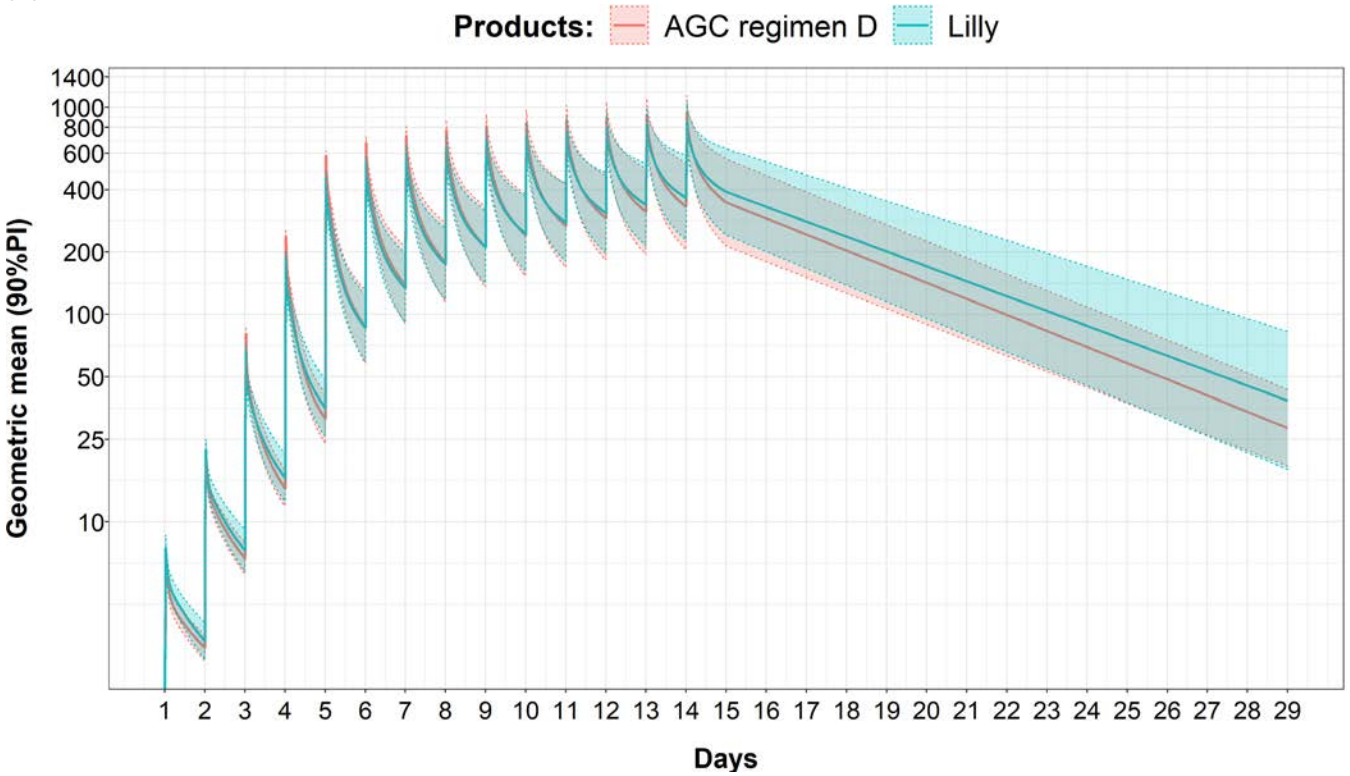


The solid red and blue lines are the geometric means of teplizumab concentrations from the AGC product (regimen B) and Lilly product (reference regimen), respectively. The colored shaded areas are the distributions (90% prediction interval [90%PI]) of teplizumab concentrations for the AGC product (red) and the Lilly product (blue). The dotted lines delimiting the shaded areas are the upper and lower bounds of the 90%PIs. AGC product dosing is regimen D (14-day daily dosing): 65 – 125 – 250 – 500 – (1030 x 10 days) µg/m2. Lilly product dosing is the reference 14-day dosing used in the pivotal TN-10 study, with a daily dosing of 51 – 103 – 207 – 413 – (825 x 10 days) µg/m2. The PK profiles are generated from the individual (conditional) PK simulations.
Source: FDA reviewer

Continued next page

Figure 5 continued

(B)



The solid red and blue lines are the geometric means of teplizumab concentrations from the AGC product (regimen B) and Lilly product (reference regimen), respectively. The colored shaded areas are the distributions (90% prediction interval [90%PI]) of teplizumab concentrations for the AGC product (red) and the Lilly product (blue). The dotted lines delimiting the shaded areas are the upper and lower bounds of the 90%PIs. AGC product dosing is regimen D (14-day daily dosing): 65 – 125 – 250 – 500 – (1030 x 10 days) µg/m2. Lilly product dosing is the reference 14-day dosing used in the pivotal TN-10 study, with a daily dosing of 51 – 103 – 207 – 413 – (825 x 10 days) µg/m2. The PK profiles are generated from the individual (conditional) PK simulations.

Source: FDA reviewer

Table 4 summarizes the daily PK comparability results between the AGC product under the adjusted dosing regimen (regimen D) and the Lilly product under the reference 14-day regimen (used in the pivotal TN-10 study). Regimen D corrects the difference in exposure between products. The Cmax after dose 4 to dose 6 are numerically slightly above the strict PK comparability criteria. However, the Cmax values resulting from dose 4 to dose 6 are well below those observed later on during the 14-day treatment from both products. Therefore, these higher Cmax values do not represent a concern regarding the potential acute toxicity or adverse reactions of the proposed regimen D.

Table 4. Comparison of the Daily PK exposure Metrics between the AGC product (Regimen D) and the Lilly product (Reference Regimen)

Time (end of Day)	GMR (90% CI)		
	AUC[0-Tlast]	**Ctrough**	**Cmax after each dose**
24 h (Day 1)	0.893 (0.868 - 0.92)	0.927 (0.892 - 0.963)	0.879 (0.855 - 0.905)
48 h (Day 2)	0.918 (0.889 - 0.948)	0.915 (0.876 - 0.956)	0.998 (0.975 - 1.021)
72 h (Day 3)	0.963 (0.929 - 0.998)	0.888 (0.844 - 0.934)	1.222 (1.199 - 1.245)
96 h (Day 4)	1.007 (0.968 - 1.048)	0.888 (0.836 - 0.944)	*1.259 (1.24 - 1.279)**
120 h (Day 5)	1.072 (1.028 - 1.118)	1.013 (0.94 - 1.092)	*1.264 (1.248 - 1.281)**
144 h (Day 6)	1.09 (1.043 - 1.14)	1.032 (0.954 - 1.115)	*1.24 (1.218 - 1.262)**
168 h (Day 7)	1.091 (1.041 - 1.144)	1.017 (0.939 - 1.101)	1.219 (1.193 - 1.246)
192 h (Day 8)	1.085 (1.033 - 1.14)	0.999 (0.921 - 1.084)	1.199 (1.169 - 1.229)
216 h (Day 9)	1.076 (1.022 - 1.134)	0.981 (0.902 - 1.067)	1.181 (1.148 - 1.214)
240 h (Day 10)	1.067 (1.011 - 1.126)	0.962 (0.883 - 1.049)	1.164 (1.129 - 1.201)
264 h (Day 11)	1.057 (0.999 - 1.117)	0.944 (0.864 - 1.031)	1.148 (1.11 - 1.187)
288 h (Day 12)	1.046 (0.987 - 1.108)	0.925 (0.844 - 1.013)	1.132 (1.092 - 1.174)
312 h (Day 13)	1.035 (0.975 - 1.099)	0.907 (0.826 - 0.995)	1.116 (1.074 - 1.16)
336 h (Day 14)	1.025 (0.964 - 1.089)	0.889 (0.809 - 0.978)	1.101 (1.057 - 1.147)
672 h (Day 28)	0.953 (0.883 - 1.028)	*0.74 (0.669 - 0.818)**	NA
AUCinf	0.94 (0.87 - 1.016)	NA	NA

* The 90%CI of the Geometric mean ratio (GMR) outside the PK comparability criteria of 80% to 125%, calculated from on a single simulation using rich PK sampling and the PROTECT sub-study population individual PK parameters. NA: not applicable.
Source: FDA reviewer

Table 4 shows that even with the adjusted dosing regimen (regimen D) for the AGC product, the Ctrough at the end of day 28 (or Day 29) after the 14-day treatment will still be below the typical PK comparability bounds with a GMR of 74%. The PK difference might be due to the higher proportion of NAb on Day 28 for the AGC product. However, the AUC[0-Day 29] is well within the PK comparability criteria with a GMR of 95.3%. Figure 5 (B) shows that Ctrough on Day 29 from the AGC product (under the adjusted regimen D) and the Lilly product (under the refence 14-day regimen) are largely overlapping, suggesting that the PK difference in Ctrough on Day 29 is likely not clinically meaningful. Furthermore, Figure 2 shows that even at a higher PK difference on Day 29 (GMR of 58% before dose adjustment) the CD3 target engagement by teplizumab on CD3+ T cells (expressed as % CD3 occupancy) was comparable between the AGC and Lilly product in PROTECT sub-study.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Serum concentrations of teplizumab were determined using the validated Meso Scale Discovery's electrochemiluminescence (MSD-ECL) method and the antibody titers were determined using a validated MSD-ECL bridging assay.

Pharmacokinetics:

- The samples of PROTECT study were analyzed using the method ICD 788 Version 1.02, titled "An MSD-ECL Method for the Quantitation of PRV-031 in Human Serum". The method validation was evaluated in the Clinical Pharmacology review of the original BLA submission and was considered adequate.
- In brief, the MSD-ECL method had a calibration range of 2.5- 125 ng/mL using a 40 µl human serum aliquot and the precision and accuracy of every batch of analysis were evaluated using quality control (QCs) samples at 3 concentrations (7.5, 15 and 90 ng/mL) spanning the calibration range.
- The mean accuracy (% difference from nominal) and mean precision (%CV) of the back-calculated calibration standards for the entire study sample analysis ranged between -5.0% to 4.9% and 2.5% to 4.4%, respectively and is within the standard limits of less than 15% (20% at the LLOQ).
- The mean accuracy (% difference from nominal) and mean precision (%CV) of the QCs for the entire study sample analysis ranged between -2.4% to -0.4% and 5.7% to 7.9%, respectively and is within the standard limits of less than 15%.
- Around 10% of the PROTECT study samples were re-assayed and 95% (within acceptable limits of > 66.7%) of the results for the incurred sample reanalysis were within ± 30% deviation.

Overall, the performance of the method was robust to reliably measure the serum concentrations of teplizumab.

CD3 occupancy on T cells:

The CD3 occupancy was measured using a flow cytometric assay. It measures the occupancy of the CD3 receptor by teplizumab on the surface of T lymphocytes in the peripheral blood, by identifying competition of CD3 occupancy/staining with fluorochrome-conjugated OKT3 ex vivo. Teplizumab and OKT3 have the same binding site on the CD3ε chain. Available binding sites of CD3ε on T cells can be detected by staining ex vivo with OKT3-fluorescein isothiocyanate (FITC) peripheral blood mononuclear cells (PBMCs) from subjects treated with teplizumab in vivo. The

OKT3-FITC signal measured by flow cytometry is proportional to available CD3 molecules in the blood of the subject, so that an observed reduction in OKT3-FITC signal is directly proportional to the binding (occupancy) of teplizumab to CD3 in the blood of the subject. The method was not a validated method and was conducted as per the Standard Operating Procedure developed at the (b) (4)

Reviewer comments: The bioanalytical method for quantification of teplizumab in serum, met the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development'. The assay for CD3 receptor occupancy was also found adequate to support the use as an exploratory PD marker.

4.2 Summary of PROTECT PK/PD Study

Title: PRV-031-001 (PROTECT): "A Phase 3, Randomized, Double-Blind, Multinational, Placebo-Controlled Study to Evaluate Efficacy and Safety of Teplizumab (PRV-031), a Humanized, FcR Non-Binding, anti-CD3 Monoclonal Antibody, in Children and Adolescents with Newly Diagnosed Type 1 Diabetes (T1D)."

PK/PD Sub study objective: The objective of this sub study was to characterize the PK profile and obtain possible PD markers (CD3 receptor occupancy, T cell activation, and circulating lymphocyte counts) following 12-day dosing of the two teplizumab products (AGC Biologics and Eli Lilly).

Study population:
The PROTECT trial is an ongoing trial in patients aged 8 to 17 years and were newly diagnosed with type 1 diabetes (T1D) at the time of enrollment.

Study design:

The ongoing parent study (PROTECT) is a Phase 3, randomized, double-blind, placebo-controlled, multinational, multicenter study. Approximately 300 participants will be enrolled and randomly assigned at a ratio 2:1 to either the teplizumab group (N=200) or the placebo group (N=100). The analyses for the PK/PD sub study included all patients who received teplizumab (Lilly or AGC) at the time of data cut for the analyses (Aug 2021) and did not include the patients who received placebo.

Treatments and dosing:

The PK/PD sub study of PROTECT only included analyses of participants after they completed the first 12-day course of treatment with teplizumab. The second course of treatment was

administered after an interval of approximately 6 or 12 months following the course 1 and was not a focus in this sub study or review.

Unlike the 14-day regimen in the Protégé and TN-10 studies, the 12-day course in the PROTECT study had 2-day ramp-up phase (instead of a 4-day ramp up) with the 10-day fixed-, maximal dosing period like the 14-day course, as shown in Table 5. The total amount of teplizumab given in the 12- and 14-day regimens were 9.034 and 9.031 mg/m^2, respectively. In this study, the average duration of teplizumab infusion was around 0.5 h for both products on each dosing day.

Table 5. Dosing regimen used in PROTECT (12-day) versus previous studies (14-day)

Day	**14-day course** **1 course in At-risk (TN-10);** **2 courses in Protégé (0 and 6 months)**	**12-day course** **2 courses in PROTECT (0 and 6 months)** **First course data used for PK/PD sub study**
1	51 µg/m^2	106 µg/m^2
2	103 µg/m^2	425 µg/m^2
3	207 µg/m^2	850 µg/m^2
4	413 µg/m^2	850 µg/m^2
5	826 µg/m^2	850 µg/m^2
6	826 µg/m^2	850 µg/m^2
7	826 µg/m^2	850 µg/m^2
8	826 µg/m^2	850 µg/m^2
9	826 µg/m^2	850 µg/m^2
10	826 µg/m^2	850 µg/m^2
11	826 µg/m^2	850 µg/m^2
12	826 µg/m^2	850 µg/m^2
13	826 µg/m^2	–
14	826 µg/m^2	–
Cumulative	**~9.0 mg/m^2**	**~9.0 mg/m^2**

Source: Adapted from PROTECT (prv-031-001) study protocol

Blood Sampling:

Sparse blood sampling was obtained as below, following the course 1 of treatment in the PROTECT PK/PD sub study, as shown in Table 6.

Table 6. Schedule of blood sampling in PROTECT PK/PD sub study

Pharmacokinetics (PK)	Teplizumab serum concentration	• Pre-infusion: Days 1, 4, 9, 12 • 45 ± 15 min after the end of infusion: Day 9 • Day 28
Possible PD markers (PD)	CD3 receptor occupancy by teplizumab and activation status of T cells (North American sites only) 1. Receptor occupancy on CD3+, CD4+CD8 and CD4-CD8+ cells 2. Activation status of T cells (anti-CD69 positivity on CD3+T cells, CD4+ T cells and CD8+ T cells	• Pre-infusion: Days 1, 4, 9, 12 • 45 ± 15 min after the end of infusion: Day 9 • Day 28
	Total lymphocyte counts obtained from routine hematology tests Lymphocyte profiles including 1. time to Nadir, 2. Nadir and 3. lymphocyte AUC over 28 days.	• Baseline and on Days 2, 4, 6, 9, 12 and 28.
Anti-drug antibodies (ADA)	1. Incidence 2. Titer values	• Pre-infusion: Days 1, 12 • Days 28, 56

Source: Adapted from PROTECT (prv-031-001) study protocol

Study endpoints:

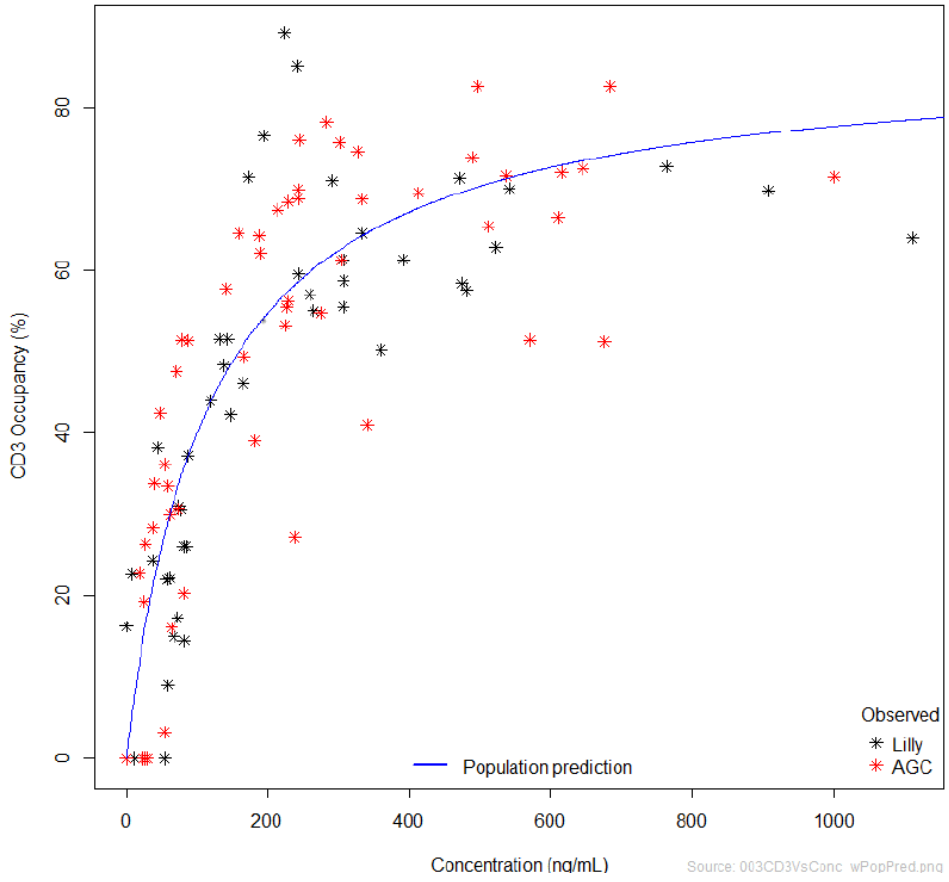
The primary PK endpoints: PK parameters including the maximum concentration (C_{max}), total Area under the concentration-time curve till Day 13 after the last dose on Day 12 ($AUC_{0\text{-}day13}$) and the total Area under the concentration-time curve extrapolated to time infinity (AUC_{inf}) were estimated from the sparse PK concentrations using a population pharmacokinetic model (Refer POPPK section of this review for additional information).

Comparisons between products: For each PK parameter, the least square mean (LSM) and respective 90% confidence interval (CI) for each product, LSM difference between products (AGC Biologics – Eli Lilly) and corresponding 90% CI were calculated. The back transformed values were used to obtain the geometric least square mean (GLSM), ratio of GLSMs, and corresponding 90% CI between the two teplizumab products.

Results:

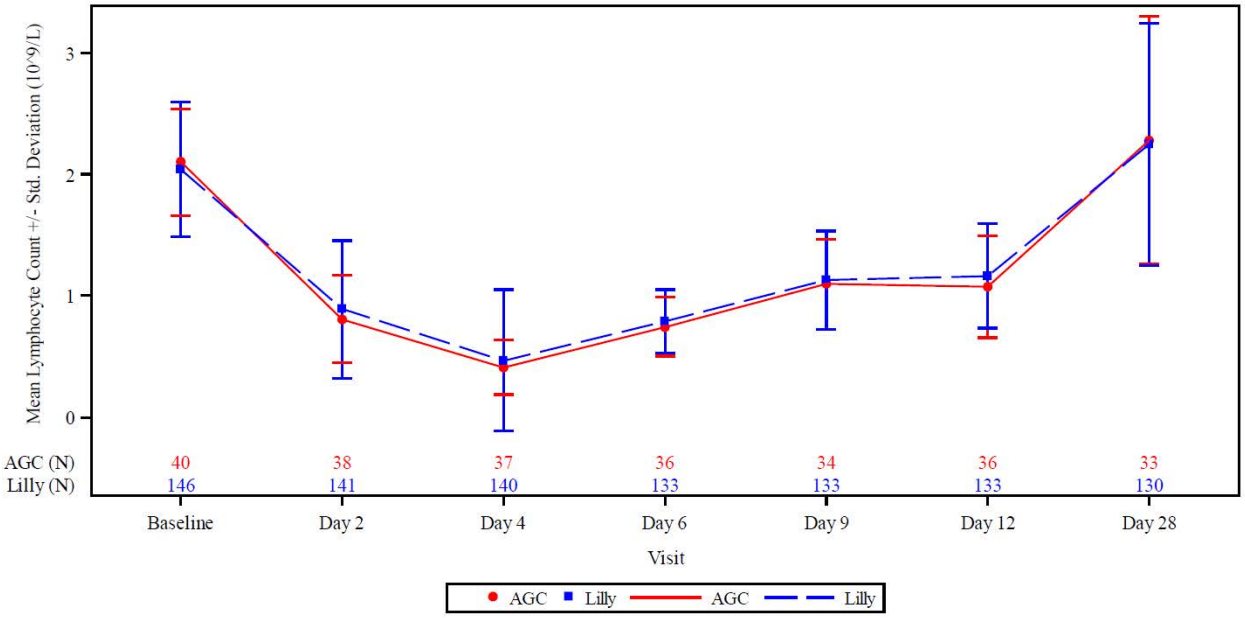
The PK and PD results are summarized in Section 3.1 of the review. In the consolidated scatter plot analysis shown in Figure 6, the relationship of CD3 occupancy vs concentrations was similar between the teplizumab products. As in the previous studies of teplizumab, the depletion in lymphocytes was a transient phenomenon following teplizumab dosing with the nadir in lymphocyte counts seen around the 5th day of the 14-day dosing regimen. The overall profile in the decline and recovery in lymphocyte counts was also superimposable for both the products, as shown in Figure 7.

Figure 6. Scatter plot of the serum teplizumab concentration versus CD3 receptor occupancy by product in PROTECT sub study



Source: Applicant's Concentration-CD3 Occupancy Report, Figure 2, page 44.

Figure 7. Mean (SD) of lymphocyte counts from baseline to Day 28 by product in PROTECT sub study

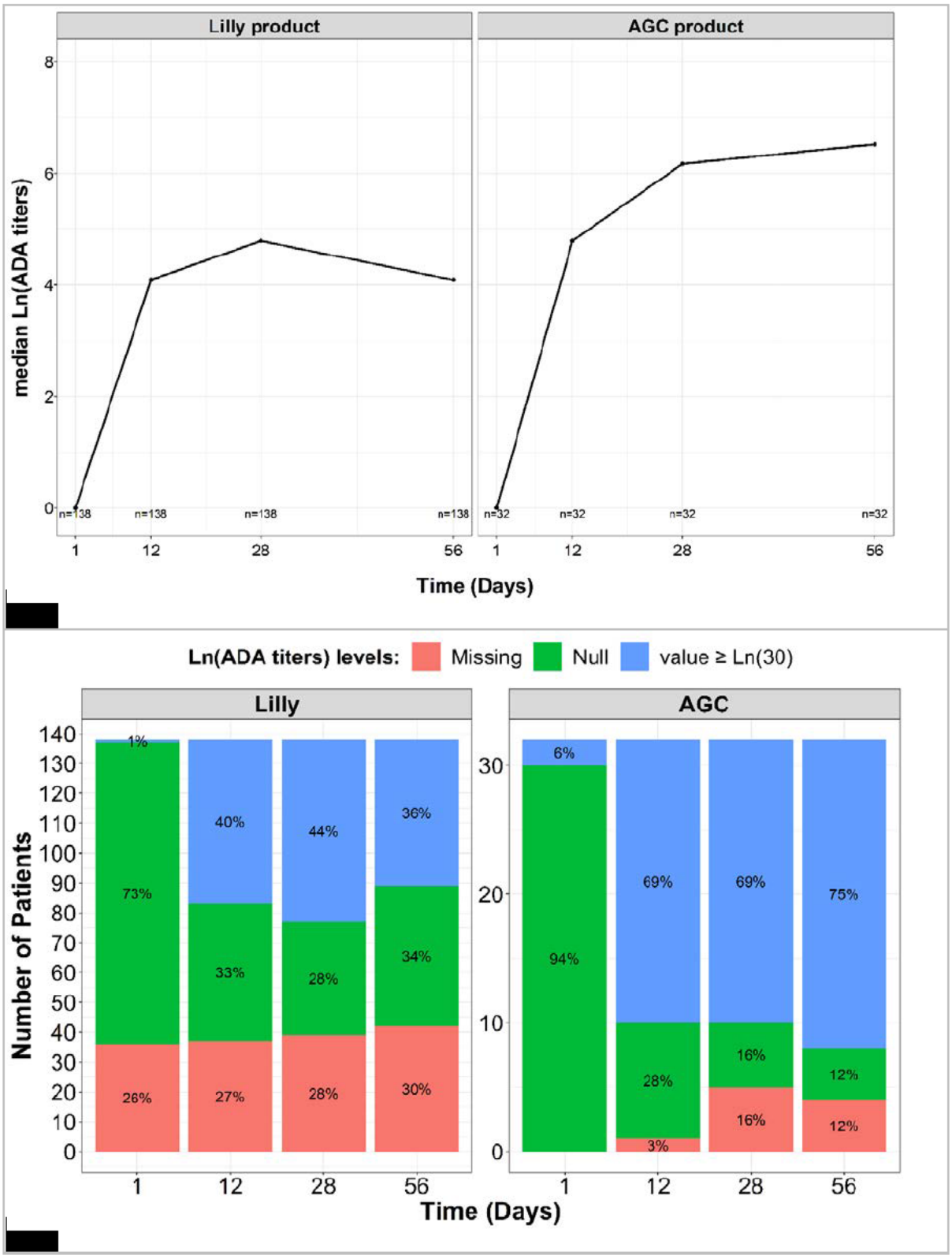


Source: Applicant's PK/PD Substudy Report, Figure 11, page 34.

The results for immunogenicity assessments are discussed here. The incidence (%) and titers of anti-drug antibodies (ADA) to teplizumab were evaluated in subjects on Days 1 (baseline) and Days 12 during the 12-day dosing regimen and during the follow-up on Days 28 and 56. The incidence of ADA between the products are compared under the population pharmacokinetic model section of this review. The median titers of the anti-drug antibodies (ADA) and the proportion of samples contributing to the titers for both the products, are presented in Figure 8.

Most samples had no detectable titers during the baseline evaluation on Day 1 indicated by Null values. The median ADA titers were found to increase with time for both the products. Of the evaluated samples, the median titers were found to be higher in the AGC arm however around 30% of samples in Lilly arm are not analyzed (missing) at the time of resubmission by Applicant, thus precluding any definitive conclusions. Overall, the impact of ADA on the serum clearance of teplizumab was found to be comparable between the two products, based on the population model and values for Ln (ADA) until 6-7 were predicted to have a negligible impact on the clearance (Refer POPPK section of this review for additional information on the impact of ADA on clearance). In general, the Ln (ADA) values did not reach values close to 7 during the 12-day dosing period, when circulating serum concentrations of teplizumab are present. Thus, the ADA impact on PK was found to be negligible regardless of the product.

Figure 8. Comparison of titers and proportion of samples for Anti-drug antibodies (ADA) by product in PROTECT sub study



Source: FDA reviewer

4.3 Pharmacometric Review

The joint population PK modeling was considered appropriate for describing the observed teplizumab concentrations in healthy subjects and patients under different dosing regimens, and therefore, for estimating teplizumab exposure and performing PK simulations and predictions. More specifically, the developed joint population PK (popPK) model was utilized to support the current submission as outlined below (Table 7):

Table 7. Utility of the Population PK Modeling

Utility of the final model		**Reviewer's Comments**
Derive exposure metrics and PK parameters	• The PK model was used to characterize the PK of teplizumab from 3 different products used during the clinical development program: study PRV-031-004 (single dose study healthy patients), TN-10 study (patients at risk of T1D1) and Protégé study and PROTECT sub-study (in patients with T1D). • The PK model was used to identify and quantify the effect of various covariates on teplizumab exposure, namely the difference in PK from the 3 studied teplizumab products, the effect of dosing regimens, anti-drug antibodies (ADA) as well as population or study on teplizumab PK . • The PK model was used to derive teplizumab exposure metrics (Cmax, Ctrough and AUC) from the PROTECT sub-study for PK comparability purposes between teplizumab products (Lilly product vs. AGC product) due to the sparse nature of PK sampling. • Finally, the PK model was used to perform PK simulations for to propose an adjusted dosing regimen for the to-be-marketed AGC product and match its exposure to the Lilly product used in the pivotal TN-10 study.	• Body weight was a significant and relevant covariate on teplizumab exposure and justified the body surface area based dosing. • ADA appeared mainly on day 8 to day 12 after treatment initiation with a peak on day 56 to day 91. ADA were a statistically significant covariate on the PK of teplizumab. At the highest levels of Ln(ADA titers) of 6 to 7, teplizumab CL was estimated to increase by 11% to 33%. However, these ADA titers occurs late after the end of the single course 14-day regimen, when teplizumab concentrations are relatively low. Teplizumab median (range) half-life for the to-be-marketed AGC product was estimated to be 4.5 days (4.2 – 5 days). • The PK model can adequately be used to predict the PK exposure metrics (Cmax, Ctrough and AUC) from the PROTECT sub-study for PK comparability purposes between teplizumab products. • The PK model derived PK metrics showed that the AGC product had 27% and 22% lower AUCinf and Ctrough (after last dose) than the Lilly product, respectively. Therefore, the AGC product failed the PK comparability to the Lilly product. • The optimal adjusted dosing regimen for the AGC product was identified to be : 65 – 125 – 250 – 500 – (1030 x 10 days) µg/m2 (regimen D)

The current pharmacometrics review evaluates the following:

a. The adequacy of the PK model to describe teplizumab PK from the different studies and predict different PK exposure metrics particularly from the PK comparability PROTECT sub-study between the Lilly product (used in the pivotal TN-10 study) and the to-be-marketed (commercial) AGC product.
b. The PK comparability results from the PROTECT sub-study based on the developed PK model and the adequacy of the proposed adjusted dosing regimen for the commercial AGC product to match its exposure to the Lilly product.

4.2.1 Applicant's Population PK Analysis

In the previous BLA submission, 2 separate population PK models of teplizumab were developed describing the PK from 3 regimens (with 2 courses of treatment each, separated by 6 months) of the Protégé study in newly diagnosed T1D patients (Protégé model or model 177 in previous review) and separately describing the PK from the single low dose (207 μg/m^2) of the PRV-031-004 study in healthy subjects (model 020 in the previous review).

The pivotal TN-10 study PK data, in subjects at risk of developing type 1 diabetes (sought indication for the current BLA), were not included in the previously developed PK models (Protégé or PRV-031-004 study), as TN-10 study collected few PK samples (n=98) in 25 of the 44 subjects randomized to teplizumab, with about half (48 of 98) of the samples were trough samples and the rest were collected randomly post dose. However, additional PK analyses, performed in the previous BLA, showed that the Protégé model appropriately described the observed TN-10 study concentrations.

The Protégé study used a product manufactured by MacroGenics, the PK bridging study PRV-031-004 used products manufactured by Eli Lilly (49 subjects) and AGC Biologics (51 subjects) and TN-10 study used products manufactured by MacroGenics (16 patients with PK) and Eli Lilly (9 patients with PK). The PK exposures between the MacroGenics product and the Lilly product were shown to be comparable, with comparable efficacy between products in TN-10 study.

In the PK bridging PRV-031-004 study, the to-be-marketed AGC Biologics product (AGC product) failed to show PK comparability to the Eli Lilly product (Lilly product) used in the pivotal TN-10 study. The Applicant conducted a pharmacokinetic/ pharmacodynamic (PK/PD) sub-study of an ongoing PROTECT study to compare the PK and PD characteristics of the two products (AGC and Lilly products) when dosed in the therapeutic setting. The ongoing PROTECT study is a phase 3 trial assessing efficacy and safety of teplizumab in children and adolescents with newly diagnosed T1D. The PROTECT study was initiated with the Lilly product and transitioned to the AGC product, and the dosing regimen studied is a 12-day dosing regimen, with different daily dosing from the 14-day Herold regimen used in the pivotal TN-10 study (Table 8).

Because sparse PK sampling is being collected in the PROTECT sub-study, a population PK (popPK) model is required to obtain individual estimates of PK parameters and exposure metrics (AUC, Cmax, Ctrough) for PK comparability assessment. However, the previously developed 2 PK models had different structures and parameters that led to different predictions of PK exposure, when simulating the PK under the same dosing regimen. The Protégé model could not simultaneously describe high and low dosing regimens (i.e., the full 14-day regimen or Herold regimen, (b) (4) In addition, the data for the AGC product were only available following a single low dose in PRV-031-004, thus rendering predictions for an ascending dosing regimen (as the Herold regimen), using either PK models, unreliable.

Due to these discrepancies, the FDA recommended developing a joint population PK model of teplizumab based on data from Protégé (Course 1 only), TN-10, PRV-031-004, and PROTECT sub-study (Course 1 only; all data collected by 06-Aug-2021) studies, which describes all populations (newly diagnosed T1D patients, at-risk T1D patients, and healthy subjects), all dosing regimens, and all teplizumab products employed in these studies.

The developed joint PK model was ultimately used to obtain estimates of teplizumab individual PK parameters from the PROTECT sub-study and derive PK exposure metrics for the PK comparability analysis between the Lilly product and AGC product. Table 9 shows the planned PK and anti-drug antibodies (ADA) sampling from the different studies.

The PROTECT PK sub-study enrolled 169 patients (137 under Lilly product and 32 under AGC product) and contributed to the PK model with 625 quantifiable concentrations (500 from Lilly product arm and 125 from AGC product arm). A total of 21 BQL (below quantification limit, 16 in Lilly product arm and 5 in AGC product arm) concentrations were excluded from the analysis. The lower limit of quantification (LLOQ) was 2.5 ng/mL as for the other studies (for Protégé, the LLOQ was 2.442 ng/mL). In the AGC product cohort, BQL values occurred after day 25 in 25% of PK samples (5/20 samples). In the Lilly product cohort, most BQL values occurred after day 24 in 12% of PK samples (14/112 samples), 2 BQL values occurred less than 4 hours after the first dose infusion. The application of the M3 method to handle BQL values from all studies did not improve the fit or changed the PK parameter estimates.

The summary statistics for the demographic characteristics and either maximum ADA concentrations or titers are presented by study in Table 10. Table 11 and Table 12 summarize the daily ADA titers in the PROTECT sub-study and PRV-031-004 (single dose) study, respectively. ADA titers in the single dose study (PRV-031-004) appeared after Day 5 to Day 8, when teplizumab concentrations (from AGC and Lilly product) were already very low or BQL values. Table 13 summarizes the daily ADA concentrations in the Protégé study. ADA titers in the TN-10 study were collected on only one occasion (3 to 4 months) after treatment initiation (Table 9and Table 10).

Table 8. Listing of Studies included in the Population PK Analysis

Study Identifier	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Route of Administration; Dosage Regimen**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
Protégé CP-MGA031-01	Efficacy (C-peptide) and safety; Population PK analysis; ADA and NAb analyses	Segment 1: Open label Segment 2: Randomized, double-blind, placebo-controlled, multicenter, multinational, 4-arm, dose-ranging study	Teplizumab intravenous infusion* (MacroGenics product) Segment 1: Open label: Full 14-day regimen (Herold Regimen): Day 0: 51 µg/m2 Day 1: 103 µg/m2 Day 2: 207 µg/m2 Day 3: 413 µg/m2 Days 4-13: 826 µg/m2 Total dose ~9034 µg/m2 Segment 2: Randomized: **Arm 1**: Full 14-day regimen (Herold Regimen) **Arm 2**: 1/3 or reduced 14-day regimen (1/3 or reduced Herold Regimen): Day 0: 17 µg/m2 Day 1: 34 µg/m2 Day 2: 68 µg/m2 Day 3: 136 µg/m2 Days 4-13: 273 µg/m2 Total dose ~2985 µg/m2 **Arm 3**: Full 6-day regimen (Curtailed Herold Regimen) Day 0: 51 µg/m2 Day 1: 103 µg/m2	Segment 1: 38 teplizumab Segment 2: 513 total: 98 placebo and 415 teplizumab	Patients with newly diagnosed T1D (treatment within 12 weeks of diagnosis)	Segment 1: Two 14-day courses, 26 weeks apart. Only course 1 was included in the current joint PK modelling. Segment 2: Two identical courses, 26 weeks apart. Only course 1 was included in the current joint PK modelling.

			Day 2: 207 µg/m2 Day 3: 413 µg/m2 Days 4-5: 826 µg/m2 Total dose ~2426 µg/m2 **Arm 4**: Placebo 14-day course			
TN-10 (At-Risk Study) ISCT-MGA031-005	Efficacy and Safety; PK analysis; ADA and NAb Analysis	Randomized, double-blind, placebo-controlled, 2-arm, multicenter study	Teplizumab intravenous infusion* (MacroGenics and Lilly products) Day 0: 51 µg/m2 Day 1: 103 µg/m2 Day 2: 207 µg/m2 Day 3: 413 µg/m2 Days 4-13: 826 µg/m2 Total dose ~9034 µg/m2	76 total: 32 placebo and 44 teplizumab (28 Lilly product and 16 MacroGenics product)	Individuals with at least 2 T1D-associated autoantibodies and dysglycemia.	Single 14-day course
PRV-031-004	Biocomparability of teplizumab manufactured at AGC Biologics (test) vs Eli Lilly (reference)	Randomized, double-blind, parallel group	Teplizumab 207 µg/m2, 30 minutes intravenous infusion	100 total: 51 AGC Biologics and 49 Eli Lilly	Healthy subjects	Single dose
PROTECT study PRV-031-001 **PROTECT sub-study**	Efficacy (C-peptide) and safety; Population PK analysis; ADA analyses Population PK, ADA and safety analyses	Randomized, double-blind, placebo-controlled, study	Teplizumab or placebo intravenous infusion Day 1: 106 µg/m2 Day 2: 425 µg/m2 Day 3-12: 850 µg/m2 Same dosing as the on-going PROTECT study	300 total: 100 placebo and 200 teplizumab 171 teplizumab: 33 AGC Biologics and 138 Eli Lilly	Children and adolescents newly diagnosed with T1D	Two courses starting at Week 1 and Week 26 or Week 52; Only the single course PROTECT sub-study was included in the current joint PK modelling.

Abbreviations: ADA=anti-drug antibodies; CSR=clinical study report; NAb=neutralizing antibodies; PD=pharmacodynamics; PK=pharmacokinetics; T1D=type 1 diabetes. *Per protocol duration of intravenous infusion: at least 30 minutes.

Source: Adapted from the applicant's Summary of Clinical Pharmacology Studies, Table 1, page 15.

Table 9. Protocol Specified Collection Days for PK and Anti-drug antibodies measurements

	Protégé study Segment 1		Protégé study Segment 2		TN-10 study [b]	PRV-031-004 study	PROTECT PK sub-study
Protocol Specified Collection Days	**Course 1**	**Course 2 [a]** ***(Not used in the current updated joint PK model)***	**Course 1**	**Course 2 [a]** ***(Not used in the current updated joint PK model)***	**One Course study**	**Single dose**	**One Course sub-study**
PK: teplizumab serum concentration	Days 0, 1-13 (pre-dose and end of infusion) Random Samples: 14, 28, 56	Days 182, 183-190 (pre-dose and end of infusion) Random Samples: 196, 210, 224, 273	Days 0, 5 (pre-dose) Random Samples: 14, 28, 56	Days 182,187, 196, 210, 224, 273	Days 0,10,11,13: pre-dose and at random sampling	On Day 1, PK samples were drawn pre-dose and 0.5 hour (end of infusion), 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 18 hours after the start of infusion. On Day 2, PK samples were drawn at 24 hours and 36 hours after the start of the infusion. Day 3, 5, 8, 15	Day1: predose, Day 4: predose, Day 9: predose and 45 ± 15 min after the infusion is completed, Day 12: predose, Day 28: at random
Anti-drug antibodies (ADA)	Days 0, 28, 56, 91	Days 182, 210, 224, 273, 364, 546, 728	Days 0, 28, 56, 91	Days 182, 210, 224, 273, 364, 546, 728	Day 0 and Month 3	Day 1, 2, 3, 4, 5, 8, 15	Day 1, Day 12, Day 28, Day 56, and Day 182

[a] Course 2 of treatment was administered 26 weeks apart from Course 1 of treatment (i.e., after 6 months wash-out period).

[b] TN-10 study, in subjects at risk of developing type 1 diabetes, was not included in the population PK analysis. TN-10 study was a randomized, double-blind, placebo-controlled, 2-arm (teplizumab and placebo), multicenter study. Only 1 course of the Herold Regimen was administered.

Source: Adapted from the applicant's Summary of Clinical Pharmacology Studies, Table 2, page 23.

Table 10. Summary of Demographic Characteristics and Maximum Anti-Drug Antibody levels by Study

	Protégé study			TN-10 study		PRV-031-004 study		PROTECT sub-study	
	MGNX product Reference regimen (N=237)	MGNX product reduced regimen (N=101)	MGNX product curtailed regimen (N=104)	Lilly product Reference regimen (N=9)	MGNX product Reference regimen (N=16)	AGC product single dose (N=51)	Lilly product single dose (N=49)	AGC product PROTECT regimen (N=32)	Lilly product PROTECT regimen (N=137)
Age (years)									
Mean (SD)	18.4 (7.47)	17.9 (6.09)	18.1 (6.87)	23.8 (15.9)	19.1 (10.6)	-1.00 (0)	-1.00 (0)	11.7 (2.28)	12.0 (2.55)
Median [Min, Max]	16.0 [8.00, 35.0]	17.0 [8.00, 34.0]	16.0 [8.00, 33.0]	13.0 [10.0, 49.0]	15.5 [9.00, 46.0]	-1.00 [-1.00, -1.00]	-1.00 [-1.00, -1.00]	12.0 [8.00, 16.0]	12.0 [8.00, 17.0]
Body weight (kg)									
Mean (SD)	57.5 (15.7)	59.8 (16.9)	60.5 (18.0)	66.7 (37.7)	61.0 (20.8)	70.8 (9.45)	71.0 (8.42)	46.2 (14.2)	47.5 (15.3)
Median [Min, Max]	55.0 [36.0, 113]	56.2 [36.0, 94.2]	58.5 [36.0, 118]	50.1 [32.6, 144]	57.7 [26.8, 94.7]	72.7 [51.1, 83.5]	72.3 [53.4, 85.4]	49.0 [22.7, 72.0]	46.0 [24.2, 100]
BSA (m2)									
Mean (SD)	1.61 (0.262)	1.64 (0.283)	1.66 (0.295)	1.70 (0.574)	1.64 (0.346)	1.81 (0.148)	1.81 (0.132)	1.40 (0.299)	1.42 (0.285)
Median [Min, Max]	1.59 [1.15, 2.41]	1.62 [1.19, 2.16]	1.64 [1.16, 2.45]	1.47 [1.12, 2.78]	1.61 [0.976, 2.18]	1.85 [1.50, 2.03]	1.83 [1.53, 2.00]	1.47 [0.880, 1.90]	1.42 [0.930, 2.31]
Gender									
Male	155 (65.4%)	61 (60.4%)	71 (68.3%)	6 (66.7%)	9 (56.3%)	21 (41.2%)	20 (40.8%)	18 (56.3%)	75 (54.7%)
Female	82 (34.6%)	40 (39.6%)	33 (31.7%)	3 (33.3%)	7 (43.8%)	30 (58.8%)	29 (59.2%)	14 (43.8%)	62 (45.3%)
max. Ln(ADA conc.)[ng/mL]									
Mean (SD)	3.89 (3.09)	4.01 (3.15)	4.22 (3.11)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Median [Min, Max]	4.88 [0, 10.2]	5.09 [0, 9.06]	5.39 [0, 9.64]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]
Missing	0 (0%)	0 (0%)	0 (0%)	9 (100%)	16 (100%)	51 (100%)	49 (100%)	32 (100%)	137 (100%)
maximum Ln(ADA Titer)									
Mean (SD)	NA (NA)	NA (NA)	NA (NA)	3.28 (4.15)	3.25 (2.83)	4.78 (4.05)	4.20 (3.71)	6.81 (2.92)	4.69 (3.71)
Median [Min, Max]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	0 [0, 9.64]	4.09 [0, 8.25]	5.48 [0, 11.0]	4.79 [0, 11.0]	6.87 [0, 11.7]	5.48 [0, 11.7]
Missing	237 (100%)	101 (100%)	104 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	28 (20.4%)

Note: max. Ln(ADA conc.)=maximum natural-logarithm (Ln) of ADA concentrations. In Protégé study, ADA concentrations (LLOQ of 48.85 ng/mL*) and not titers were measured. In the other studies, ADA titers were measured using a three-tiered approach, with a titer threshold of 30.*
Source: FDA reviewer (based on the population PK dataset)

Table 11. Summary of Daily ADA titers in PROTECT sub-study

	PROTECT sub-study							
	Day 1 (predose)*		Day 12		Day 28		Day 56	
	AGC product (N=32)	Lilly product (N=138)	AGC product (N=32)	Lilly product (N=138)	AGC product (N=32)	Lilly product (N=138)	AGC product (N=32)	Lilly product (N=138)
Ln(ADA titers)								
Mean (SD)	0.405 (1.31)	0.114 (0.666)	4.17 (2.42)	3.29 (2.76)	6.29 (3.38)	4.13 (3.56)	6.38 (3.11)	3.78 (3.79)
Median [Min, Max]	0 [0, 5.48]	0 [0, 4.79]	4.79 [0, 8.25]	4.09 [0, 9.64]	6.17 [0, 11.7]	4.79 [0, 11.0]	6.52 [0, 11.7]	4.09 [0, 11.7]
Missing	0 (0%)	36 (26.1%)	1 (3.1%)	37 (26.8%)	5 (15.6%)	39 (28.3%)	4 (12.5%)	42 (30.4%)
ADA category*								
Missing	0 (0%)	36 (26.1%)	1 (3.1%)	37 (26.8%)	5 (15.6%)	39 (28.3%)	4 (12.5%)	42 (30.4%)
Null	30 (93.8%)	101 (73.2%)	9 (28.1%)	46 (33.3%)	5 (15.6%)	38 (27.5%)	4 (12.5%)	47 (34.1%)
Value ≥ Ln(30)*	2 (6.3%)	1 (0.7%)	22 (68.8%)	55 (39.9%)	22 (68.8%)	61 (44.2%)	24 (75.0%)	49 (35.5%)

* Day 1 (predose) represent baseline (control) ADA collected before initiation of the study treatment. The ADA titer threshold value is 30 in the ADA assay. All titers below the threshold are considered as zero.

Note: On Day 28, the neutralizing antibodies (NAb) represented 45% (10/22) and 28.4% (25/88) for the AGC product and the Lilly product, respectively. On Day 56, the NAb represented 57.1% (4/7 samples) and 53% (44/83 samples) for the AGC product and the Lilly product, respectively.

Source: FDA reviewer (based on the population PK dataset)

Table 12. Summary of Daily ADA titers in PRV-031-004 study

	PRV-031-004 study											
	Day 1 (predose)		Day 2		Day 3		Day 5		Day 8		Day 15	
	AGC (N=51)	Lilly (N=49)	AGC (N=51)	Lilly (N=49)	AGC (N=51)	Lilly (N=48)	AGC (N=51)	Lilly (N=47)	AGC (N=50)	Lilly (N=48)	AGC (N=49)	Lilly (N=48)
Ln(ADA titers)												
Mean (SD)	0.0939 (0.670)	0.0694 (0.486)	0.0939 (0.670)	0.0694 (0.486)	0.0939 (0.670)	0 (0)	0.254 (1.08)	0 (0)	1.20 (2.01)	0.430 (1.26)	4.89 (4.07)	4.29 (3.69)
Median [Min, Max]	0 [0, 4.79]	0 [0, 3.40]	0 [0, 4.79]	0 [0, 3.40]	0 [0, 4.79]	0 [0, 0]	0 [0, 6.17]	0 [0, 0]	0 [0, 6.87]	0 [0, 4.79]	5.48 [0, 11.0]	4.79 [0, 11.0]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	2 (4.2%)	0 (0%)	0 (0%)
ADA positivity *												
Negative	50 (98.0%)	48 (98.0%)	50 (98.0%)	48 (98.0%)	50 (98.0%)	48 (100%)	48 (94.1%)	46 (97.9%)	36 (72.0%)	41 (85.4%)	17 (34.7%)	17 (35.4%)
Positive	1 (2.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	0 (0%)	3 (5.9%)	1 (2.1%)	14 (28.0%)	7 (14.6%)	32 (65.3%)	31 (64.6%)
Neutralizing ADA												
no ADA	50 (98.0%)	48 (98.0%)	50 (98.0%)	48 (98.0%)	50 (98.0%)	48 (100%)	48 (94.1%)	46 (97.9%)	36 (72.0%)	41 (85.4%)	17 (34.7%)	17 (35.4%)
Positive	1 (2.0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.0%)	0 (0%)	1 (2.0%)	0 (0%)	5 (10.0%)	1 (2.1%)	15 (30.6%)	13 (27.1%)
Negative	0 (0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	0 (0%)	0 (0%)	2 (3.9%)	1 (2.1%)	9 (18.0%)	6 (12.5%)	17 (34.7%)	18 (37.5%)

* Day 1 (predose) represent baseline (control) ADA collected before the single dose administration. ADA positivity is for the confirmatory step of a three-tiered approach.

Source: FDA reviewer (based on the Immunogenicity Safety Analysis Dataset: adis.xpt)

Table 13. Summary of Daily ADA titers in Protégé study

	Protégé study					
	Day 0 (N=200)	**Day 14 (N=1)**	**Day 28 (N=198)**	**Day 56 (N=195)**	**Day 91 (N=196)**	**Day 226 (N=1)**
Ln(ADA concentration) [ng/mL]						
Mean (SD)	0.191 (0.940)	3.98 (NA)	3.04 (2.78)	2.68 (3.10)	2.93 (3.25)	4.30 (NA)
Median [Min, Max]	0 [0, 5.49]	3.98 [3.98, 3.98]	4.20 [0, 10.6]	0 [0, 10.1]	0 [0, 9.88]	4.30 [4.30, 4.30]
Missing	2 (1.0%)	0 (0%)	0 (0%)	1 (0.5%)	1 (0.5%)	0 (0%)
ADA category						
Null	190 (95.0%)	0 (0%)	86 (43.4%)	107 (54.9%)	103 (52.6%)	0 (0%)
Value ≥ Ln(48.85)*	8 (4.0%)	1 (100%)	112 (56.6%)	87 (44.6%)	92 (46.9%)	1 (100%)
Missing	2 (1.0%)	0 (0%)	0 (0%)	1 (0.5%)	1 (0.5%)	0 (0%)

*The ADA concentration threshold value is 48.85 ng/mL representing the LLOQ of the ADA assay.
Note: the neutralizing antibodies (NAb) assessed on Day 56 represented 88.9% (16/18 samples evaluated) of the MacroGenics product.
Source: FDA reviewer (based on the population PK dataset)

Structural and Base PK model

The PK of teplizumab following an IV administration (of at least 30 minutes) was described by a 3-compartment model, with linear non-specific elimination from the central compartment, binding and target-mediated drug disposition (TMDD) in all 3 compartments (central, peripheral, and fast or rapidly-equilibrating peripheral compartment), as well as an additional binding and TMDD through a non-renewable pool of target from the peripheral compartment. The quasi-steady-state (QSS) approximation of the TMDD was used in the PK model (as previously used for the Protégé model). Compared to the previously developed Protégé model, the current joint PK model (from all studies) included an additional fast peripheral compartment (3rd compartment) to describe the rapid decline of drug concentrations in the initial hours after dosing, captured by the intensive sampling in study PRV-031-004, and included an additional elimination pathway through binding and TMDD through a non-renewable pool of target from the 2nd peripheral compartment to describe the higher CL of teplizumab under the lower dosing regimens (reduced 14-day regimen and full 6-day regimen) studied in the Protégé study. Finally compared to the previously developed 2 PK models, the current joint PK model estimated an internalization rate constant for the MacroGenics and Lilly products.

The 3-compartment QSS TMDD model was parameterized in terms of CL, central and 2 peripheral volumes of distribution (Vc, Vp, Vp2), inter-compartmental clearances (Q and Qp2), concentration of target at baseline (BASE), the quasi-steady-state constant (KSS), an internalization rate constant (Kint) for all products except for the AGC product, target degradation rate constant (Kdeg), concentration of no-renewable target at baseline (RMAX) and an elimination/association rate constant to non-renewable target (Kb).

The inter-individual variability (IIV) was estimated for teplizumab CL, Vc, Vp, Q, Qp2, Kb, and on the residual error. The IIV on V1 and Q2 was included only for subjects with dense sampling (i.e., study PRV-031-004 and segment 1 of the Protégé study). The residual variability was best described by a proportional error model, with a lower residual variability for study PRV-031-004.

Covariate analysis

The following covariates were included in the final joint PK model:

- Body weight on CL, Vc, Vp and Vp2, using a power function standardized to a body weight of 60 kg.
- ADA concentrations (HAHA2) from the Protégé study on CL, and the ADA titer (LTITR) from TN-10 study and PROTECT sub-study as corrected-covariate on CL, using a proportional linear model where HAHA2 or LTITR were corrected by a threshold value (e.g., HAHA2-thershold). HAHA2 (natural-logarithm [Ln] of maximum ADA measurements up to day 120 after first dose) was corrected by a fixed threshold of 4 (i.e., Ln of ADA LLOQ of 48.85

ng/mL). LTITR (Ln of maximum ADA measurements up to day 56) was corrected by a fixed threshold of 3.4 (i.e., Ln of ADA titer cut point of 30). Below these thresholds the ADA effect on teplizumab CL is assumed to be absent.

- The Lilly product as covariate on KSS, using a multiplicative effect.
- The AGC product treatment arm in study PRV-031-004 on CL, using a multiplicative effect
- The AGC product treatment arm in the PROTECT sub-study on CL, using a multiplicative effect.

Final model

The parameter estimates from the final joint population PK model describing teplizumab pharmacokinetics from all data and products (Course 1 of Protégé study, TN-10 study, PRV-031-004 study and PROTECT sub-study) are listed in Table 14.

According to the Applicant's PK model, the Lilly product (used in TN-10 study, PRV-031-004 study and PROTECT sub-study) has 1.68 fold higher KSS compared to the MacroGenics product and the AGC product.

In study PRV-031-004 (single dose of 207 µg/m2 in healthy subjects), the AGC product was estimated to have 3.28 fold higher CL compared the Lilly product or MacroGenics product. However, in the PROTECT sub-study the AGC product was estimated to have 1.73 fold higher CL compared to the Lilly product.

Kint was estimated to very low and statistically not different from zero for the AGC product (either in study PRV-031-004 or the PROTECT sub-study) and could not be reliably (precisely) estimated by the PK model. Therefore, Kint for the AGC product was fixed to 0. No other differences in the PK parameters were observed between the MacroGenics, the Lilly and the AGC products.

In the Protégé study, the ADA effect on the CL of the MacroGenics product (CL_{HAHA2}) was estimated to be 0.136 (slope of fractional increase), i.e., at the highest measured median Ln(ADA concentration) of 6, CL was estimated to increase by 27%.

In study TN-10 and PROTECT sub-study that measured ADA titers instead of ADA concentrations, the Applicant PK model found comparable ADA effect on CL of the Lilly product (TN-10 and PROTECT studies) and MacroGenics (TN-10 study only). The separate estimation of ADA effect on the CL of the MacroGenics product compared to the Lilly product was not found to be statistically significant. The estimated slope of fractional increase of CL with ADA in the TN-10 study and PROTECT sub-study was 0.0775. Therefore, at the highest measured median Ln(ADA titer) of 7, teplizumab CL was estimated to increase by 28%.

Regarding the AGC product cohort of the PROTECT sub-study, the estimate of the ADA effect on the CL of the AGC Biologics product was nearly zero with a very high relative standard error (RSE). Therefore, the ADA effect on teplizumab CL was fixed to zero for the AGC product.

In the healthy subjects' study (PRV-031-004), the ADA titers appeared late after the single dose administration. The immunogenicity was detected in a very few subjects before Day 8 post-dose (n=4 over 100 subject in both the AGC and Lilly products arms). By Day 8, when ADA titers were detected in 21 subjects (14 in AGC and 7 in Eli Lilly treatment arms), teplizumab concentrations were very low (below 5 ng/mL for almost all subjects) or BQL (in all but 3 subjects for AGC product, and in 12 subjects for the Lilly product). In addition, 5 of the 14 ADA positive samples in AGC arm and 1 over the 7 positive ADA samples in Lilly arm were neutralizing antibodies (NAb). Therefore, the ADA effect on teplizumab CL could not be informed after a single dose study PRV-031-004 and can be considered not relevant. The PK difference between the AGC product and the Lilly product in the PRV-031-004 study was already observed before the appearance of ADA and NAb, particularly on Day 8. Therefore, it was concluded the PK difference between product is likely not the driver of the PK differences between products.

The interindividual random effect (ETA) shrinkage, on the PK parameters that are affected by the clinically relevant covariates, was 19.1 and 42.5 for CL and KSS, respectively. The estimated residual error in PRV-031-004 study (single dose study with rich PK sampling) was lower compared to the other studies and represented 27% of the overall residual variability (29.4%) estimated from the other studies.

The estimates of precision for the model parameters (RSE and asymptotic 95% confidence intervals) were provided for each of the parameters. Non-parametric bootstrap was unfeasible due to long run times. All fixed-effect parameters were precisely estimated (RSE ≤ 20%), except for the effect of LTITR on CL (RSE = 31.4%). The majority of inter-individual variability (IIV) parameters were also precisely estimated (RSE of 8.5 - 16%) except for IIV for Qp2 and Kb (RSE = 27.6% and 42.8%, respectively). The use of the M3 method to account for BQL observations found that the exclusion of BQL observations in the current PK modeling did not affect the estimated PK model parameters.

Table 14. Parameter Estimates from the Final Joint Population PK Model

Parameter		Estimate	RSE (%)	95%CI
CL (L/day)	θ1	1.65	4.19	1.52 ; 1.79
V_c (L)	θ2	2.27	3.42	2.11 ; 2.42
Q (L/day)	θ3	8.84	5.74	7.84 ; 9.83
V_p (L)	θ4	5.75	3.68	5.34 ; 6.17
BASE (ng/mL)	θ6	160	5.64	142 ; 178
K_{SS} (ng/mL)	θ7	20	6.3	17.6 ; 22.5
V_{CWT}, V_{PWT}	θ8	0.733	5.92	0.648 ; 0.818
CL_{WT}	θ9	0.519	13.1	0.386 ; 0.653
CL_{HAHA2}	θ10	0.136	13.8	0.0993 ; 0.173
Kint (1/day)	θ12	0.0286	8.56	0.0238 ; 0.0334
Kdeg (1/day)	θ13	0.123	14	0.0891 ; 0.157
Qp_2 (L/day)	θ14	54.5	6.5	47.6 ; 61.5
Vp_2 (L)	θ15	0.976	4.28	0.894 ; 1.06
Kb * 1000 (1/day/(ng/mL))	θ16	0.276	14.8	0.196 ; 0.356
R_{MAX}	θ17	1310	15.9	898 ; 1710
$CL_{LTITR\ TRT\ 4,\ 7}$	θ18	0.0775	31.4	0.0297 ; 0.125
$Thresh_{LTITR}$	θ19	3.4	NA	NA
Kss_{Lilly}	θ20	1.68	7.78	1.43 ; 1.94
CL_{TRT6}	θ21	3.28	8.06	2.76 ; 3.8
$Kint_{AGC}$	θ22	0	NA	NA
CL_{TRT8}	θ23	1.73	9.76	1.4 ; 2.06
$CL_{LTITR\ TRT\ 8}$	θ24	0	NA	NA

SE: Standard Error; RSE: Relative Standard Error; %RSE: 100·SE/PE, where PE is a parameter estimate; 95% CI: 95% confidence interval; CL: clearance; Vc, Vp, and Vp2: volumes of central and 2 peripheral compartments; Q and Qp_2: inter-compartmental clearance of the peripheral compartments; BASE: concentration of target (in drug units) at baseline; K_{SS}: quasi-steady-state constant; Kint: internalization rate constant; K_{deg}: target degradation rate constant; Kb: association rate constant for non-renewable target; Kb: association rate constant for non-renewable target; R_{MAX}: concentration of no-renewable target (in drug units) at baseline; CL_{WT}, V_{CWT}, V_{PWT}: power coefficients for dependence of CL, Vc, and Vp on body weight; CL_{HAHA2}, CL_{LTITR}: slope of fractional increase of CL with HAHA2 in Protégé or with LTITR in TN-10 and PROTECT, respectively; $Thresh_{LTITR}$: threshold for LTITR; Kss_{Lilly}: multiplicative effect of Lilly product on K_{SS}; CL_{TRT6} and CL_{TRT8}: multiplicative effect of TRT6 (AGC in Study 004) or TRT8 (AGC in PROTECT) on CL; $Kint_{AGC}$: Kint for AGC; $CL_{LTITR\ TRT\ 8}$ slope of fractional increase of CL with LTITR in AGC PROTECT

Continued next page

Table 14 continued

Parameter		Estimate	RSE (%)	95%CI	CV (%)	Shrinkage (%)
ω^2_{CL}	Ω(1,1)	0.124	8.48	0.103 ; 0.145	0.352	18.8
ω^2_{Kss}	Ω(2,2)	0.177	13	0.132 ; 0.222	0.42	42.7
ω^2_{Q}	Ω(3,3)	0.272	10.7	0.215 ; 0.329	0.522	40.3
ω^2_{Vp}	Ω(4,4)	0.0932	13.7	0.0681 ; 0.118	0.305	33.4
ω^2_{σ}	Ω(5,5)	0.0386	10.8	0.0304 ; 0.0469	0.197	36.5
ω^2_{Qp2}	Ω(6,6)	0.179	27.6	0.0819 ; 0.275	0.423	29.1
ω^2_{Vc}	Ω(7,7)	0.0319	16.1	0.0218 ; 0.0419	0.179	13.2
ω^2_{Kb}	Ω(8,8)	0.342	42.8	0.0552 ; 0.63	0.585	73.9
σ_{prop}	θ5	0.293	2.38	0.28 ; 0.307	-	-
EPS_{ST4}	θ11	0.27	4.16	0.248 ; 0.292	-	-

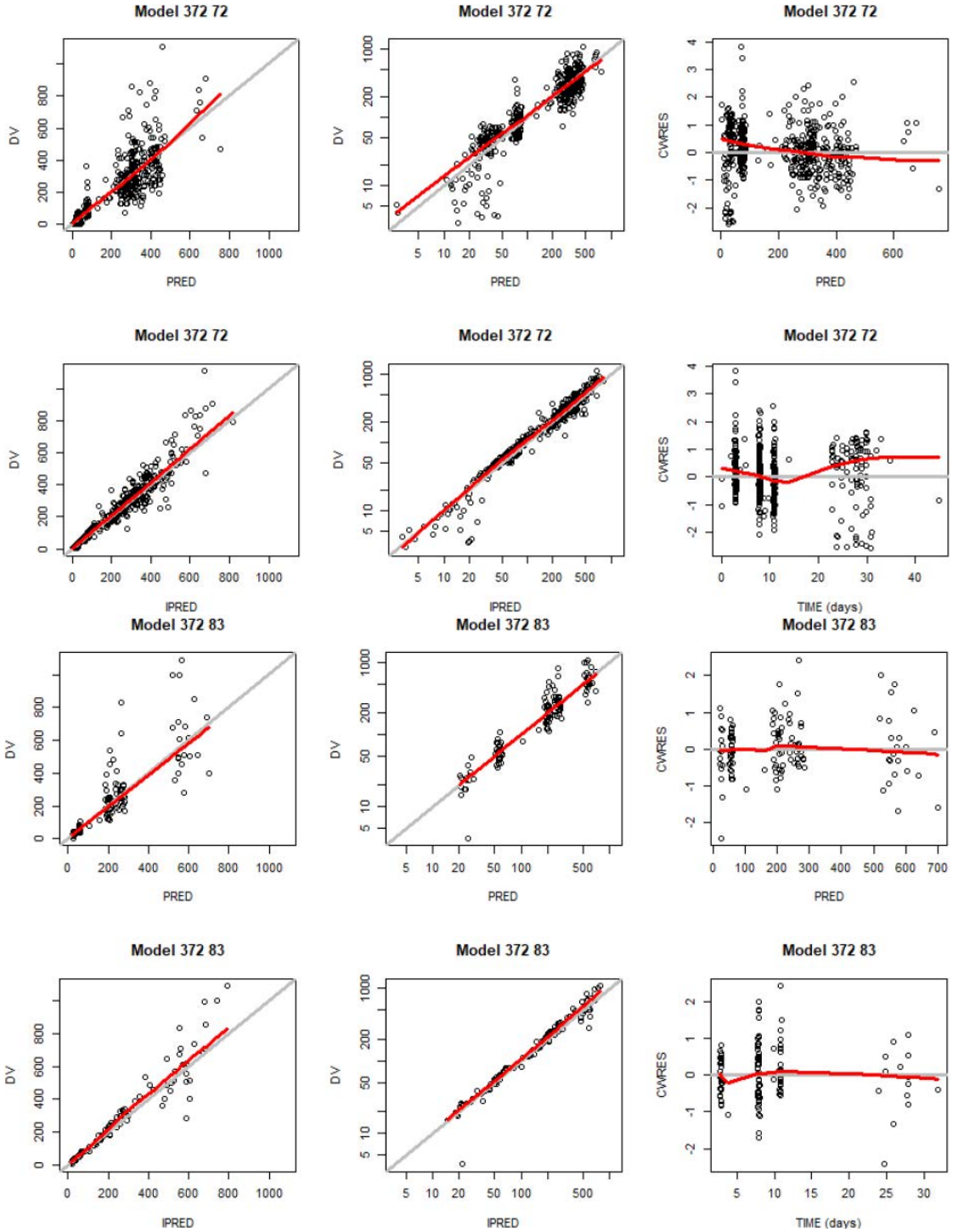
SE: Standard Error; RSE: Relative Standard Error; %RSE: 100·SE/PE, where PE is a parameter estimate; 95% CI: 95% confidence interval; CV: coefficient of variation; ω^2_{CL}, ω^2_{Kss}, ω^2_{Vp}, ω^2_{Q}, ω^2_{Kb}, ω^2_{σ}: variances of inter-individual random effects for CL, Kss, Vp, Q, Kb, and residual error; ω^2_{Qp2}, ω^2_{Vc}: variances of inter-individual random effects for Qp_2 and Vc for subjects with dense sampling; EPS_{ST4}: fraction of standard deviation for the residual error in healthy subjects (study PRV-031-004).

Source: Applicant's Population PK Report Update (model 372), Tables 2 and 3, pages 12 and 13.

The goodness-of-fit (GOF) plots, stratified by study, regimen and teplizumab product, showed that the joint-PK model is able to appropriately describe all of the observed data for the different studies and teplizumab products. Figure 9 shows the GOF plots for the Lilly and AGC products cohorts of the PROTECT sub-study (i.e., the study used to evaluate the PK comparability between teplizumab products, with the Lilly product being the reference and the AGC product representing the to-be-marketed/commercial product). In Figure 9, the plots of the observed concentrations versus the population predicted as well as the individual predicted concentrations show random normal scatter around the identity lines, indicating absence of systematic bias. The conditional weighted residuals versus time, time after dose or population predicted concentrations also show random normal scatter around zero with no specific patterns.

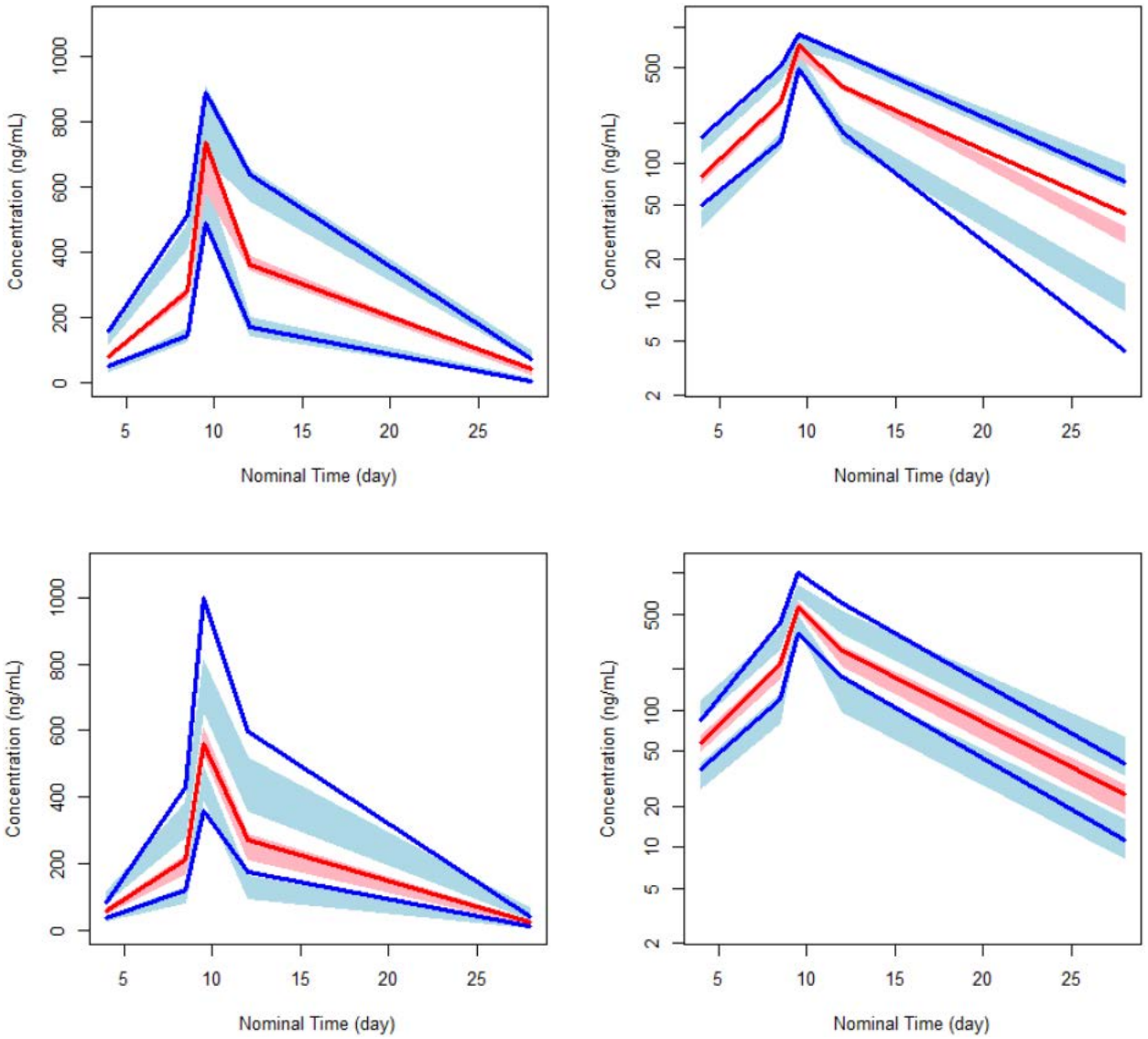
The prediction-corrected Visual Predictive Check (pcVPC) plots of concentration versus time, stratified by study, regimen and teplizumab product, indicated good agreement of the simulated and observed data from the different studies, regimens, and products. However, the pcVPC plots from the PROTECT sub-study (Figure 10) shows from that the population PK model has the tendency to underestimate the median observed teplizumab concentration in the Lilly product cohort after Day 20.

Figure 9. Goodness of Fit Plot from the Final PK Model (model 372) for the PROTECT sub-study



The upper (model 372 72) and lower (model 372 83) panels are the GOF plots for the Lilly product and AGC product of the PROTECT sub-study, respectively. DV: Observed concentrations; PRED: population predictions; IPRED: individual predictions; CWRES: conditional weighted residuals. The gray solid lines (y=x or y=0) are identity and reference lines. The bold red lines are the loess (local regression smoother) lines. All plots are using arithmetic scales except for the middle column plots that are on log scales.
Source: Applicant's Population PK Report Update (model 372), Figures 8 and 9, pages 24 and 25.

Figure 10. Visual Predictive Check plots from the Final PK Model for the PROTECT sub-study



The upper and lower panels represent the pcVPC for the Lilly product and AGC product of the PROTECT sub-study, respectively. The left figures are on arithmetic scales and the right figures are on semi-log scales. The solid lines are median (red), and 5th and 95th percentiles (blue) of observed concentrations. The shaded regions show the 90% confidence intervals on these quantities obtained by simulations from the model 372. The simulated values were computed from 500 simulated trials with dosing, sampling, and covariate values in the dataset. Nominal Time for data on Day 9 was slightly modified to separate troughs and peaks on the plots.

Source: Applicant's Population PK Report Update (model 372), Figures 32 - 33, pages 49 - 50.

Reviewer's Assessment of the joint population PK analysis and the ADA effect on teplizumab clearance from the PROTECT sub-study

- The Applicant's joint PK model adequately describes the observed concentrations from all studies, dosing regimens and products.
- The PK parameter from the final model were estimated with a good precision (RSE ≤ 15.9%), except for the estimated common effect of ADA titers on teplizumab CL from the Lilly product (in TN-10 study and PROTECT sub-study) and MacroGenics product (in TN-10 study only) with an RSE of 31.4%
- The applicant PK model evaluated the ADA titers effect on CL as a constant covariate, using the maximum observed Ln(ADA titer) for each individual in the TN-10 study and PROTECT sub-study for the Lilly product. However, the ADA titer effect was estimated to be absent for the AGC product in the PROTECT sub-study, and this even though the AGC product cohort showed a higher proportion of patients with measurable ADA titers (Table 11) and neutralizing antibody (NAb) positivity (on Day 28 after treatment initiation, Table 11).
- The reviewer's separate assessment of the effect of ADA titers in the PROTECT sub-study, as a time-varying covariate on the CL of the Lilly product and the AGC products, found a positive ADA effect on the ACG product's clearance (Table 15). The reviewer's PK model with a common ADA effect to both products on CL decreased the objective function values (OFV) by 20 points (p value < 0.001, for 1 degree of freedom [df]) compared to the Applicant's model. The ADA effect for the Lilly product and AGC product in the PROTECT sub-study was not found to be statistically different, with a difference in OFV of 0.08 points (p > 0.05, 1 df) between a PK model with separate ADA effects for each product and a reduced PK model with a common ADA effect on CL. The reviewer's PK model estimated that at the highest measured median Ln(ADA titer) of 6 to 7, the teplizumab CL increased by 11% to 33% for either the Lilly product or the AGC product.

  The ADA effect on CL in study TN-10 was estimated separately from the PROTECT sub-study, in the reviewer's PK model. In TN-10 study, the ADA assessment was performed only at month 3 or 4 after start of the 14-day single course treatment. Therefore, ADA titer could not be used as a time-varying covariate. In addition, teplizumab was already cleared from the systemic circulation by the time of ADA samples collection, rendering the estimation of ADA effect on CL less reliable. In fact, according to the reviewers' PK model (Table 15), the estimated ADA effect on CL of either the Lilly or MacroGenics product (in TN-10 study) was negligeable and statistically not different from zero, with an estimated slope of fractional increase in CL of 0.0357 and a high RSE of 139% (likely to lack of informative PK and ADA data). Table 15 summarizes the reviewer's PK model. Most of the PK parameters were comparable to the Applicant's PK model, except for the estimated covariate ADA effect on CL in the TN-10 study and PROTECT sub-study. The inclusion of ADA titers as a time-varying covariate on CL using a power model in the PROTECT sub-study decreased the OFV by 20 points (p < 0.001, 1 df). In contrast, a linear model to describe the ADA titers effect in PROTECT sub-study increased the OFV by 11 points.

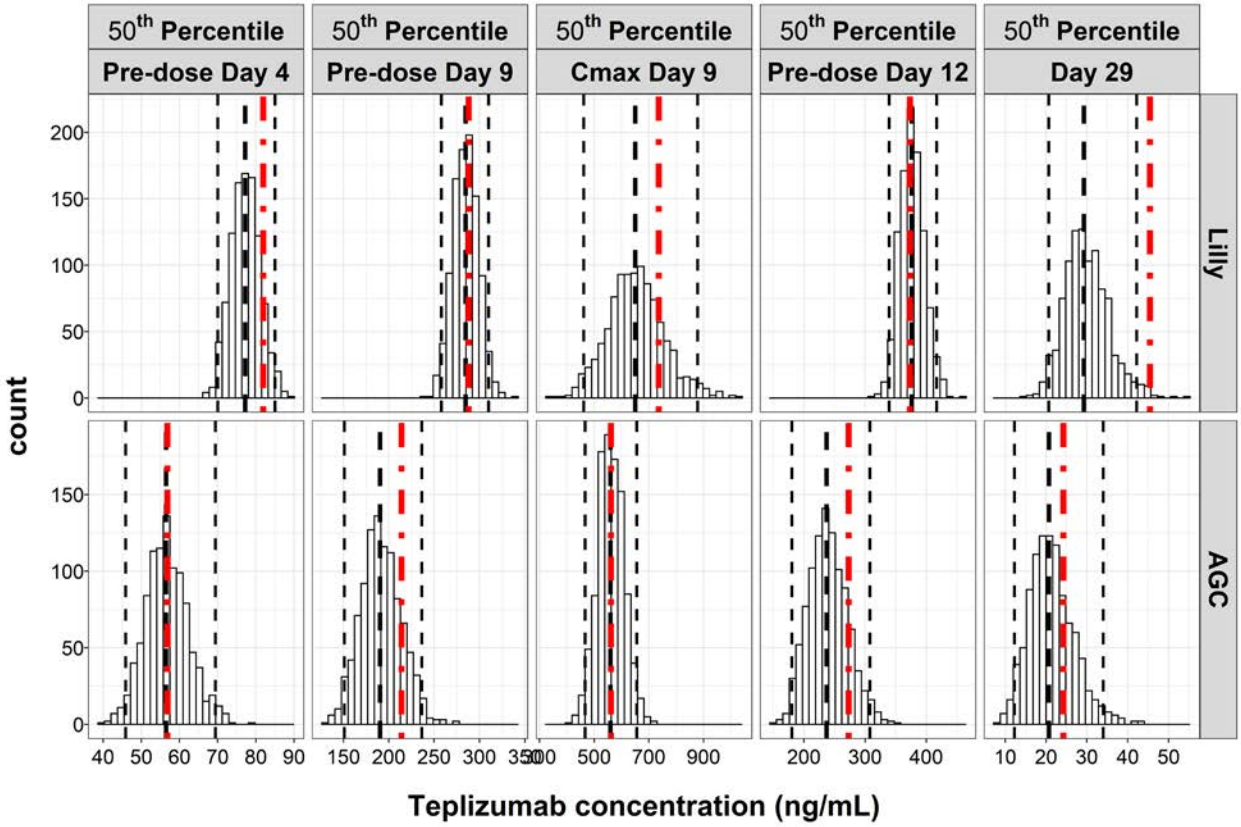
Table 15. Parameter Estimates from the Reviewer's Updated Joint Population PK Model

Parameters	**Estimate**	**[%RSE]**
CL (L/day)	1.68	4.1%
Vc (L)	2.27	3.3%
Q (L/day)	8.75	6%
Vp (L)	5.79	3.5%
BASE (ng/mL)	161	5.6%
KSS (ng/mL)	20.1	6.1%
Vc_{WT} and Vp_{WT}: Power exponent on (WT/60)	0.727	5.6%
CL_{WT}: Power exponent on (WT/60)	0.469	14.5%
CL_{HAHA2}: slope of ADA concentration effect on MacroGenics CL (Protégé study)	0.122	14.8%
Kint (1/day)	0.0281	8.3%
Kdeg (1/day)	0.123	13.3%
Qp2 (L/day)	54.5	6.7%
Vp2 (L)	0.964	4.2%
Kb × 1000 (1/day/(ng/mL))	0.257	13.3%
RMAX	1420	14.9%
$CL_{LTITR\ TN\text{-}10}$: slope of ADA titer effect on CL in TN-10 study (Lilly and MacroGenics)	0.0357	139%
$Thresh_{LTITR}$: ADA titer threshold (cut point)	3.4 (fixed)	NA
Kss_{Lilly}	1.68	7.8%
$CL_{AGC\ Healthy}$: multiplicative effect of AGC product on CL in study PRV-031-004	3.21	8.2%
$Kint_{AGC}$	0 (fixed)	NA
$CL_{AGC\ PROTECT}$: Multiplicative effect of AGC product on CL in PROTECT sub-study	1.63	9.9%
$CL_{LTITR\ PROTECT}$: power exponent for ADA titer effect on CL of AGC and Lilly in PROTECT*	3.34	21.5%
Variance on CL	0.134	9%
Variance on Kss	0.168	12.7%
Variance on Q	0.345	10.3%
Variance on Vp	0.0691	16.6%
Variance on the proportional residual error	0.0379	10.5%
Variance on Qp2	0.187	29.7%
Variance on Vc	0.0287	15.6%
Variance on Kb	0.134	9%
Proportional residual error (%CV)	29.3%	2.4%
Fraction of the proportional residual error for study PRV-031-004 (healthy)	27%	4.1%

*ADA titer covariate in PROTECT sub-study was included as: CL=typical CL x [1+ (LTITR-$Thresh_{LTITR}$)/5)^ $CL_{LTITR\ PROTECT}$], where 5 is a reference Ln(ADA titer) or LTITR. NA: not applicable.
Source: FDA reviewer

- Figure 11 represents the quantitative predictive check (QPC) plots from the Reviewer's PK model at each sampling time point from the PROTECT sub-study (i.e., the PK comparability sub-study). There is a good agreement between the 50th percentiles (medians) of the observed teplizumab concentrations and the simulated concentrations for each product at the various sampling times, with the 50th percentiles of the observed concentrations (red dot-dashed vertical line) at each sampling time point falling within the 95% CIs (black dotted lines) of the 50th percentiles of the simulated concentrations (500 replicates). At Day 29 the population PK simulations tend to slightly underestimate the median observed teplizumab concentration for the Lilly product only, with the median observed concentration (red dot-dashed vertical line) falling at the upper bound of the 95%CI (precision, black dotted line) of the simulated 50th percentile (bold black dotted line).

Figure 11. Quantitative Visual Predictive Check (QPC) at Different Sampling Time Points for Teplizumab Products in PROTECT Sub-Study



Note: The vertical dot-dashed red line, in each panel, represents the 50th percentile of the observed teplizumab concentration at each sampling time point. The vertical dashed black lines, in each panel, represent the median (in bold) of the simulated concentrations at each sampling time point, and the 95% confidence intervals of the 50th percentiles of the simulated concentrations (from 500 dataset replicates per teplizumab product).
Source: FDA reviewer

- The QPC plots and the GOF plots including the observed versus individual predicted concentrations suggest that the PK model is able to reliably predict teplizumab concentrations from both products and can be used for simulations and to assess PK comparability. Table 16 shows that the PK model is able to correctly predict the observed differences in PK concentrations, at each sampling time point, between the Lilly product and AGC product in the PROTECT sub-study, based on individual PK simulations.

Table 16. Comparison of the Observed and Model-Predicted Teplizumab Concentrations At Each Sampling Time Point in PROTECT Sub-Study

	PK comparability results		
	AGC product Geometric mean (%CV)	**Lilly product Geometric mean (%CV)**	**GMR (90%CI)**
Observed Cmin on Day 4	57.5 (29%) [n=31]	82.2 (35%) [n=124]	70% (62.8% - 78%)
Model-predicted Cmin on Day 4	55.8 (24%)	75.9 (25%)	73.5% (67.8% - 79.6%)
Observed Cmin on Day 9	215 (40%) [n=30]	289 (40%) [n=121]	74.5% (65.4% - 84.9%)
Model-predicted Cmin on Day 9	201 (31%)	281 (28%)	71.4% (64.9% - 78.5%)
Observed Cmin on Day 12 (before last dose)	287 (45%) [n=26]	368 (38%) [n=120]	78% (68.2% - 89.3%)
Model-predicted Cmin on Day 12	254 (35%)	374 (30%)	67.9% (60.8% – 75.8%)
Observed concentrations on Day 29	22.3 (19%) [n=6]	38.2 (54%) [n=20]	58.4% (40% - 84%)
Model-predicted concentrations on Day 29	21.3 (15%)	36.6 (35%)	58.3% (45.5% - 74.7%)

GMR (90%CI): geometric mean ratio (90% confidence interval), derived from Student's t-test (with Levene Test for equality of variances) on natural log-transformed PK exposure metrics. The model-predicted are based on individual (conditional) PK simulations using the individual PK parameters of the PROTECT sub-study patients.
Source: FDA reviewer

- Based of the population PK analysis, the AGC product has a saturable binding to target CD 3 receptors but no target-mediated elimination through intracellular internalization, suggesting that the AGC product has linear non-specific elimination. Therefore, an increase in AGC product dosage for the purpose of exposure-matching to the Lilly product is not expected to saturate the elimination of teplizumab. Both teplizumab products were estimated to have comparable median half-lives (4.5 days and 4.4 days for the AGC and the Lilly product in PROTECT sub-study).

4.2.2 Alternative Dosing Regimens proposed by Applicant for the AGC Biologics Product to Match the Lilly Product exposure

The AGC product failed for the second time the PK comparability to the Lilly product (i.e., in study PRV-031-004 study and PROTECT sub-study). In the PROTECT sub-study, the AGC product was found to have lower exposure than the Lilly product under the PROTECT study regimen (Table 17), with the model predicted AUCinf, AUC[0-24h after last dose] and the observed Ctrough before last dose failed to pass the PK comparability criteria (i.e., 90% confidence interval [CI] of the geometric mean ratios between AGC and Lilly products exposure metrics within 80% to 125%). The Applicant's analysis used samples from all patients regardless of missing doses or early treatment discontinuation, including for the assessment of the observed Ctrough.

Table 17. Applicant's Comparison of the Observed and Model-Predicted PK Exposure Metrics from PROTECT Sub-Study

PK exposure metrics	**Applicant evaluation**
	GMR (90% CI) [a]
Predicted **Cmax** after last dose (ng/mL)	0.88 (0.840 - 0.923)
Predicted **AUC(0-tlast)** [b] (ng*day/mL)	0.86 (0.769 - 0.955)
Predicted **AUCinf** (ng*day/mL)	0.83 (0.744 - 0.924)
Observed Cmin before last dose [Day 12] (ng/mL)	0.86 (0.7 - 1.066)

[a] GMR (90%CI): geometric mean ratio (90% confidence interval) derived from the analysis of variance (ANOVA) model using natural log-transformed PK parameters as the dependent variable and product as a factor under the assumption of unequal variance.
[b] AUC(0-Tlast): tlast represents 24 hours after the last planned dose (Dose 12).
Adapted from Applicant's PK/PD Substudy Tables and Figures, Tables 4.1 to 4.2, page5 to 8.

The Applicant's PK simulations from the joint PK model were performed to find an alternative regimen to the reference 14-day (Herold) regimen for the AGC product, in order to match the PK exposure between the AGC product (under the alternative regimen) and the Lilly product (under the reference regimen). The PK simulations to determine the appropriate alternative 14-day regimen for the AGC product was based on:

a. individual (conditional) PK simulations using the individual PK parameters from the AGC and Lilly products cohorts of the PROTECT sub-study
b. population (average) PK simulations using the typical model PK parameters and performed under median BSA and median weight of subjects in the PROTECT sub-study and no ADA effect.

Table 18 summarizes the alternative dosing regimens proposed by the Applicant to match the PK exposure between the AGC product and Lilly product. Regimen A was the Applicant's preferred regimen likely because it has the (b) (4) in cumulative dose compared to the reference regimen.

Table 18. Applicant's Proposed Alternative Regimens A, B and C for the AGC product

	Daily dose (µg/m²)					Cumulative dose (µg/m²) [Relative increase from reference]
	Day 1	Day 2	Day 3	Day 4	Days 5-14	
Reference TN-10 trial regimen Herold 14-day (Lilly)	51	103	207	413	826	9,034 [reference]
AGC Regimen A	(b) (4)					(b) (4) [21%]
AGC Regimen B						[24%]
AGC Regimen C						[35%]

Source: Adapted from Applicant's BLA Resubmission Topics (m1), Table 3 , page 6.

Table 19 summarizes the PK comparability results (geometric mean ratio and 90%CI) for the model predicted AUCinf, Cmax after last dose, and Ctrough before last dose (Ctrough13: Ctrough after dose 13), derived from both the conditional PK simulations as well as the population (typical) PK simulations. According to the Applicant, (b) (4)

Table 19. Comparison of the Predicted PK Exposure Metrics between the Alternative Regimens and the Reference (Herold) Regimen

	AUC_{inf} (ng*day/mL)			C_{max} (ng/mL)			$C_{trough13}$ (ng/mL)		
Simulation Method	**Conditional**		**Typical (average)**	**Conditional**		**Typical (average)**	**Conditional**		**Typical (average)**
AGC Bio Regimens	Ratio Geo Mean	90% CI	Ratio	Ratio Geo Mean	90% CI	Ratio	Ratio Geo Mean	90% CI	Ratio
Regimen A	0.958	0.885-1.04	0.859	1.07	1.03-1.11	1.008	0.883	0.803-0.971	0.779
Regimen B	0.99	0.911-1.07	0.885	1.11	1.07-1.15	1.042	0.917	0.834-1.01	0.809
Regimen C	1.08	1.0-1.17	0.97	1.09	1.05-1.14	1.028	0.934	0.849-1.03	0.823

Regimen A = Ref 104.1; Regimen B = Ref 103.1; Regimen C = Ref 7.1
Typical simulations performed using median BSA and weight of subjects in the PROTECT study and no ADA
AUCinf: calculated as AUC[0-day 128] using an accumulation compartment in the PK model.
Source: Applicant's BLA Resubmission Topics (m1), Table 4 , page 7.

Table 19 shows discrepancies in the geometric mean ratios for AUCinf and particularly Ctrough13 estimated from the conditional (individual) PK simulations compared to the typical (average) PK simulations. The FDA reviewer's assessment identified that these discrepancies are due to the fact that the Applicant's PK model did not appropriately account for the ADA effect on teplizumab

CL from the AGC product cohort (as discussed in the assessment of the population PK model, section 4.2.1.

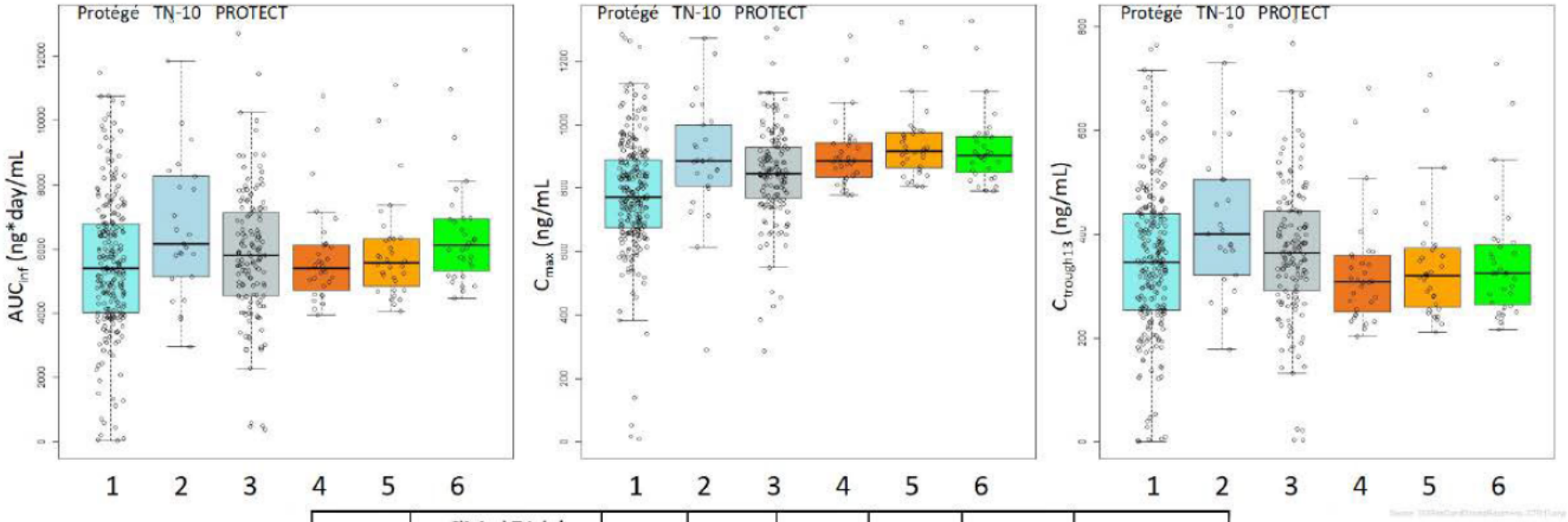
Figure 12 shows the distribution of the model-predicted teplizumab exposure metrics (AUCinf, Cmax and Ctrough13) in the historical clinical studies under their reference regimen and for the AGC product cohort of the PROTECT sub-study under the alternative regimens (A, B or C). According to the Applicant, (b) (4)

The predicted daily Cmax and Ctrough for the alternative regimens are shown in Figure 13 (Regimens A and B) and Figure 14 (Regimen C) alongside the predicted values from the Protégé study, TN-10 study and the Lilly product cohort of PROTECT sub-study.

(b) (4)

. In addition, the Applicant noted that the safety data from the PROTECT study reviewed every 4 months by the Data Monitoring Committee have shown no safety concerns.

Figure 12. Predicted teplizumab exposure metrics (AUCinf, Cmax and Ctrough13) in the historical clinical studies and PROTECT sub-study, under the reference and alternative regimen for the AGC product

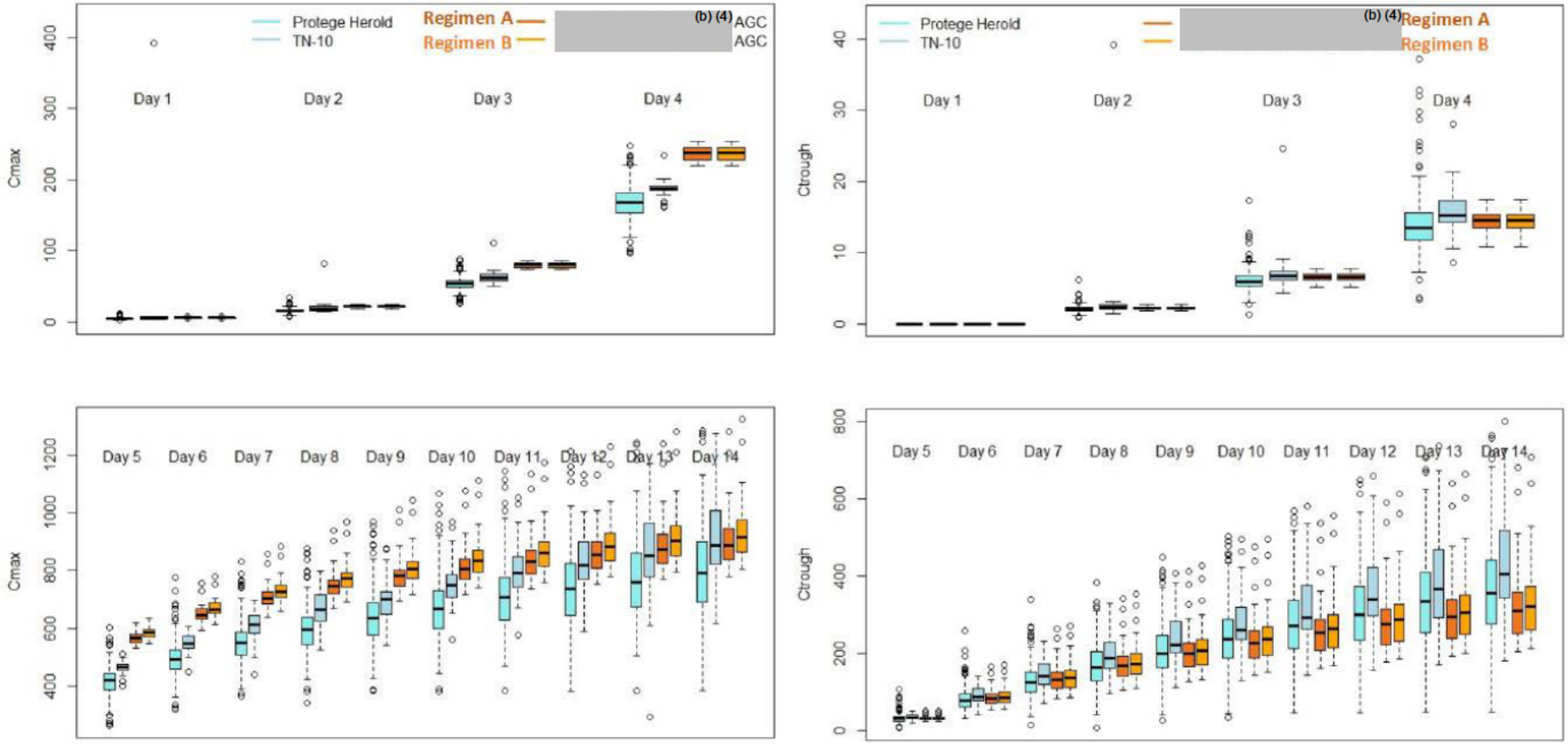


Number	Clinical Trials/ Alternative Regimens	Day 1	Day 2	Day 3	Day 4	Days 5-14	Cumulative Dose (µg/m²)
1, 2	Protégé and TN-10 Herold 14-day regimen (Eli Lilly)	51	103	207	413	826	9,034
3	PROTECT 12-day regimen (Eli Lilly)	106	425	850	850	850 (D5-12)	9,031
4	Regimen A (AGC Bio)	(b) (4)					
5	Regimen B (AGC Bio)						
6	Regimen C (AGC Bio)						

Protégé and TN-10 exposures represent all patients who received the Herold 14-day regimen in these studies; PROTECT exposures represent patients who received the Eli Lilly product in the PROTECT study. Regimen A, Regimen B and Regimen C are simulated PK data for alternative AGC Biologics regimens using the PROTECT study subjects who received the AGC Biologics product. The boxes indicate the median (line within a box) values as well as Q1 to Q3 interquartile ranges (IQRs). The whiskers indicate Q1-1.5 IQR and Q3+1.5 IQR. The data points outside the whiskers indicate outlier values.

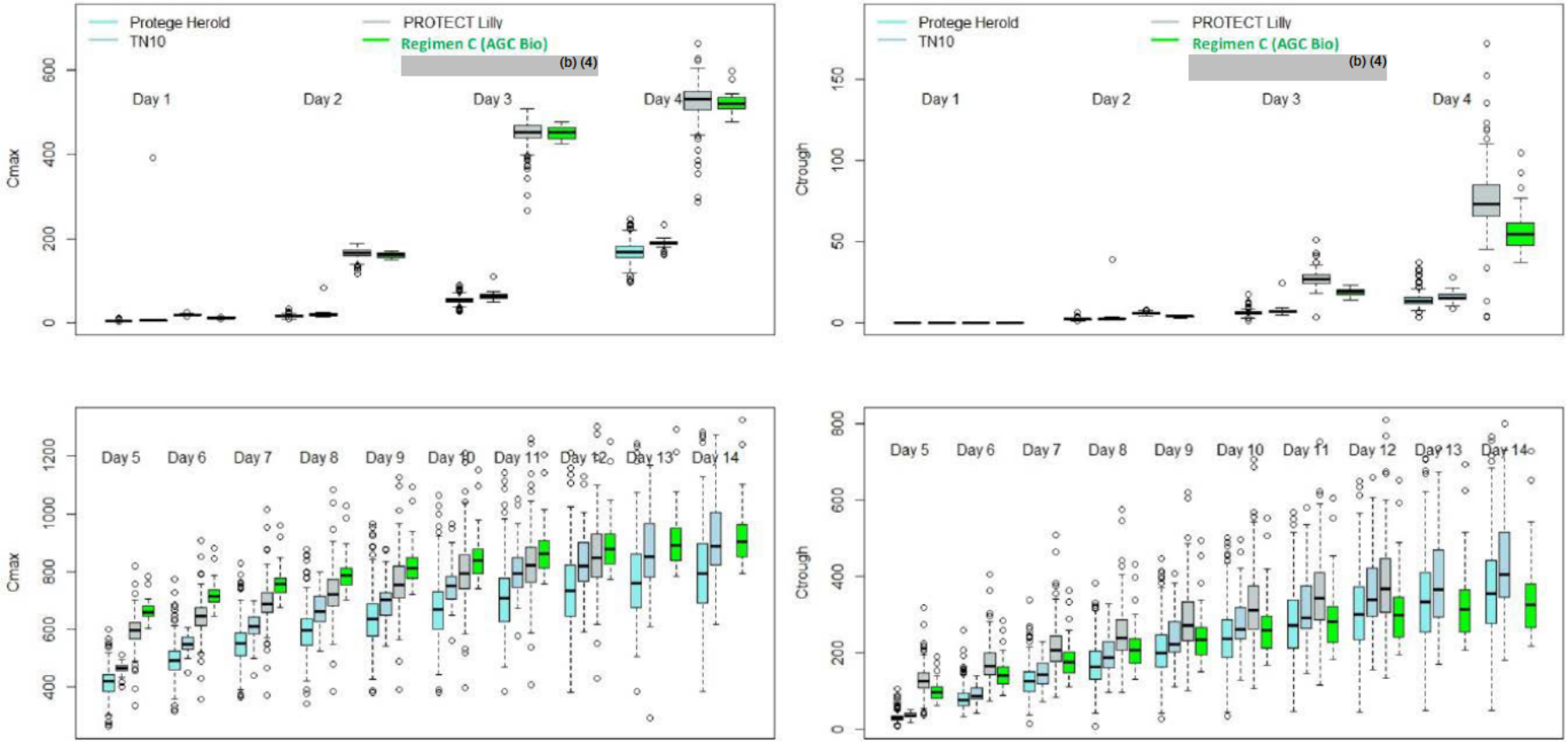
Source: Applicant's BLA Resubmission Topics (m1), Figure 2, page10.

Figure 13. Predicted Cmax and Ctrough During a 14-day Treatment in Protégé study and TN-10 studies (Reference 14-day regimen) and in the AGC Product Cohort of PROTECT sub-study (for Regimens A and B)



Source: Applicant's BLA Resubmission Topics (m1), Figure 3, page11.

Figure 14. Predicted Cmax and Ctrough During a 14-day Treatment in Protégé and TN-10 studies (Reference 14-Day Regimen), the Lilly Product Cohort of PROTECT Sub-study (PROTECT 12-day regimen), and the AGC product arm of PROTECT sub-study (Regimen C)



Source: Applicant's BLA Resubmission Topics (m1), Figure 4, page12.

Reviewer's assessment of the PK comparability between the AGC product and Lilly product and the proposed alternative dosing regimens for the AGC product

The reviewer's evaluation of the PK comparability between the AGC product and the Lilly product in the PROTECT sub-study was not consistent with the Applicant's evaluation, either for the observed Ctrough before last dose or for the model-predicted exposure metrics using either the Applicant's PK model or the FDA reviewer's PK model. A higher than the reported difference in PK exposure was found between both products (Table 20). According to reviewer's evaluation, the AGC product had 27% and 22% lower AUCinf and Ctrough (after last dose) than the Lilly product, respectively.

Table 20. Comparison of the Observed and Model-Predicted PK Exposure Metrics from PROTECT Sub-Study, under the Planned PROTECT Study Regimen and Duration of Infusion

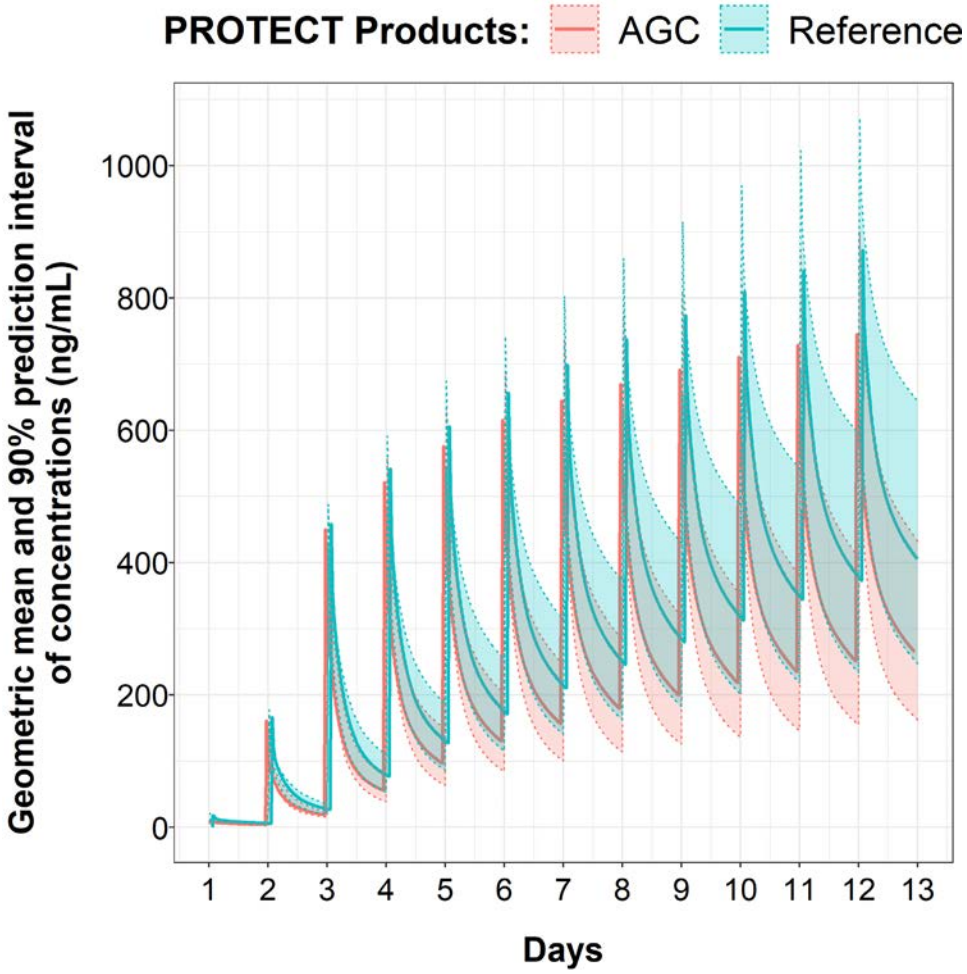
Predicted (Otherwise mentioned) PK exposure metrics	**Reviewer's evaluation**			**Applicant's evaluation**
	AGC GM [a] (%CV)	**Lilly GM (%CV)**	**GMR (90% CI) [a]**	**GMR (90% CI)**
Cmax after last dose (ng/mL)	745 (12%)	872 (13%)	0.854 (0.821 - 0.89)	0.88 (0.840 - 0.923)
AUC(0-Tlast) [b] (ng*day/mL)	2797 (19%)	3598 (19%)	0.777 (0.732 - 0.826)	0.86 (0.769 - 0.955)
AUCinf [c] (ng*day/mL)	4528 (22%)	6176 (25%)	0.733 (0.678 - 0.792)	0.83 (0.744 - 0.924)
Observed Cmin before last dose (Day 12) [number of observations] [d]	287 (45%) [n=26]	368 (38%) [n=120]	0.78 (0.682 - 0.893)	0.86 (0.7 - 1.066)
Cmin before last dose (Day 12)	251 (30%)	373 (29%)	0.674 (0.614 - 0.740)	Not reported
Cmin after last dose (Day 13)	265 (30%)	400 (30%)	0.664 (0.604 - 0.730)	Not reported

[a] GM: geometric mean, GMR (90%CI): geometric mean ratio (90% confidence interval), derived from Student's t-test (with Levene Test for equality of variances) on natural log-transformed PK exposure metrics.
[b] AUC(0-Tlast): Tlast represents 24 hours after the last planned dose (Dose 12), calculated using the trapezoidal linear-up and log-down method.
[c] AUCinf: calculated using the trapezoidal linear-up and log-down method.
[d] Observed Cmin before last dose (Day 12) in patients who received all their 11 doses.
Source: FDA reviewer

The discrepancy with the Applicant's assessment for Ctrough before the last dose is likely due to the fact the Applicant's analysis disregarded missing doses or early treatment discontinuations. The discrepancies regarding the predicted Cmax, AUC(0-Tlast) and AUCinf was not properly addressed by the Applicant after our information request. However, the accuracy of our estimations was corroborated by our ability to replicate the Applicant's PK comparability results from the alternative regimens (A, B and C), when simulating with the Applicant's PK model.

Figure 15 shows the model-predicted PK profiles for the AGC product (red) and the Lilly product (blue), under the PROTECT study 12-day dosing regimen. Teplizumab geometric mean concentrations from the AGC product (red) are located at the lower bound of the 90%PI (90% prediction interval) of all concentrations (i.e., distribution representing the between-subject variability) from the Lilly product (blue shaded area). Therefore, Figure 15 suggests that 50% of patients under the AGC product will have concentrations below or as low as the concentrations observed in only 5% of patients under the Lilly product.

Figure 15. Model-Predicted PK Profiles of the AGC Product and the Lilly Product (Reference) in the PROTECT Sub-Study



The solid red and blue lines are the geometric means of teplizumab concentrations from the AGC product and Lilly product, respectively. The colored shaded areas are the distributions (90% prediction intervals [90%PIs]) of teplizumab concentrations for the AGC product (red) and the Lilly product (blue). The dotted lines delimiting the shaded areas are the upper and lower bounds of the 90%PIs. The PK profiles are generated from the individual (conditional) PK simulations.
Source: FDA reviewer

Table 21 shows the FDA reviewer's evaluation of the proposed alternative regimens A, B or C for the AGC products using the FDA reviewer's PK model for simulations. The PK comparability results for exposure matching using conditional (individual) PK simulations are in concordance with the population (average) simulations findings. The proposed alternative regimens B and C meet the PK comparability criteria for AUCinf, Cmax (after last dose), Ctrough before last dose (Ctrough13), and Ctrough after last dose (Ctrough14). Even though the GMR point estimate or the lower bound of the 90%CI of the GMR is close to 80%, the applicant's preferred regimen A does not meet the strict PK comparability criteria for Ctrough14, when considering either the conditional or the average PK simulations.

Table 21. Comparison of the Predicted PK Exposure Metrics between the Alternative Regimens (for AGC product) and the Reference 14-Day Regimen (for Lilly product)

	GMR (90% CI) [a]				**Passes PK comparability**
	AUCinf [b]	**Cmax (After last dose)**	**Ctrough13 (Before last dose)**	**Ctrough14 (After last dose)** *Not reported by Applicant*	
Conditional simulations (using PROTECT sub-study patients' PK parameters)					
Regimen A	0.910 (0.842 – 0.984)	1.065 (1.022 - 1.109)	0.872 (*0.795* - 0.958)	0.856 (*0.779* - 0.942)	Not Ctrough14
Regimen B	0.94 (0.869 - 1.016)	1.101 (1.057 - 1.147)	0.906 (0.826 - 0.995)	0.889 (0.808 - 0.978)	Yes
Regimen C	1.03 (0.952 - 1.113)	1.089 (1.045 - 1.134)	0.926 (0.843 - 1.016)	0.898 (0.816 - 0.988)	Yes
Population (average) simulations [c] *(using typical PK parameters under same ADA conditions)*					
Regimen A	0.904 (0.899 - 0.91)	1.034 (1.031 - 1.037)	0.815 (0.809 - 0.821)	*0.799 (0.793* - 0.805)	Not Ctrough14
Regimen B	0.928 (0.922 - 0.934)	1.066 (1.063 - 1.069)	0.841 (0.835 - 0.847)	0.824 (0.818 - 0.83)	Yes
Regimen C	1.021 (1.015 - 1.027)	1.055 (1.052 - 1.058)	0.861 (0.855 - 0.867)	0.834 (0.828 - 0.841)	Yes

[a] GMR (90%CI): geometric mean ratio (90% confidence interval), derived from Student's t-test (with Levene Test for equality of variances) on natural log-transformed of PK exposure metrics.

[b] AUCinf: calculated using the trapezoidal linear-up and log-down method.

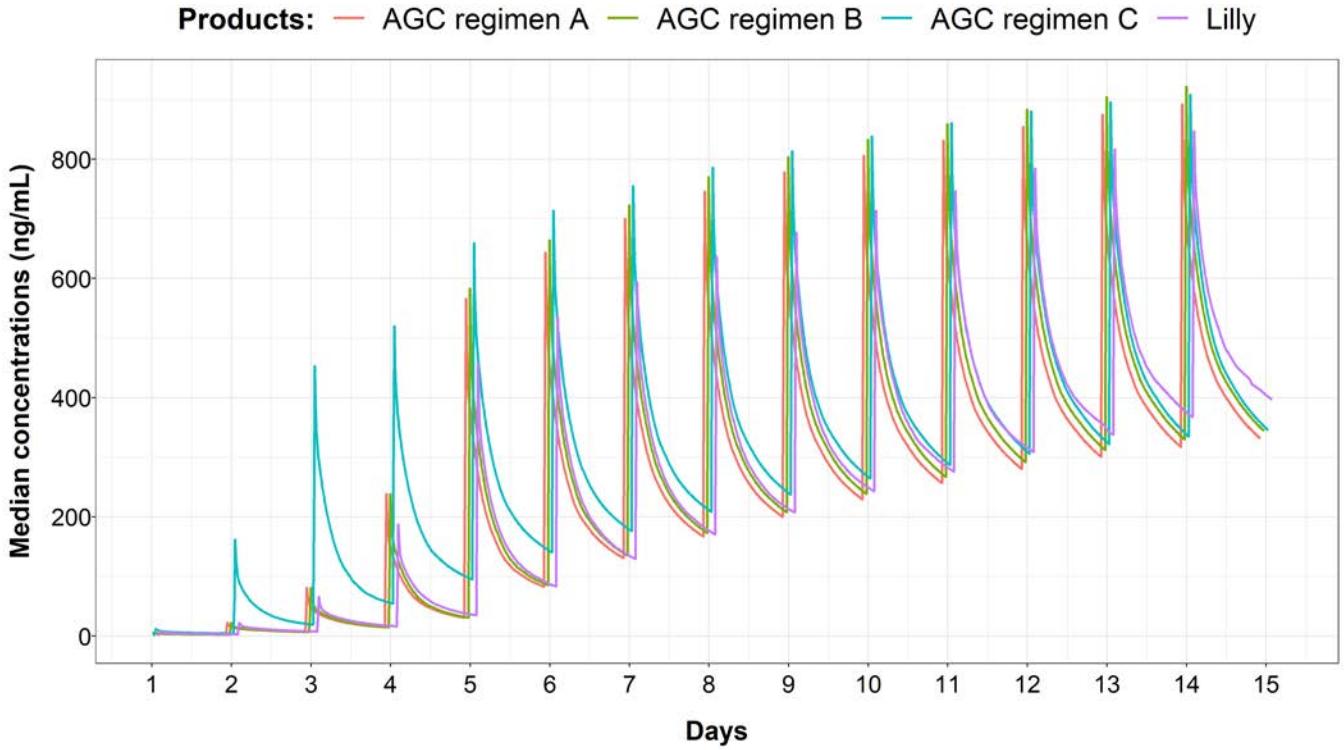
[c] Average or population simulations: Monte-Carlo simulations (500 replicates of the PROTECT sub-study dataset, with subjects' BSA and weight and no ADA titers) were performed to calculate the uncertainty (90%CI) of the GMR, using Student's t-test (with Levene Test for equality of variances) on natural log-transformed median PK exposure metrics calculated from each replicate (500 replicates).

Figure 16 shows the model-predicted median PK profiles from the AGC product under the proposed 3 alternative 14- day regimen and from the Lilly product (reference) under the

reference (Herold, i.e., TN-10 study) 14-day regimen. Regimen C does not provide additional advantages compared to Regimen B in term of matching the Lilly product reference exposure. In fact, the GMR and their 90%CI for AUCinf, Cmax (after last dose) and Ctrough14 are numerically very close (Table 21, Figure 16). However, regimen C is associated with unnecessarily higher exposure and Cmax values between Day 2 to 4 compared regimen B (Figure 16), as regimen C doses are 3.4 to 1.7-fold the doses in regimen B between Day 2 to 4 (Table 18).

Regimen B was considered the most appropriate regimen for the AGC product in order to much the overall exposure to the Lilly product under the reference (Herold) regimen. However, on Day 1 of regimen B, the dose of (b) (4) µg/m^2 was found not optimal to meet the PK comparability criteria for Cmax (after first dose) and AUC[0-24h], with a GMR (90%CI) of 0.796 (0.777 - 0.815) and 0.818 (0.795 - 0.843), respectively. On Day 1 of regimen B, a dose of (b) (4) µg/m^2 instead of (b) (4) µg/m^2 allows to meet the PK comparability criteria for Cmax and AUC[0-24h] based on conditional PK simulations, with a GMR (90%CI) of 0.879 (0.855 - 0.905) and 0.893 (0.868 - 0.92), respectively (Table 22).

Figure 16. Model-Predicted PK Profiles of the AGC Product (Alternative Regimens) and the Lilly Product (Reference Regimen)

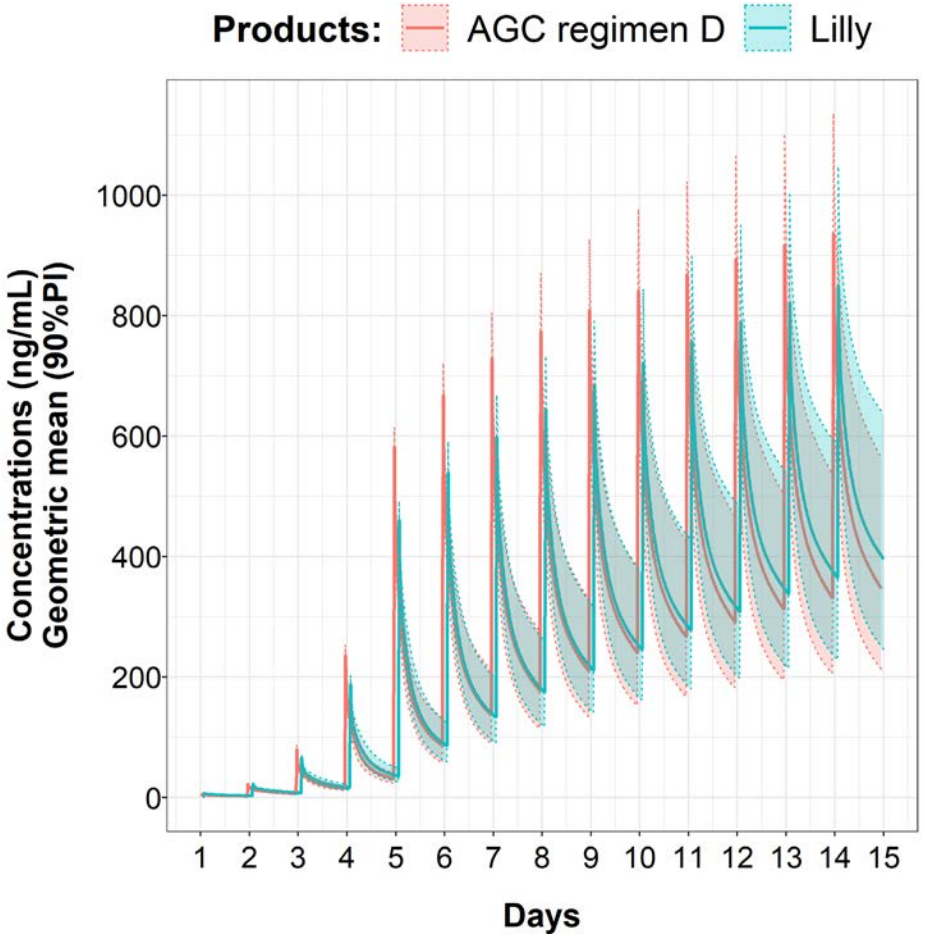


Reference 14-day regimen (daily dose): 51 – 103 – 207 – 413 – (825 x 10 days) µg/m2.
Regimen A (daily dose): (b) (4)
Regimen B (daily dose):
Regimen C (daily dose):
Source: FDA reviewer

The modified regimen B (regimen D), with the daily dosing of 65 – 125 – 250 – 500 – (1030 x 10 days) µg/m2 is considered the optimal regimen for exposure matching with the Lilly product (under the reference 14-day regimen). Figure 17 (A and B) shows the model-predicted PK profiles for the AGC product (red) and the Lilly product (blue), under the regimen D and the reference (Herold or TN-10 study) 14-day regimen, respectively. The average and the variability in teplizumab product are overlapping during the 14-day treatment.

Figure 17. Model-Predicted PK Profiles of the AGC Product (Regimen D) and the Lilly Product (Reference Regimen), on Arithmetic scale (A) and semi-logarithmic scale (B).

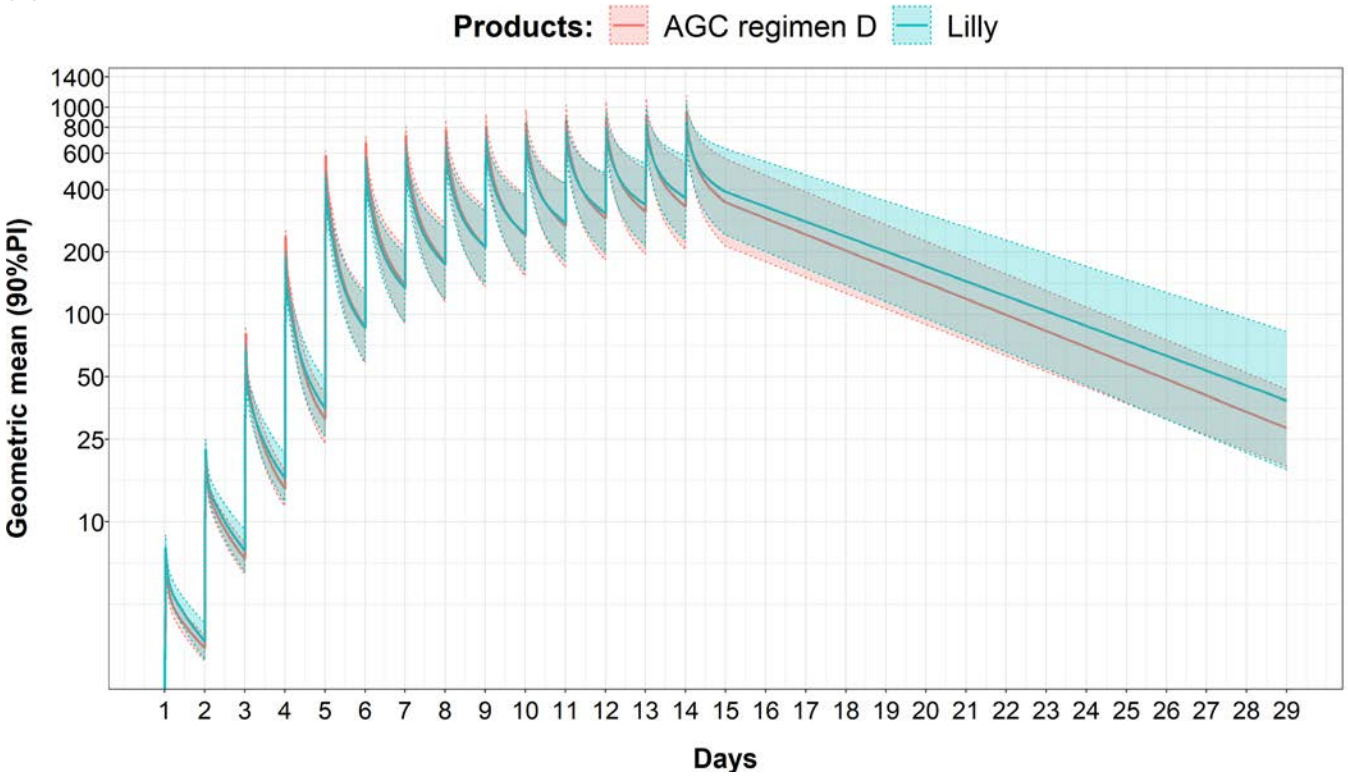
(A)



The solid red and blue lines are the geometric means of teplizumab concentrations from the AGC product (regimen B) and Lilly product (reference regimen), respectively. The colored shaded areas are the distributions (90% prediction intervals [90%PIs]) of teplizumab concentrations for the AGC product (red) and the Lilly product (blue). The dotted lines delimiting the shaded areas are the upper and lower bounds of the 90%PIs. AGC product dosing is regimen D (14-day daily dosing): 65 – 125 – 250 – 500 – (1030 x 10 days) µg/m2. Lilly product dosing is the reference 14-day dosing used in the pivotal TN-10 study, with a daily dosing of 51 – 103 – 207 – 413 – (825 x 10 days) µg/m2. The PK profiles are generated from the individual (conditional) PK simulations.
Source: FDA reviewer
Continued next page

Figure 17 continued

(B)



The solid red and blue lines are the geometric means of teplizumab concentrations from the AGC product (regimen B) and Lilly product (reference regimen), respectively. The colored shaded areas are the distributions (90% prediction intervals [90%PIs]) of teplizumab concentrations for the AGC product (red) and the Lilly product (blue). The dotted lines delimiting the shaded areas are the upper and lower bounds of the 90%PIs. AGC product dosing is regimen D (14-day daily dosing): 65 – 125 – 250 – 500 – (1030 x 10 days) µg/m2. Lilly product dosing is the reference 14-day dosing used in the pivotal TN-10 study, with a daily dosing of 51 – 103 – 207 – 413 – (825 x 10 days) µg/m2. The PK profiles are generated from the individual (conditional) PK simulations.

Source: FDA reviewer

Table 22 summarizes the daily PK comparability results between the AGC product under the adjusted dosing regimen (regimen D) and the Lilly product under the reference 14-day regimen (used in the pivotal TN-10 study). Regimen D corrects the difference in exposure between products. The Cmax after dose 4 to dose 6 are numerically slightly above the strict PK comparability criteria. However, the Cmax values resulting from dose 4 to dose 6 are well below those observed later on during the 14-day treatment from both products. Therefore, these higher Cmax values do not represent a concern regarding the potential acute toxicity or adverse reactions of the proposed regimen D.

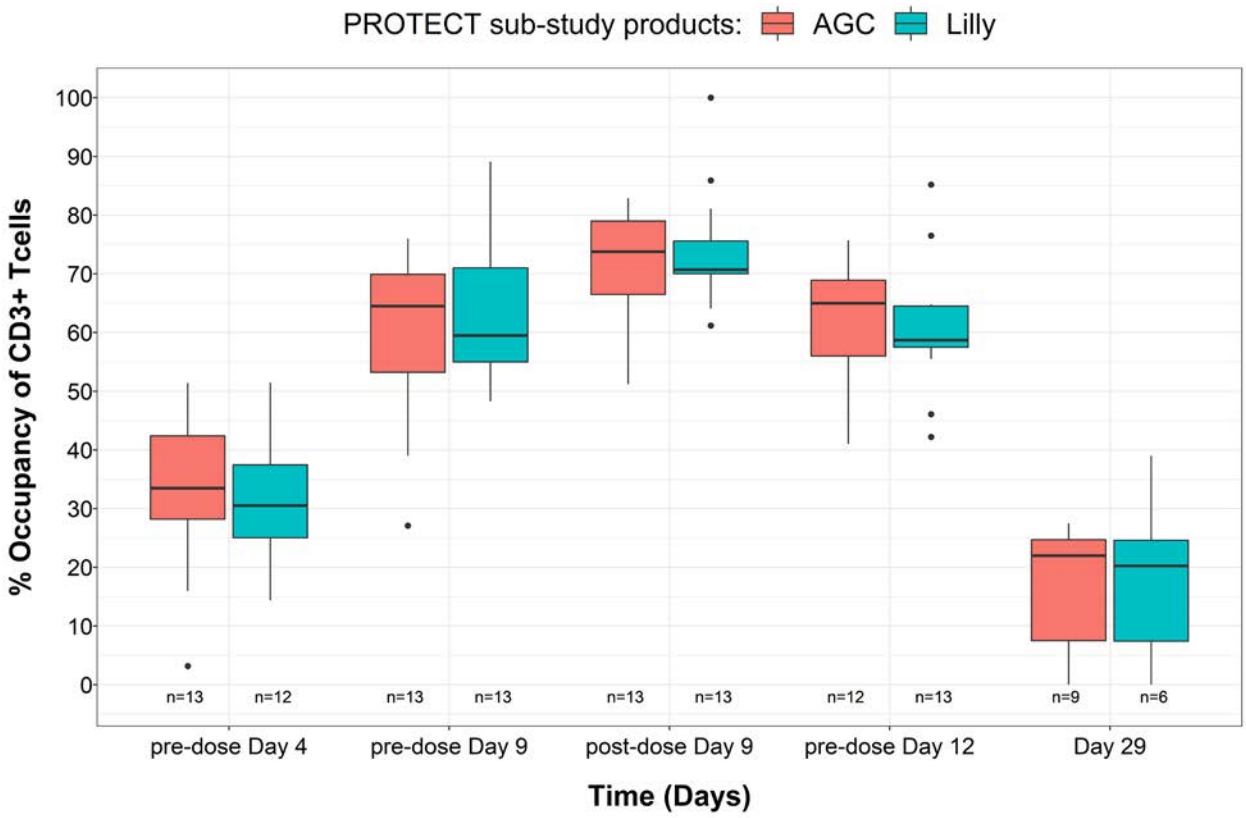
Table 22. Comparison of the Daily PK exposure Metrics between the AGC product (Regimen D) and the Lilly product (Reference Regimen)

Time (end of Day)	GMR (90% CI)		
	AUC[0-Tlast]	Ctrough	Cmax after each dose
24 h (Day 1)	0.893 (0.868 - 0.92)	0.927 (0.892 - 0.963)	0.879 (0.855 - 0.905)
48 h (Day 2)	0.918 (0.889 - 0.948)	0.915 (0.876 - 0.956)	0.998 (0.975 - 1.021)
72 h (Day 3)	0.963 (0.929 - 0.998)	0.888 (0.844 - 0.934)	1.222 (1.199 - 1.245)
96 h (Day 4)	1.007 (0.968 - 1.048)	0.888 (0.836 - 0.944)	*1.259 (1.24 - 1.279)**
120 h (Day 5)	1.072 (1.028 - 1.118)	1.013 (0.94 - 1.092)	*1.264 (1.248 - 1.281)**
144 h (Day 6)	1.09 (1.043 - 1.14)	1.032 (0.954 - 1.115)	*1.24 (1.218 - 1.262)**
168 h (Day 7)	1.091 (1.041 - 1.144)	1.017 (0.939 - 1.101)	1.219 (1.193 - 1.246)
192 h (Day 8)	1.085 (1.033 - 1.14)	0.999 (0.921 - 1.084)	1.199 (1.169 - 1.229)
216 h (Day 9)	1.076 (1.022 - 1.134)	0.981 (0.902 - 1.067)	1.181 (1.148 - 1.214)
240 h (Day 10)	1.067 (1.011 - 1.126)	0.962 (0.883 - 1.049)	1.164 (1.129 - 1.201)
264 h (Day 11)	1.057 (0.999 - 1.117)	0.944 (0.864 - 1.031)	1.148 (1.11 - 1.187)
288 h (Day 12)	1.046 (0.987 - 1.108)	0.925 (0.844 - 1.013)	1.132 (1.092 - 1.174)
312 h (Day 13)	1.035 (0.975 - 1.099)	0.907 (0.826 - 0.995)	1.116 (1.074 - 1.16)
336 h (Day 14)	1.025 (0.964 - 1.089)	0.889 (0.809 - 0.978)	1.101 (1.057 - 1.147)
672 h (Day 28)	0.953 (0.883 - 1.028)	*0.74 (0.669 - 0.818)**	NA
AUCinf	0.94 (0.87 - 1.016)	NA	NA

* The 90%CI of the Geometric mean ratio (GMR) outside the PK comparability criteria of 80% to 125%.
NA: not applicable.
Source: FDA reviewer

Table 22 shows that even with the adjusted dosing regimen (regimen D) for the AGC product, the Ctrough at the end of day 28 (or Day 29) after the 14-day treatment will still be below the strict PK comparability criteria with a GMR of 74%. The PK difference might be due to the higher proportion of NAb on Day 28 for the AGC product. However, the AUC[0-Day 29] is well within the PK comparability criteria with a GMR of 95.3%. Figure 17 (B) shows that Ctrough on Day 29 from the AGC product (under the adjusted regimen D) and the Lilly product (under the refence 14-day regimen) are largely overlapping, suggesting that the PK difference in Ctrough on Day 29 is likely not clinically meaningful. In fact, Figure 18 shows that even at a higher PK difference on Day 29 (GMR of 58% before dose adjustment) the CD3 target engagement by teplizumab on CD3+ T cells (expressed as % CD3 occupancy) was comparable between the AGC and Lilly product in PROTECT sub-study.

Figure 18. Teplizumab Occupancy (%) on CD3+ T Cells by Product in the PROTECT Sub-Study



Note: the last planned sampling day for CD3+ occupancy assessment was variable and was restricted to sampling times ranging for Day 29 to Day 30 for adequate comparison.

Source: FDA reviewer (based on the lasted combined PD dataset pkpdnonmemprotect17feb22.xpt)

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Office of Clinical Pharmacology Review

NDA or BLA Number	BLA 761183
Link to EDR	\\CDSESUB1\evsprod\BLA761183\0003
Submission Date	02 Nov 2020
Submission Type	351(a), Priority review (Rolling submission)
Brand Name	Tzield
Generic Name	Teplizumab
Dosage Form and Strength	Solution 1 mg/mL
Route of Administration	Intravenous infusion
Proposed Indication	Delay of clinical type 1 diabetes in at-risk individuals
Applicant	Provention Bio, Inc.
Associated IND	102629 and 100262
OCP Review Team	Harisudhan Thanukrishnan Ph.D., Elyes Dahmane Ph.D., Manoj Khurana Ph.D., Justin Earp Ph.D.
OCP Final Signatory	Shirley Seo Ph.D., Director, Division of Cardiometabolic and Endocrine Pharmacology

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1. EXECUTIVE SUMMARY

Provention Bio submitted this original BLA 761183 seeking approval of teplizumab dosed as an intravenous infusion for the delay of T1 diabetes (T1D) in subjects at-risk (also presumed as Stage 2 T1D). T1D is a lifelong disorder leading to uncontrolled blood glucose elevation (hyperglycemia). T1D is a progressive disease, thought to result from an autoimmune destruction of the insulin-producing β-cells of the pancreas.

Currently there are no approved treatments for the delay of T1D.

Teplizumab (also known as PRV-031, hOKT3γ1 [Ala-Ala], and MGA031) is a humanized 150 KD monoclonal antibody (mAb) that binds to the CD3-ε epitope of the T cell receptor. In addition to the proposed treatment for delay in T1D, (b) (4)

The pivotal study for this BLA is the At-Risk TN-10 study, in which 76 individuals (8-45 y old) with confirmed Stage 2 T1D were randomized to receive one course of 14-day treatment with either teplizumab (n=44) or placebo (n=32) . Majority (~72%) of the participants were children (<18 y) and more than half were siblings of subjects with clinical (Stage 3) T1D. Teplizumab treatment delayed the time to diagnosis of clinical T1D compared with placebo (43% of teplizumab treated subjects eventually developed T1D vs 72% of placebo). The annualized rates of diagnosis of clinical T1D were 14.9% per year in the teplizumab group and 35.9% per year in the placebo group.

In addition to the single pivotal study, the submission draws supportive evidence for efficacy using levels of c-peptide as a biomarker which was extrapolated from the larger Phase 2/3 studies previously conducted in Stage 3 T1D patients in Protégé and Encore. The primary source of clinical pharmacology information is also from Protégé and Encore studies. In addition, applicant had initiated manufacturing of commercial product from a new batch of drug substance at a new facility (AGC Biologics) and submitted results from a bio-comparability study to establish equivalence between the clinical (Eli Lilly and MacroGenics) and the to-be-marketed product (manufactured by AGC Biologics). The results of the pivotal bio-comparability study failed to establish an appropriate bridge between the clinical trial and the to-be-marketed teplizumab products. The applicant also acknowledged (b) (4) if approved.

1.1 Recommendations

The Office of Clinical Pharmacology, Divisions of Cardiorenal and Endocrine Pharmacology and Pharmacometrics reviewed the information contained in BLA 761183. The OCP review team recommends a complete response (CR) until the sponsor can adequately address the issue related to lack of comparability between the clinical trial and to-be-marketed drug products. The key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence for effectiveness was from a single pivotal randomized, placebo-controlled Phase 2 study (TN-10) in at-risk population for Type 1 diabetes (pre-symptomatic diabetics/ stage 2) who received a single 14-day course of teplizumab
General dosing instructions	Teplizumab dosing is based on body surface area (BSA) and is administered as a 30-minute intravenous infusion once daily, as per the following schedule for a total of 14 days with a cumulative dose of 9034 µg/m^2 (~9 mg/ m^2; 18 mg in a typical subject weighing 70 kg and a BSA of 1.92m^2. Day 1: 51 µg/m^2 Day 2: 103 µg/m^2 Day 3: 207 µg/m^2 Day 4: 413 µg/m^2 Days 5-14: 826 µg/m^2
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose modifications are recommended in patient subgroups. Intrinsic/extrinsic factors are not expected to impact the exposure to this monoclonal antibody.
Labeling	The labelling language proposed by the applicant is generally adequate.
Bridge between the to-be-marketed and clinical trial formulations	A PK bridging study in healthy volunteers was conducted to compare the to-be-marketed formulation with the clinical trial formulation. The results failed to show PK comparability between the two products as their total and partial exposures differed significantly, despite a comparable C_{max} after the 30-minute intravenous infusion.
Other (specify)	None

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Teplizumab is a humanized monoclonal antibody that targets the cluster of differentiation 3 (CD3) antigen, which is co-expressed with the T-cell receptor (TCR) on the surface of T lymphocytes. Though the mechanisms of action of teplizumab for the proposed indication has not been confirmed, it appears to involve a weak agonistic activity on signaling via the TCR-CD3 complex which is thought to expand regulatory T-cells and reestablishment of immune tolerance.

The clinical pharmacokinetics of teplizumab is summarized below:

The 14-day intravenous dosing regimen involves a 4-day ramp up followed by repeated doses of 826 µg/m2 on days 5-14. The repeated intravenous infusions result in increasing serum drug levels and steady state will not be achieved at the end of dosing on Day 14. The average accumulation ratio for AUC between Day 5 and Day 14 (the first and the last day with the full dose administration) is 3.4. The predicted mean (±SD) total AUC for the 14-day dosing regimen is 6421 ± 1940 ng•day/mL with Cmax and Cmin of 826 ± 391 and 418 ± 225 ng/mL, respectively on Day 14.

Distribution:

The estimated mean central and peripheral volume of distribution from population PK analysis is 3.4 and 6.9 L, respectively.

Elimination:

Teplizumab clearance is likely driven by the binding to the CD3 receptors on the surface of T cells and this target mediated drug disposition (TMDD) leads to saturable elimination and non-linear relationship between the dose and exposure. Teplizumab is expected to be degraded into smaller peptide fragments by catabolic pathways. The mean clearance of teplizumab was estimated from population PK analysis to be 2.3 L/day and terminal half-life is ~4 days.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The applicant has proposed a body surface area (BSA) based single 14-day course of teplizumab administered as a daily IV infusion over 30 minutes. Patients will receive doses of 51 µg/m^2, 103 µg/m^2, 207 µg/m^2, and 413 µg/m^2 on Days 1–4, respectively, and one dose of 826 µg/m^2 on each of Days 5–14, for a total cumulative dose of 9034 µg/m^2 (~9 mg/m^2). Less than 10% of the total dose is given on the first 4 days of ramp-up as a precaution to avoid adverse reactions, e.g., cytokine release syndrome.

This single 14-day course administering a total of 9 mg/m^2 teplizumab dose was the only dosing regimen that was evaluated in the pivotal study, which also was the single pivotal study evaluating teplizumab for the proposed indication- delay in subjects at-risk for type 1 diabetes. The proposed regimen appears safe and effective based on this pivotal study result (also see Statistical and Clinical reviews).

2.2.2 Therapeutic individualization

No therapeutic individualization is warranted for teplizumab based on intrinsic or extrinsic factors. Teplizumab is expected to be catabolized into smaller peptides and is not expected to inhibit or induce major CYPs or transporters. Exposure to teplizumab after BSA-based regimen was found to be independent of age and body weight.

2.3 Outstanding Issues

At this time, establishing comparability of the commercial to-be-marketed drug product with clinical trial product is an outstanding issue that may likely not get resolved within the current review cycle. A potential action plan to address this issue is currently not known and is pending further discussions with the applicant.

2.4 Summary of Labeling Recommendations

General labeling recommendations were provided to improve the clarity and relevance of clinical pharmacology information conveyed to the healthcare provider. Additional details that summarized pharmacokinetic or estimated parameters from supporting studies were deemed non-essential and were recommended for removal from the label. A statement mentioning the lack of dose- or exposure-response relationship for the proposed indication was also included.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Teplizumab [also referred to as to as PRV-031, MGA031, or (b) (4) 311] is a recombinant humanized monoclonal antibody (mAb). The antibody is expressed from a genetically engineered, stable Chinese hamster ovary (CHO) cell line in a chemically defined medium. The teplizumab drug substance for studies conducted by MacroGenics was manufactured by MacroGenics (2005-2006) and Eli Lilly, (b) (4) . Since 2019, AGC biologics had taken up the manufacturing of the drug substance for the clinical and commercial formulations.

Early non-clinical and Phase 2 trials in Stage 3 T1D were conducted between 1999-2005 by academic investigators and academic consortia, including the Immune Tolerance Network and Type 1 Diabetes TrialNet. In 2005, teplizumab was acquired by MacroGenics and in collaboration with Eli Lilly, continued the clinical development program which included 2 Phase 3 trials (Protégé and Encore) to investigate the preservation of beta cell function in newly diagnosed T1D.

1. Protégé study (CP-MGA031-01) was conducted between 2007 and 2011
2. Protégé Extension study (CP-MGA031-02) was conducted between 2009 and 2011
3. Encore study (CP-MGA031-03) was conducted between 2009 and 2012

The applicant (Provention Bio) has taken up the clinical development of teplizumab since May 2018. The applicant is also developing teplizumab for the treatment of newly diagnosed type 1 diabetes (Stage 3) T1D. Of the 10 completed T1D clinical trials, 9 were conducted in Stage 3 T1D and 1 was conducted in Stage 2 T1D. The Stage 2 study (TN-10, ISCT-MGA031-005) in the at-risk population forms the basis for the BLA (pivotal study) with supportive efficacy and safety data from the Stage 3 studies.

Key regulatory milestones related to the BLA submission are listed below:

- Provention Bio was granted a Breakthrough Therapy Designation for teplizumab in Stage 2 T1D based on TN-10 study results, in Aug 2019
- FDA accepted Provention Bio's request for rolling review in Feb 2020
- FDA accepted Provention Bio's statistical analysis plan for C-peptide meta-analysis as a basis for providing the supportive evidence for efficacy in Jun 2020
- a thorough QT (TQT) study waiver was granted in Jul 2020

The pivotal TN-10 study evaluated teplizumab in subjects at-risk (stage 2) for T1D after a single full 14-day dosing regimen. However, there was minimal information on teplizumab exposure from this study as PK was limited to sparse samples obtained in a few subjects on the last 4 days of dosing. The main clinical pharmacology information for this BLA comes from the two Phase 3 studies Protégé (Study: CP-MGA031-01) and Encore (Study: CP-MGA031-03), that are considered supportive studies as they evaluated the PK and markers of PD as well as efficacy of teplizumab in a different population- the newly diagnosed T1D (Stage 3) patients. In the Protégé and Encore studies, newly diagnosed T1D subjects received 2 courses of teplizumab administered 6 months apart. Three regimens of teplizumab along with placebo were tested in a randomized blinded fashion in both the studies. The 3 dosing regimens were: Full 14-day regimen (cumulative dose of ~9.0 mg/m^2), One-third 14-day regimen (cumulative dose of ~3 mg/m^2) and Full 6-day regimen (cumulative dose of ~2.4 mg/m^2).

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Teplizumab binds to the CD3ε (epsilon side chain), a component of the T-cell receptor complex and appears to induce regulatory cytokines and expand regulatory T cells via a weak agonistic activity on signaling via the TCR-CD3 complex. CD3 binding of teplizumab is postulated to induce Treg and inhibit autoreactive T cells and improve self-tolerance to the pancreatic islet beta cells in high-risk patients
QT Prolongation	The concentration-QT analysis (from Encore study) indicated a mean placebo corrected ΔQTcF (ΔΔQTcF) at 1 h post dose on Day 5 to be -4 ms and no increase in values with serum concentrations up to 400 ng/mL. There is no evidence from nonclinical or clinical data to suggest that teplizumab has the potential to delay ventricular repolarization. A thorough QT study (TQT) was waived due to a low likelihood of the biologic for direct ion channel interactions.
General Information	
Bioanalysis	Serum samples of TN-10 study containing teplizumab were analyzed by a validated Meso Scale Discovery's electrochemiluminescence (MSD-ECL) method with a working range of 2.5 to 125 ng/mL. Serum samples from the Protégé and Encore studies, were analyzed by a validated quantitative sandwich enzyme immunoassay with a

	working range of detection of 0.24 to 15.63 ng/mL. Further details are provided in Section 4.1.
Healthy vs. Patients	No direct comparison conducted; teplizumab has never been dosed to healthy volunteers except for the single dose bio comparability study.
Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	Sparse PK samples were obtained in recent onset T1D patients and a population PK model was used to estimate the total AUC following the 14-day dosing regimen. Steady state is not expected to be achieved at the end of dosing on Day 14. The predicted mean (±SD) total AUC for the 14-day dosing regimen was 6421 ± 1940 ng•day/mL with C_{max} and C_{min} of 826 ± 391 and 418 ± 225 ng/mL, respectively on Day 14.
Maximally Tolerated Dose or Exposure	In the investigator-initiated study (Study 2), a cumulative dose of 1818 µg/m^2 (approximately twice the proposed dose) was administered in a 12-day course. This was associated with increased frequency of adverse events leading to study termination.
Dose Proportionality	A non-linear increase is observed between administered doses and drug levels, likely due to the target-mediated disposition (TMDD) where CD3 coating and modulation by teplizumab can lead to the saturation of binding sites with a concomitant reduction in circulating CD3+ T cells.
Accumulation	The average accumulation ratio for AUC between Day 5 and Day 14 (the first and the last day with the full dose administration) is predicted to be 3.4. Steady state is not expected to be achieved at the end of dosing on Day 14.
Immunogenicity	The majority (~60-70%) of study subjects developed anti-drug antibodies (ADA) to teplizumab in response to the single 14-day course. The drug clearance was predicted to increase in subjects that may develop higher ADA levels after the end of the 14-day course. In the protégé and encore studies done in stage 3 T1D patients, the impact of ADA on teplizumab exposure was greater (clearance increased by up to 438%) during course 2, when the 14-day regimen was repeated after 6 months. However, the ADA status appears not to impact the drug's effect on decline in c-peptide during long-term follow up in T1D patients.
Absorption	
T_{max}	Teplizumab is administered as an intravenous infusion for 30 minutes and reaches maximum plasma concentration (826 ± 391 ng/mL) at the end of infusion on Day 14.
Distribution	
Volume of Distribution	The central and peripheral volume of distribution from population PK analysis are 3.4 L and 6.9 L, respectively.
Elimination	
Metabolism	Teplizumab is expected to be degraded into smaller peptide fragments by catabolic pathways. The clearance of teplizumab

	following the single full 14-day dosing regimen was estimated from population PK analysis to be 2.3 L/day.
Terminal Elimination Half-Life	The terminal elimination half-life $t_{1/2\beta}$ after 14-day regimen is estimated to be 4 ± 1.8 days
Drug Interactions	Teplizumab is expected to be catabolized into smaller peptides and is not expected to inhibit or induce major CYPs or transporters. A general caution is advised in considering treatment with concomitant medications having adverse event profiles that may overlap with those of teplizumab, such as drugs associated with liver function abnormalities, cytopenias, hypotension, or other immunosuppressive drugs.

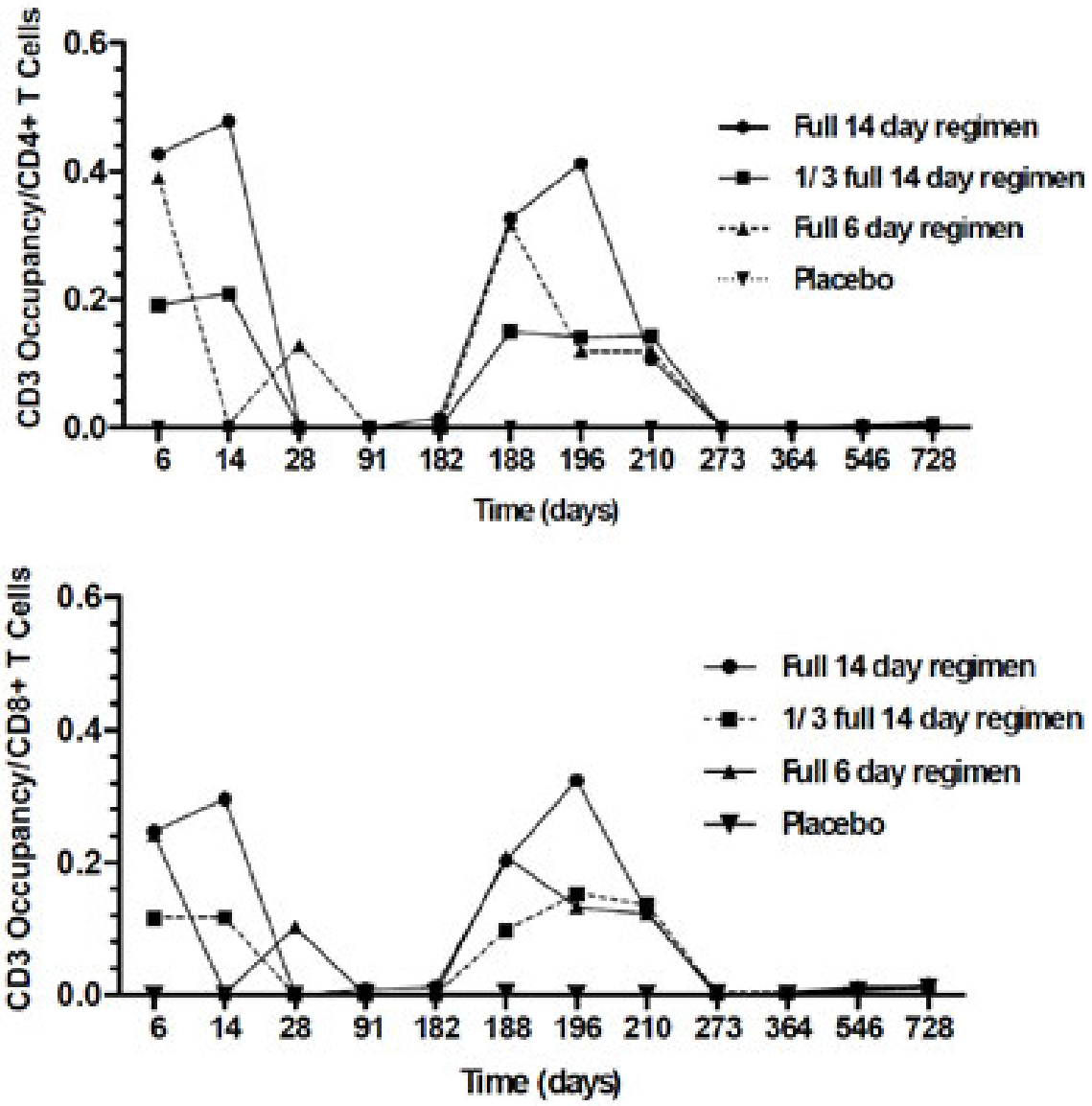
3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide supportive evidence of effectiveness?

The primary evidence for efficacy is the demonstration of delay in T1D diagnosis in the context of 14-day teplizumab treatment and is discussed in detail by statistical and clinical discipline reviews. However, information was available for other PD markers (e.g. CD3/T-cell receptor modulation on CD8+ and CD4 cells, CD4 cell count, Lymphocyte count, and C-peptide) that were collected to understand the hypothesized mechanism of action for teplizumab.

The longitudinal data on these markers indicated temporal changes with teplizumab treatment and in some instances with teplizumab dose as well. However, as the data on the PD markers was not consistently available from all studies and there are uncertainties in their relationship to primary efficacy assessment, these PD markers were likely only informative for empirical dose regimen selection decisions during the course of teplizumab development. The initial PD effect of teplizumab was assessed using the occupancy (coating or binding) of the CD3 receptor and subsequent clearance (modulation) of the CD3 receptor from the cell surface.

The CD3 coating and modulation was evaluated in a subset of newly diagnosed T1D patients under 3 dosing regimens in Protégé study. The occupancy and modulation on T-cells in relation to the duration and cumulative dose of teplizumab received based on the 3 dosing regimens is shown in Figure 1. Overall, maximal CD3 occupancy and modulation occurred on Day 14 or 196 (last day of dosing in Cycles 1 or 2) with the Full 14-day regimen.



Source: Figure 48, Protégé Clinical Study Report

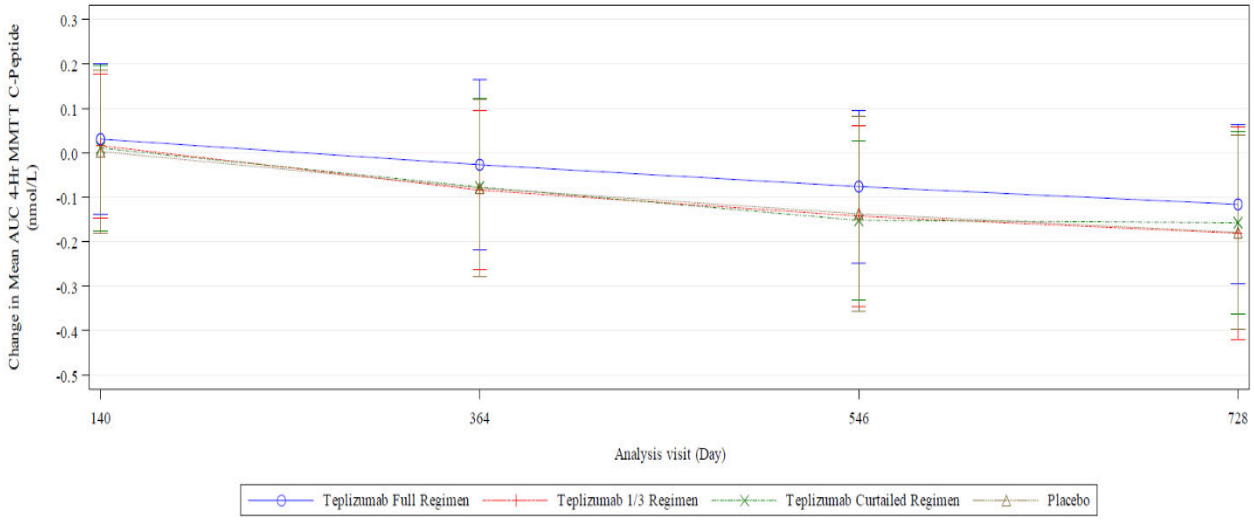
Figure 1. Mean CD3 occupancy (coating) levels on CD4+ and CD8+ T cells during follow up period in the Protégé study

The downstream effects after teplizumab dosing included a transient and reversible lymphopenia and changes in the T-cell subsets resulting from the CD3 binding of teplizumab. The mechanism of teplizumab induced lymphopenia is not known but is hypothesized to result from a cytokine-mediated margination of lymphocytes to the blood vessel wall rather than depletion. The lymphocyte nadir is observed during the 5th day of the 14-day course and starts to recover on the 6thday while treatment is continued with values typically returning to approximately 70% of baseline values on Day 14 and

generally resolved on Day 28. The total CD4+ and CD8+ lymphocyte nadirs were also on Day 5, just like the total lymphocytes with a recovery in counts occurring with continued dosing.

Further, the Full 14-day regimen also seems to draw its support from the exploratory analyses in the Protégé study, which indicated that the 14-day regimen appeared to preserve c-peptide secretion better when compared to the placebo or other dosing regimens, as shown in the Figure 5. The treatment effect on c-peptide was larger in younger children (8-11 y) and under earlier treatment initiation (≤6 weeks after diagnosis of T1D). The c-peptide effect in newly diagnosed T1D subjects at 2 years of follow-up was not observed in the 1/3rd or 6-day regimens. Hence, the Full 14-day dosing regimen was further evaluated in pivotal and other ongoing trials.

Overall, while there were temporal changes in the PD markers following teplizumab treatment in the clinical trials, there is no clear relationship that is established for teplizumab exposure or any of the above PD markers to efficacy outcomes such as measures of c-peptide AUCs or the time to delay in onset of T1D in newly diagnosed T1D or in subjects at-risk for T1D, respectively.



Source: Figure 4.1.5, Integrated Summary of Immunogenicity figures

Figure 2. Comparison of C-peptide change from baseline over time for the evaluated dosing Regimen in Protégé study

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed body-surface area (BSA) based single 14-day dosing regimen seems appropriate. Subjects at-risk for T1D (Stage 2) will receive doses of 51 µg/m^2, 103 µg/m^2, 207 µg/m^2, and 413 µg/m^2 on Days 1–4, respectively, and one dose of 826 µg/m^2 on each of Days 5–14, administered as an intravenous infusion over 30 minutes. The cumulative 14-day dose is 9034 µg/m^2 (~9 mg/m^2), but less than 10% of the total dose will be given on the first 4 days (ramp-up period) as a precaution to avoid adverse reactions, e.g., cytokine release.

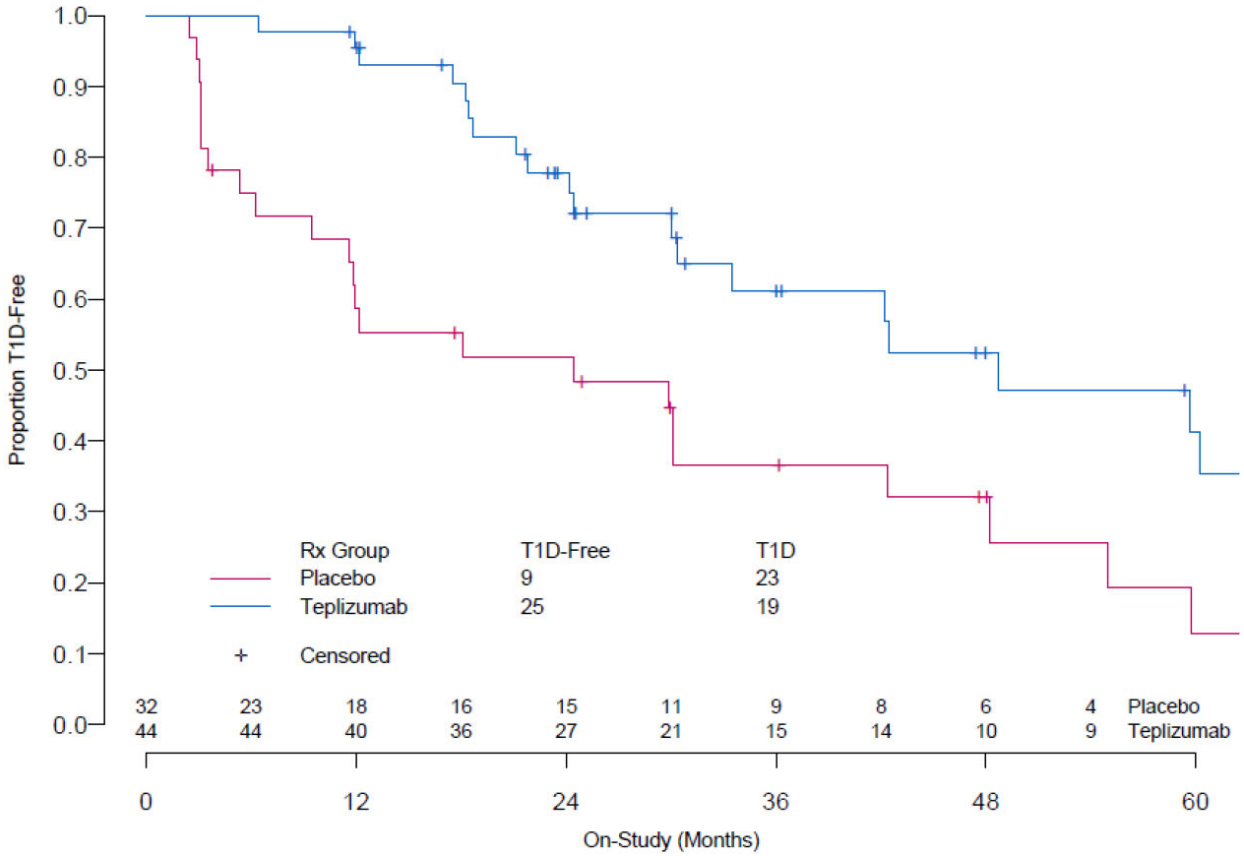
The proposed dosing regimen was evaluated in a single pivotal efficacy trial for delay of the T1D in subjects at-risk for T1D (TN-10), a population considered to have an unmet medical need. The additional information to support the selected regimen were derived from the Protégé and encore studies, that evaluated different dosing regimens of teplizumab in newly diagnosed (Stage 3) T1D patients. In the Protégé and Encore studies, three regimens of teplizumab along with placebo were tested in a randomized blinded fashion. The 3 dosing regimens were: Full 14-day regimen (cumulative dose of ~9.0 mg/m^2), One-third 14-day regimen (cumulative dose of ~3 mg/m^2) and Full 6-day regimen (cumulative dose of ~2.4 mg/m^2). The same 6-or 14-day course of treatment were repeated at Month 6 (course 2).

Though the primary endpoint was not met in the protégé study and that leading to the early termination of the encore study, various exploratory analyses indicated the Full 14-day regimen preserved c-peptide secretion better and showed larger treatment effects in younger children (8-11 y) and under earlier treatment initiation (≤6 weeks after diagnosis of T1D) when compared to the placebo or other dosing regimens. The c-peptide benefit in newly diagnosed T1D subjects at 2 years of follow-up was not observed in the $1/3^{rd}$ or 6-day regimens. In addition, only the Full 14-day regimen resulted in the maximal CD3 occupancy and modulation (Refer section 3.3.1). Hence, only a single course of Full 14-day dosing regimen was further advanced for the pivotal TN-10 study. The overall safety profile of this dosing regimen was acceptable with the most common adverse events in T1D patients being transient lymphopenia and rash which resolved spontaneously.

Subjects at-risk for T1D were chosen for the pivotal TN-10 study because of analyses from supporting studies that indicated an increased probability of response to teplizumab in patients with a higher baseline c-peptide and lower baseline insulin and HbA1c (indices of preserved beta-cell function). Hence, the intervention with teplizumab at Stage 2 or “prediabetic” stage was predicted to be more effective than intervention in Stage 3 patients with frank hyperglycemia (indicative of further deterioration in beta cell function). The BSA-based 14-day regimen was found to normalize the exposure across the body weights and total exposure of teplizumab was also found to be independent of age.

Appropriateness of the BSA based dosing as per the TN-10 study findings:

The proposed dosing regimen is supported by delayed time to Stage3 (clinical T1D) in the TN-10 study, as the median times to T1D was significantly delayed in teplizumab treated subjects (48.4 vs 24.4 months in the placebo) which resulted in lower annualized rates of clinical T1D development (14.9% vs 35.9% per year for the teplizumab and placebo groups, respectively). The effect of teplizumab on preservation of c-peptide was further evaluated by meta-analysis of data from the pivotal and supporting studies as a confirmatory evidence for BLA approval (Refer to statistical and clinical reviews for BLA 761183).



Kaplan-Meier estimates of the proportion of participants who were without clinical diabetes. The overall hazard ratio was 0.412 (95% CI: 0.216, 0.783) (p=0.006, two-sided, Cox model). The median time to T1D was 48.4 mos for teplizumab group and 24.4 mos for the placebo group. The insert shows the total number of subjects with and without clinical T1D at the conclusion of the study.

Source: Figure 1, Herold K et al; N Engl J Med 2019; 381:603-613; DOI: 10.1056/NEJMoa1902226

Figure 3. Effect of teplizumab treatment on development of T1D following 14-Day Regimen (TN-10 study)

Appropriateness of the dose in the context of Immunogenicity and its impact:

Across all studies, a majority (~60-70%) of study subjects developed anti-drug antibodies (ADA) to teplizumab in response to the single 14-day course. The drug clearance was predicted to increase in subjects that develop higher ADA levels after the end of 14-day course (HAHA2 = natural logarithm of ADA concentrations after 14-day course 1 treatment up to day 120 post-first dose). As per the POPPK prediction, for each one unit increase in HAHA2 from the LLOQ of 4, the clearance was predicted to increase by 12.2% and by up to 73% (6 times for a 6 unit increase) in a patient with the maximum observed HAHA2 of 10 (Refer POPPK review). Overall, the impact of ADA on exposure is predicted to be less as the time for onset and increase in ADA levels (> Days 28 post-first dose) seemed to lag behind the maximal teplizumab serum concentrations (< Days 28 post-first dose), thereby minimizing the overlap of PK and ADA following the proposed single 14-day dosing regimen (course 1).

However, unlike the pivotal study, most of the supporting and investigator-initiated studies investigated a second course of therapy in T1D subjects, where the 14-day regimen was repeated after 6 months.

Predictions using the data from supporting studies revealed that there was a greater impact of ADA on teplizumab exposure (clearance increased by up to 438% in few patients) after the administration of the second 14-day course (refer to appendix for detail). However, the ADA status appears not to impact the drug's effect on decline in c-peptide during long-term follow up in T1D patients (see section 3.3.1). Owing to small number of subjects evaluated in the pivotal study, it was not possible to make a definitive conclusion on any impact of ADA status on time to clinical T1D diagnosis.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No therapeutic individualization is required for teplizumab based on intrinsic or extrinsic factors. Exposure to teplizumab after BSA-based regimen was found to be independent of age and body weight.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No. As teplizumab is administered via intravenous route, a food-drug interaction is not expected. Teplizumab is expected to be catabolized into smaller peptides and is not expected to inhibit or induce major CYPs or transporters. A general caution is advised in considering treatment with concomitant medications having adverse event profiles that may overlap with those of teplizumab, such as drugs associated with liver function abnormalities, cytopenias, hypotension, or other immunosuppressive drugs

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

The to-be-marketed drug product is manufactured in a different facility from the clinical trial product and was not used in the clinical studies. The table provides an overview of drug product and bioanalytical methods that was used across the clinical studies.

Study or use	Drug substance lot manufacturer	Teplizumab Assay/ ADA Assay
Protege	MacroGenics	Old/Old
TN-10	MacroGenics and Eli Lilly	New/New
PK BRIDGING STUDY (PRV-031-004)	Eli Lilly and AGC Biologics	New/New
Proposed to-be-marketed product	AGC Biologics	New/New

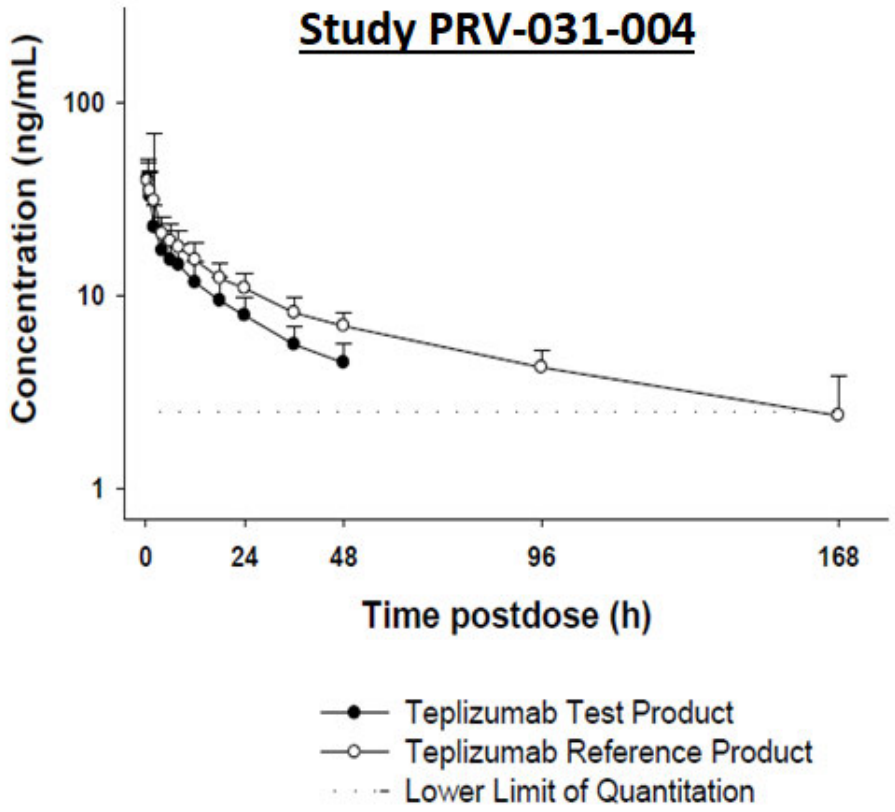
Teplizumab was previously manufactured by MacroGenics (b) (4) 2005-2006) and Eli Lilly (b) (4) 2009-2010);

Source: Table 6, Companion document to PRV-031-004 Study Report

Table 1. An overview of the teplizumab drug substance manufacturer and Assays used in clinical studies

Teplizumab drug substance batches manufactured by Eli Lilly were used to manufacture drug product lots used in part of the pivotal and supporting clinical studies. The drug substance manufactured by AGC Biologics (b) (4) are to be used in the to-be-marketed (commercial) product. The same drug product manufacturer and manufacturing site was used for the clinical and commercial products.

A pharmacokinetic (PK) bridging study PRV-031-004 in healthy volunteers (Title: A Phase 1, randomized, double-blind, parallel group, single-dose study in healthy subjects to evaluate the biocomparability of Teplizumab manufactured at two sites) was performed to evaluate the biocomparability of the commercial drug product with the clinical trial drug product. The primary endpoints of the study were observed maximum concentration (C_{max}) and trapezoidal area under the time-concentration curve (AUC) extrapolated to infinity ($AUC_{0\text{-}inf}$) with the criterion that PK bio comparability would be established if the 90% CIs for the ratio of geometric least square means (GLSMs) of C_{max} and $AUC_{0\text{-}inf}$ were wholly between 80% and 125%. The study failed to show PK comparability between the two products as their total and partial exposures differed considerably, despite a comparable C_{max} after a single IV dose (Figure 9 and Table 3). Hence, the current commercial drug product is concluded not to be comparable to the clinical trial product.



Data are expressed as mean + standard deviation

Source: Figure 1, Companion document to PRV-031-004 Study Report

Figure 4. Teplizumab Concentration-Time Profiles Following Single Dose Administration of Teplizumab Commercial Product (Test Product) and Clinical Trial Product (Reference Product)

	Teplizumab Test Product			Teplizumab Reference Product			Test versus reference
Parameter (units)	n	GLSM	90% CI of GLSM	n	GLSM	90% CI of GLSM	Ratio of GLSMs (90% CI)
C_{max} (ng/mL)	51	38.9	(36.0, 42.1)	49	41.2	(38.0, 44.6)	94.5 (84.5, 106)
AUC_{0-24} (h*ng/mL)	51	314	(297, 331)	49	396	(374, 419)	79.2 (73.2, 85.7)
AUC_{0-48} (h*ng/mL)	51	452	(429, 475)	49	598	(568, 629)	75.5 (70.3, 81.2)
AUC_{0-last} (h*ng/mL)	51	540	(495, 588)	49	1050	(960, 1140)	51.5 (45.6, 58.2)
AUC_{0-inf} (h*ng/mL)	37	706	(654, 762)	37	1450	(1350, 1570)	48.5 (43.6, 54.1)

Abbreviations: CI, confidence interval; GLSM, geometric least squares mean; n, number of subjects with valid observations; Cmax, maximum concentration; AUC, area under curve

Source: Table 14.2.1-3, PRV-031-004 Study Report

Table 2. Summary of Pharmacokinetic Parameters and Statistical Analysis of C_{max} and AUCs (Study PRV-031-004)

Additional details on the study design, PK parameters and information on the PD effects on lymphocyte counts and immunogenicity are summarized in Appendix. The applicant further predicted the total exposures for the full 14-day regimen using individual PK parameter estimates obtained from the bio comparability study. The predicted median total exposure for the commercial product under the proposed 14-day dosing regimen was ~40-45% lower in comparison to clinical trial product (Refer to section on Population PK analysis from the PK bridging study). Hence, the bridging study failed to establish PK comparability of the intended commercial product raising uncertainties on its effectiveness, as the approximately 50% lower AUC_{0-inf} of the commercial product as compared with the clinical trial product could be clinically impactful unless proven otherwise.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics:

The BLA submission included teplizumab concentration and immunogenicity data only from studies that had used a validated method for the assessment of PK as well as the anti-drug antibodies (ADA) and the neutralizing antibodies (Nab). Of the 4 studies listed in table, most data for population pharmacokinetics and immunogenicity analyses came from the protégé study with minor contribution from the encore study. TN-10 was not included in POPPK analysis and only measured concentrations at random time points in few patients on the last four days of dosing.

Study conduct	***Teplizumab analysis (performed at)***	***ADA analysis (performed at)***	***Nab analysis (performed at)***
Protégé (2007-2011)	Chemiluminescent Enzyme Immunoassay (b) (4)	ELISA (b) (4)	Cell-based (b) (4)
Encore (2009-2012)	Chemiluminescent Enzyme Immunoassay (b) (4)	ELISA (b) (4)	Not done
TN-10 (2011-2019)	MSD-ECL (b) (4)	MSD-ECL (b) (4)	Cell-based (b) (4)
PRV-031-004 (Bio comparability study-2020)	MSD-ECL (b) (4)	MSD-ECL (b) (4)	Cell-based (b) (4)

MSD-ECL- Mesoscale discovery-electrochemiluminescence; ELISA- Enzyme linked Immunosorbent assay

Source: Reviewer generated

Table 3. An overview of validated bioanalytical methods for teplizumab

METHOD 1: Chemiluminescent enzyme immunoassay (Protégé and Encore studies)

- Serum concentrations of teplizumab were determined using the validated chemiluminescent assay (ELISA) with a calibration range of 0.24- 15.6 ng/mL and supporting up to 1:1000 dilutional linearity. The working assay range for samples diluted 1:1000 is 244.2 to 15625 ng/mL.
- The assay was validated for precision, accuracy, sensitivity, dilutional recovery, cold storage stability and interference from hemolysis, bilirubin and lipemia. All standards assayed during validation were within their respective target ranges and demonstrated ≤ 15% of deviation from the nominal concentrations (≤ 20% for the LLOQ).

- The stability of teplizumab in serum was established for 24 months at -70°C or below. The study samples were analyzed before 24 months of storage and concentrations of calibration standards and at least two-thirds of the overall QC samples were equal to or better than 15% (20% at the LLOQ) from the supporting bioanalytical report for the Encore study.

METHOD 2: Mesoscale discovery-electrochemiluminescence (TN-10 and PRV-031-004 studies)

- Serum concentrations of teplizumab were determined using the validated Meso Scale Discovery's electrochemiluminescence (MSD-ECL) method with a calibration range of 2.5-125 ng/mL from a 40 µl human serum aliquot.
- The assay was validated for precision, accuracy, sensitivity, dilutional linearity, cold storage stability (18 months at around -20 °C and -80 °C), freeze thaw stability (5 cycles) and interference from hemolysis and lipemia. All standards assayed during validation were within their respective target ranges and demonstrated ≤ 15% of deviation from the nominal concentrations (≤ 20% for the LLOQ).
- The concentrations of calibration standards and at least two-thirds of the overall QC samples were equal to or better than 15% (20% at the LLOQ) from the supporting bioanalytical reports. Around 13% and 10% of TN-10 and PRV-031-004 study samples were re-assayed, respectively and all the results for the incurred sample reanalysis (ISR) were within 30% deviation.

Overall, the methods demonstrate adequate performance to reliably measure the serum concentrations of teplizumab. However, following issues related to the conduct and reporting of the bioanalysis during study sample analysis were identified and documented:

a) As per the applicant, the final PK bioanalytical report (study sample analysis report) for the protégé study couldn't be found (done at (b) (4) but later acquired by Applicant). Hence, only a summary document with a tabular listing of concentrations were provided. Regarding the lack of report for the protégé study, the Agency had agreed to accept the application for filing despite the missing original report, as it was circumstantial and as the protégé study data was generated using the same validated assay and laboratory as that of the encore study. As no protocol deviations were reported for the study sample analysis, the assumption was that the validated method was used without any modifications.

b) The TN-10 study was conducted from 2011-2019, but all the study samples were analyzed only in June 2019. The mean time elapsed between sample collection and date of analysis was 6.1 years while the long-term stability was established only for 18 months at around -80 °C. Applicant response to the information request included a listing of the individual concentrations against the time after dosing which were in the range of expected values. In addition, the distribution of the teplizumab concentrations were found comparable with values at similar time points from a more recent study (PROTECT) in which the samples were analyzed within the 18-month stability time frame. The sparse concentrations from TN-10 study was not a part of the POPPK model and were obtained for verification of serum levels on the last 4 days of dosing in a few patients.

- The immunogenicity of teplizumab was evaluated using a validated ELISA method to determine the presence of anti-teplizumab antibodies in human serum from the Protégé and encore studies. A validated mesoscale discovery-electrochemiluminescence (MSD-ECL) bridging assay was used for the ADA determination in the TN-10 and PRV-031-004 studies.
- Assay for neutralizing antibodies was done using a cell-based NAb assay developed and validated by (b) (4) for the Protégé study and later transferred to and validated by (b) (4) for the TN-10 or PRV-031-004 studies, respectively. In general, the majority of ADA were reported to be NAb positive and the overall impact of NAb on PK, PD or safety were therefore considered to be the same as that for ADA. For a more in-depth review of these assays please refer to the Drug Product review by the Office of Biotechnology Products.

Assays for C-peptide:

The studies included in meta-analyses for c-peptide covered a wide time span ~ 20 years and the corresponding testing laboratory, regulatory agencies and assay techniques were different. Some of the studies were academic investigator initiated and data from publications were relied upon. The methodology and laboratory performing c-peptide analysis was available from the publication and the corresponding manuals and validation reports from the laboratory were provided by the applicant.

The analyses for all studies in the meta-analyses were conducted at central laboratories which were certified in accordance with the local requirements for accreditation and used a manufacturer protocol that was further validated and approved in-laboratory. The assay performance is expected to be at least on par with the performance characteristics provided by the manufacturer.

The assay methods, instruments and the calibration range are listed in the table.

Study	**Matrix**	**Assay**	**Instrument Used**	**Calibration Curve**
TN-10	Serum	2-site immune enzymatic colorimetric assay	AIA 1800 Immunology analyzer In January 2015, the instrument was changed to the AIA 2000 auto-analyzer	0.2 to 30 ng/mL 0.02 to 30 ng/mL
Study 1	Plasma	Radioimmunoassay	Wallac Wizard gamma counter	0.05 to 1.0 nM (0.15 -3.02 ng/mL)
AbATE	Serum	2-site immune enzymatic colorimetric assay	AIA 600 II Immunology Analyzer In 2007, the instrument was changed to the AIA 1800 Immunology Analyzer	0.2 to 32 ng/mL
Delay	Serum	2-site immune enzymatic colorimetric assay	AIA 600 II Immunology Analyzer	0.2 to 30 ng/mL

Protégé	Serum	Chemiluminescence enzyme immunoassay	Immulite 2000 Immunoassay System	0.1 to 20 ng/mL
Encore	Serum	Chemiluminescence enzyme immunoassay	Immulite 2000 Immunoassay System	0.1 to 20 ng/mL

Source: Applicant response to information request sequence No.24, BLA 761183

Table 4. Summary of assay methods used in clinical studies included for C-peptide meta-analysis

As listed in the table, the distribution of c-peptide values was found to be comparable across the studies with consideration that baseline enrollment criterion was different across studies.

	C-Peptide (nmol/L)					
	Mean	Std Dev	Min	Max	Median	Interquartile Range
AbATE	0.49	0.42	0.008	4.56	0.40	0.46
Delay	0.49	0.36	0.0	2.60	0.42	0.41
Encore	0.53	0.48	0.015	3.87	0.40	0.50
Protege	0.52	0.56	0.017	6.52	0.36	0.53
Study1	0.36	0.28	0.001	1.90	0.29	0.37

*TN-10 study enrolled stage 2 T1D subjects and did a 2 h oral glucose tolerance test vs 4 h mixed meal tolerance test for other studies; TN-10 (Mean: 1.7 nmol/L, min-max: 0.2-8.1 nmol/L)

Source: Reviewer generated

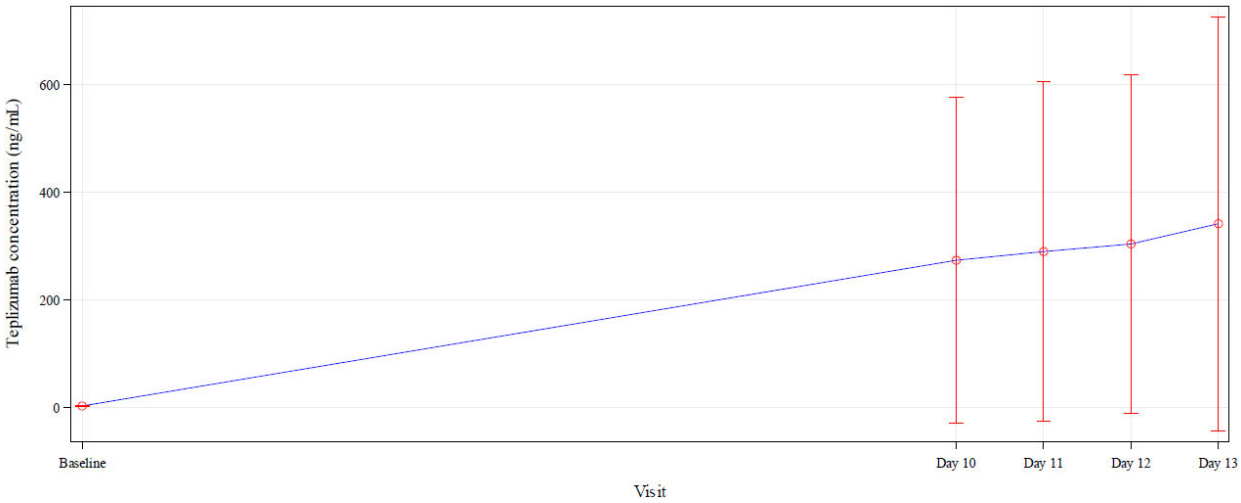
Table 5. Distribution of C-peptide values in clinical studies included for C peptide meta-analysis

Reviewer comment: The bioanalytical methods for teplizumab partially met the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development'. The rationale provided for not meeting the specific criterion on sample storage and method performance during study sample analysis were accepted and their implications are documented in this review. The assays for c-peptide were also found adequate to support the use as an efficacy biomarker.

4.2 Clinical PK and/or PD Assessments

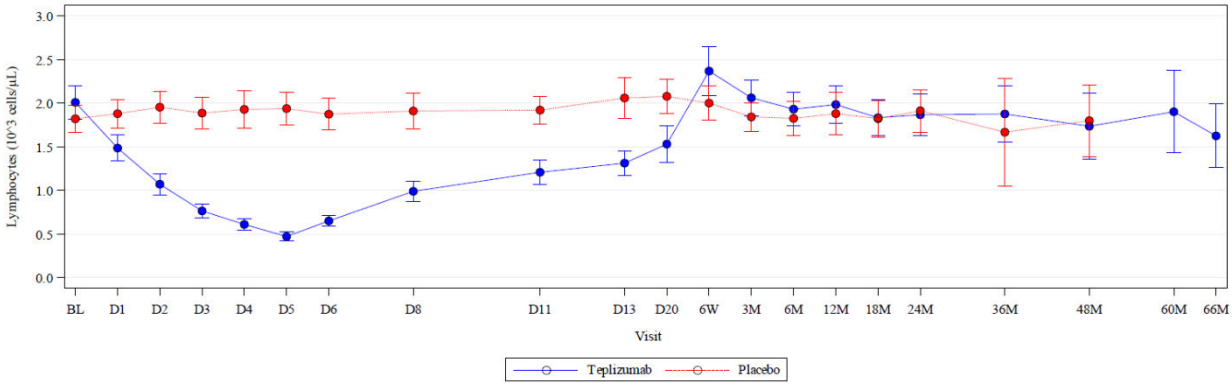
TN-10 (pivotal) study:

In TN-10 study, sparse samples were obtained in a few patients on baseline (Day 0), Days 10, 11, 12 and 13 of the 14-day regimen. As shown in the figure, a large variability was observed in the reported concentrations on each day. However, it was notable that the time points for sampling were not consistent, but obtained at random on each day, ranging from a few minutes after start of dosing to the end of dosing interval of ~23-24 h, thereby contributing to the variability in the observed plot.



Source: Figure 13, TN-10 (Addendum) Clinical Study Report

Figure 5. Mean (±SD) serum teplizumab concentration by visit in patients on active treatment (N=25) in TN-10 study



Source: Figure 16, TN-10 (Addendum) Clinical Study Report

Figure 6. Mean (±95% CI) of lymphocyte counts in response to the 14-day dosing of teplizumab in TN-10 study

<u>PRV-031-004 (Bio comparability study):</u>

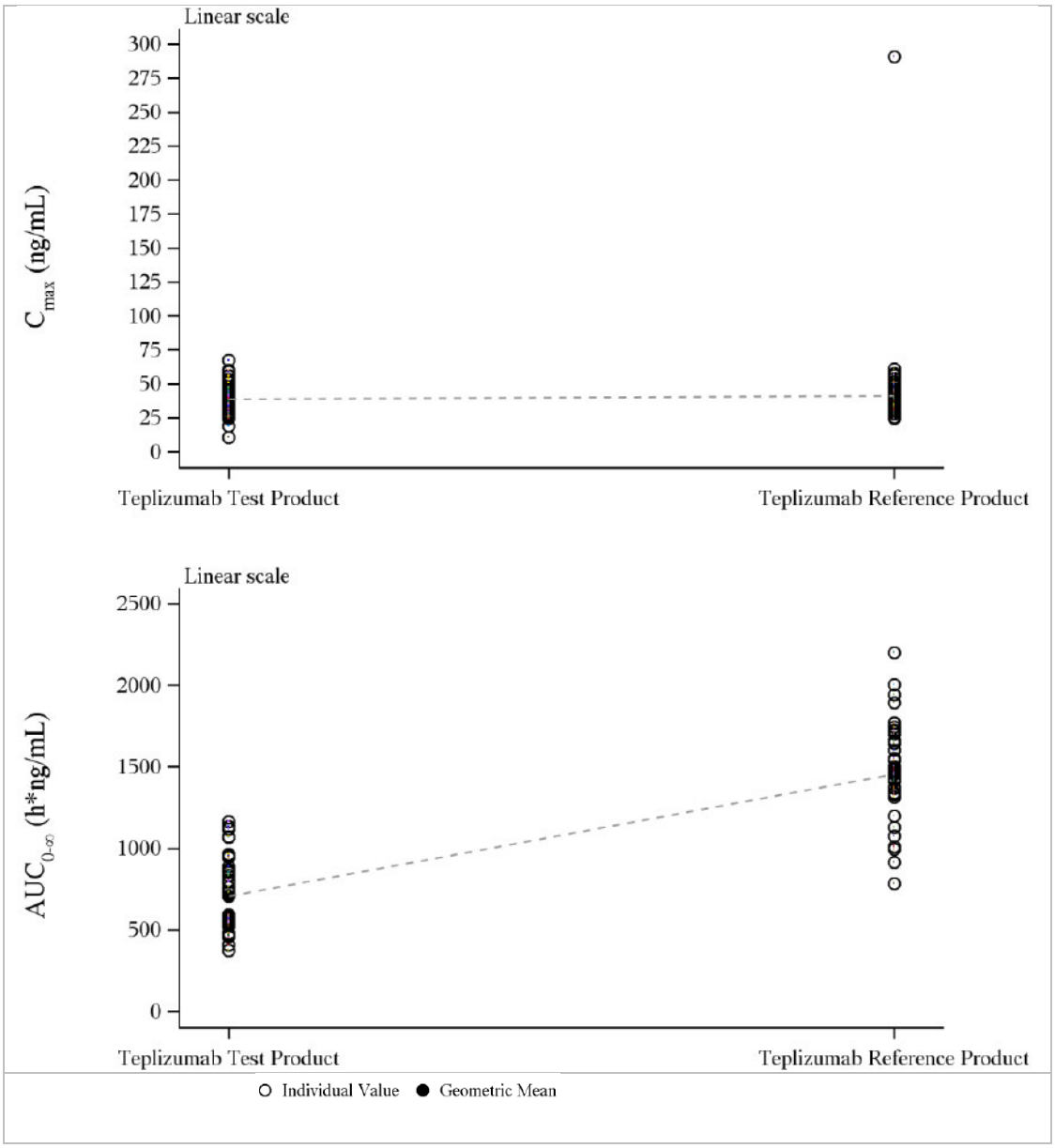
A Phase 1, Randomized, Double-Blind, Parallel Group, Single-Dose Study in Healthy Subjects to Evaluate the Bio comparability of Teplizumab (PRV-031) Manufactured at Two Sites

- The primary objective of the study was to establish bio comparability, based on pharmacokinetic (PK) and pharmacodynamic (PD) parameters, between the test (manufactured by AGC Biologics) and reference (manufactured by Eli Lilly) products of teplizumab.
- The primary endpoints were observed C_{max} and $AUC_{0-\infty}$ for the assessment of the bio comparability of reference and test products of teplizumab. Fifty (50) subjects per treatment arm (total N = 100) were estimated to provide 90% power to assure that the two-sided 90% confidence interval (CI) of the ratio of geometric means for C_{max} and $AUC_{0-\infty}$ will fall wholly within the range of 80-125%. These calculations assumed the data are log-normally distributed with an estimated within-treatment standard deviation (SD) of the log-transformed data (coefficient of variation [CV]) of 0.35 as estimated in the population PK analysis from Protégé study data. The calculations further assumed no expected treatment differences existed and a common SD across the 2 treatment groups.

Study conduct:

- In the study, 100 healthy subjects (18-50 y) were enrolled and analyzed: 51 in the test product group, 49 in the reference product group. On Day 1, each subject was randomly assigned, in a 1:1 ratio and received a single dose of 207 $\mu g/m^2$ body surface area (BSA) of either the test or reference product of teplizumab via intravenous infusion for 30 minutes.
- On Day 1, PK samples were drawn pre-dose and at 0.5 h (end of infusion), and 1, 2, 4, 6, 8, 12, and 18 h after the start of infusion. On Day 2, samples were drawn at 24 h and 36 h after the start of infusion. Additional samples were obtained on Days 3, 5, 8, and 15 (final visit).
- The PD parameter chosen by applicant was the change from baseline in absolute lymphocyte count that was obtained at pre-dose, and 8 h after dosing and on Days 2, 3, 5, 8, and 15. The PD parameters, $AUC_{0\text{-last, PD}}$ and nadir change from baseline, were further assessed.
- The immunogenicity endpoints were comparison of the incidence and titer of ADA and incidence of NAb from baseline over time, after dosing of test or reference products of teplizumab. The results of ADA and NAb were expressed as frequencies and percentages of positive samples relative to the total number of evaluable samples.

Overall, the geometric mean partial AUC_{0-48} were lower in subjects receiving the test product than those in subjects receiving the reference product. Majority of subjects receiving test product did not have measurable teplizumab concentrations beyond Day 3.

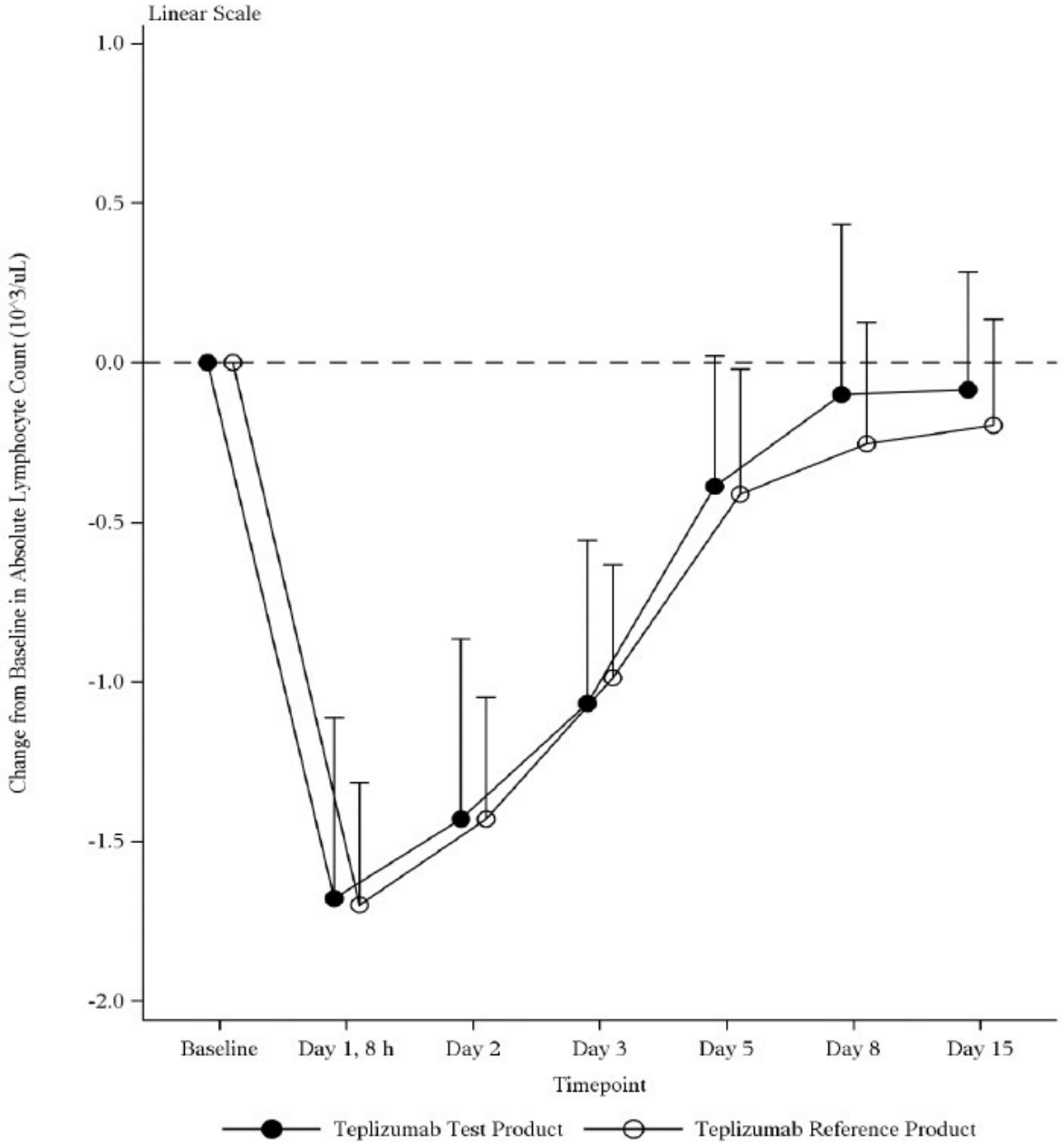


Source: Figure 14.2.1-3, Figures for PRV-031-004 Study Report

Figure 7. Comparison of individual and geometric means for test and reference products of teplizumab in Study PRV-031-004

The comparison of reduction in circulating lymphocyte counts revealed no differences between the test and reference products, as shown in the figure. However, it is also notable that the validity of lymphocyte count as a surrogate marker for the proposed indication is not yet established. Hence, PK parameters were considered as the sole criterion for the bio comparability assessment from a regulatory perspective (for comparison of product's quality attributes).

The number of ADA positive subjects increased over time. ADA was not observed until Day 5 and Day 8 for the test and reference products, respectively. By Day 15, most (~62%) of the subjects developed ADA on both test and reference products. The titers of ADA to teplizumab from Day 1 through Day 8 ranged from 30 to 960 among subjects with positive ADAs. On Day 15, the median ADA titer was higher in the subjects receiving the test product (1920) than that in the reference product group (480).



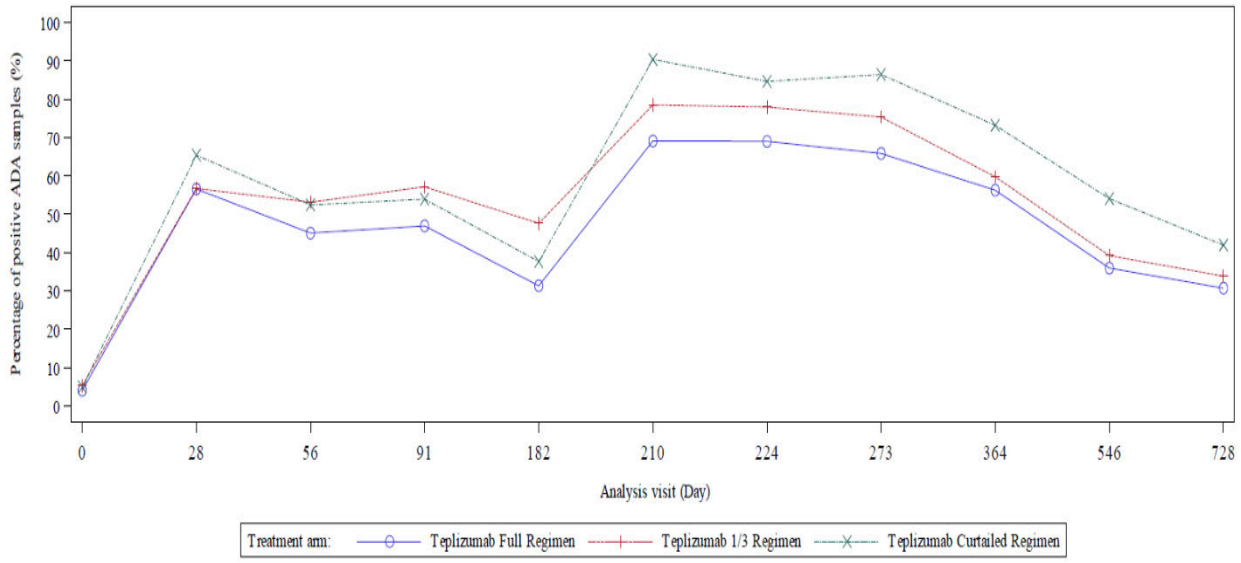
Test=AGC Biologics, Reference=Eli Lilly
Source: Figure 2, PRV-031-004 Study Report

Figure 8. Mean (SD) of change from baseline in lymphocyte counts in response to a single dose of 207 µg/m²

4.3 Summary of Immunogenicity Assessment

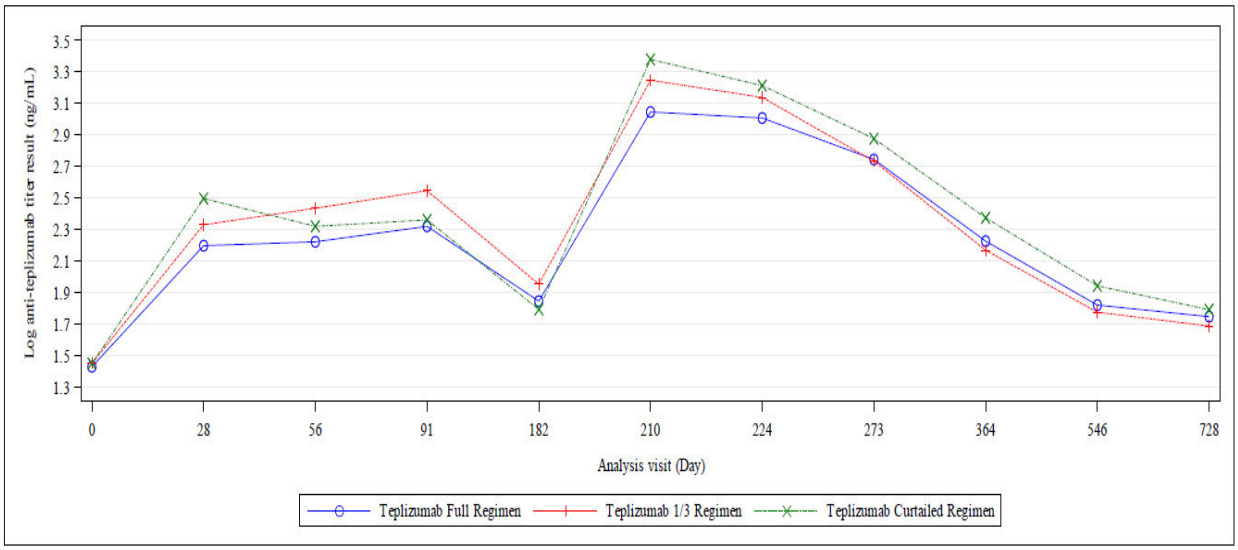
The dosing paradigm for teplizumab for the indication in this BLA (delay of clinical T1D in at-risk individuals) includes a single 14-day course. Supporting studies in the newly diagnosed T1D indication, had dosing schemes with repeat courses (eg, course 1 and course 2) that were administered 6 months apart. Majority of ADA analyses were from the protégé study.

As shown in the figures, there was a small increase in the incidence of ADA in the Cycle 2, however higher levels of immunogenicity were seen in the second cycle for the three regimens evaluated in the protégé study.



Source: Figure 1.6.1.1, Figures for Integrated Summary of Immunogenicity

Figure 9. Proportion of subjects of positive ADA samples by treatment and timepoint in Protégé (Segment 2)

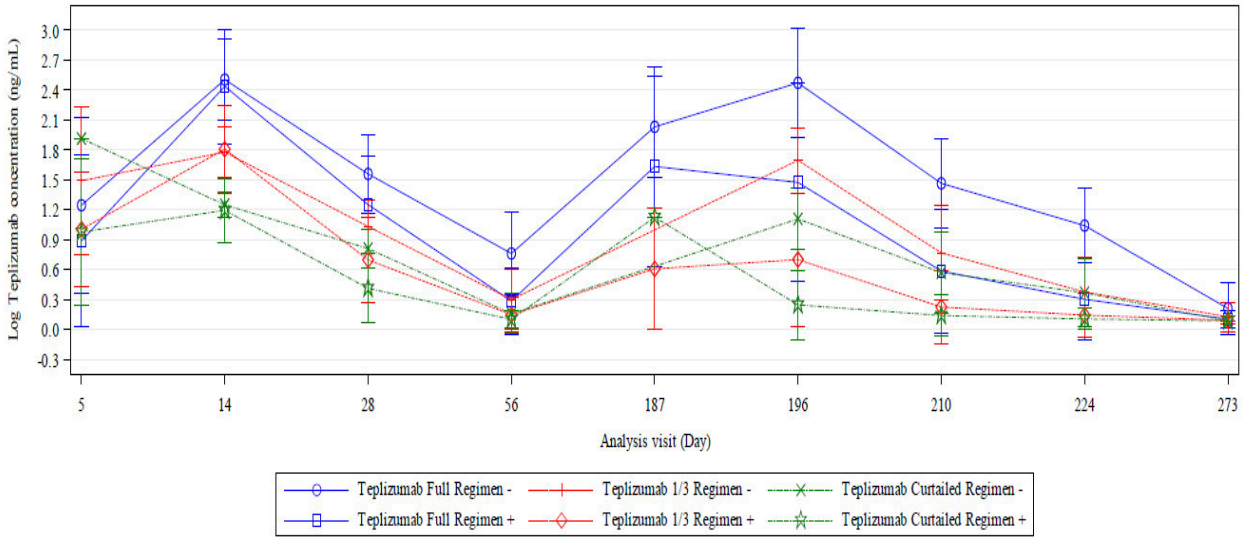


Source: Figure 1.2.2.1, Figures for Integrated Summary of Immunogenicity

Figure 10. Mean ADA titer (Log values) by treatment and timepoint in Protégé (Segment 2)

As illustrated in the figure, the mean log titers after course 1 of therapy were below 2.5 (corresponds to < 6 on a ln scale). As per the POPPK predictions, the impact of ADA values in this range is predicted to be < 24% on the clearance following the course 1. Further, the values of ADA during initial 14 days of therapy are anticipated to be further lower when the systemic exposure to teplizumab is at its maximum.

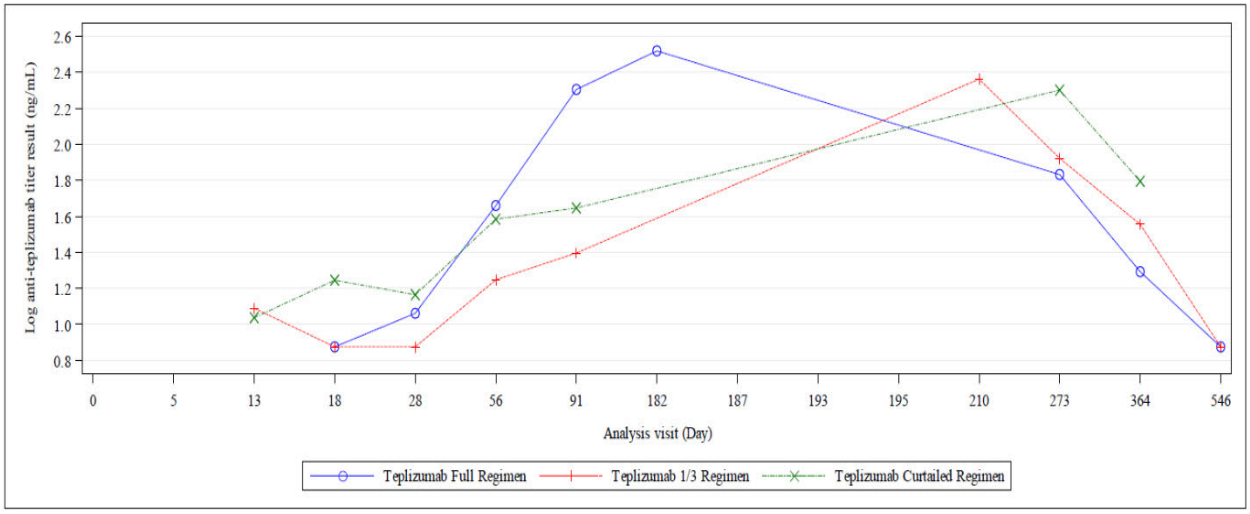
Teplizumab PK concentrations after course 1 were similar when compared between the ADA status, in contrast to after course 2 of the therapy.



Source: Figure 2.1.1, Figures for Integrated Summary of Immunogenicity

Figure 11. Mean (±SD) line plots for PK concentrations over time by ADA status in Protégé (Segment 2)

The Encore study was interrupted as the primary endpoint was not achieved in the protégé study. However, the ADA data from encore study which also had a repeat dosing course, are in similar lines to the protégé study, as shown in the figure. However, due to lower sample size and change of sampling plans a meaningful comparison of PK concentrations was not possible.



Source: Figure 1.2.2.1, Figures for Integrated Summary of Immunogenicity

Figure 12. Mean ADA titer (Log values) by treatment and timepoint in Encore

4.4 Population PK and/or PD Analyses

4.4.1 Applicant's Population PK Analysis

(b) (4)

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4.4.3 Exposure-PD response analysis from Protégé study

As a supportive evidence to evaluate the biocomparability between the Eli-Lilly and AGC biologics products, exposure-response analyses for two pharmacodynamic (PD) markers were evaluated using available PK-PD data from Protégé study. The exposure from Protégé study was deemed comparable to the predicted exposure from Eli Lilly product. The first pharmacodynamic outcome evaluated was the AUC of total lymphocyte count change from baseline over the first 28 days of treatment. The second pharmacodynamic outcome evaluated was the change from baseline in C-peptide at 2 years. All exposure-PD response analyses were performed using nonlinear least squares modeling approach with SAS® 9.4 and the PROC NLIN procedure (method: Gauss-Newton).

4.4.3.1 Exposure versus total lymphocyte decline relationship

Analysis on the relationship between AUC of lymphocyte count decline and teplizumab exposure was conducted from the Protégé study data.

Lymphocyte counts were collected following the first treatment course (Days 0 - 28). Lymphocyte count change from baseline during the first 28 days was used to calculate the total lymphocyte change (AUC 0-28days) using a trapezoidal rule for each subject. When calculating total lymphocyte change, the missing lymphocyte counts at Day 28 were imputed using the treatment-specific average lymphocyte count change at Day 28. For the intermittent missing lymphocyte counts between Day 0 and Day 28, the missing values were imputed using the linear interpolation.

Teplizumab exposure (cumulative or total AUC from day 0 to infinity, AUCinf) following the 1st treatment course (cycle 1) of Protégé study was estimated from the final population PK model developed in T1D patients.

An Emax model (fixed Hill coefficient=1) was used to describe the relationship between total lymphocyte change and teplizumab exposure in subjects who received teplizumab (1/3 regimen, 6-day curtailed regimen, or full 14-day regimen).

The parameter estimates are presented in Table 18, and the predicted total lymphocyte change during the first 28 days versus teplizumab AUCinf is presented in Figure 30. The Emax model demonstrated that as the teplizumab AUCinf increased, the total lymphocyte decline increased, until reaching a plateau. According to the model, teplizumab AUCinf responsible for half of the maximum effect (EC50) was estimated to be 306.5 ng*day/mL. The estimated EC80, EC90, and EC95 corresponded to teplizumab AUCinf of 1226, 2759 and 5824 ng*day/mL, respectively. The teplizumab AUCinf of 1,500 ng*day/mL, depicted in Figure 30, corresponds to the EC83 (i.e., 83% of Emax).

Table 18. Parameter Estimates from the Emax Model: Protégé Study (Cycle 1)

Parameter	Estimate	Approx Std Error	Approximate 95% Confidence Limits	
E0	1.3475	6.7920	-12.0038	14.6988
Emax	21.0024	6.5502	8.1264	33.8784
EC50	306.5	220.4	-126.8	739.7

Source: Applicant's Statistical Report of PK/PD/Efficacy Analyses, Table 2, page 4.

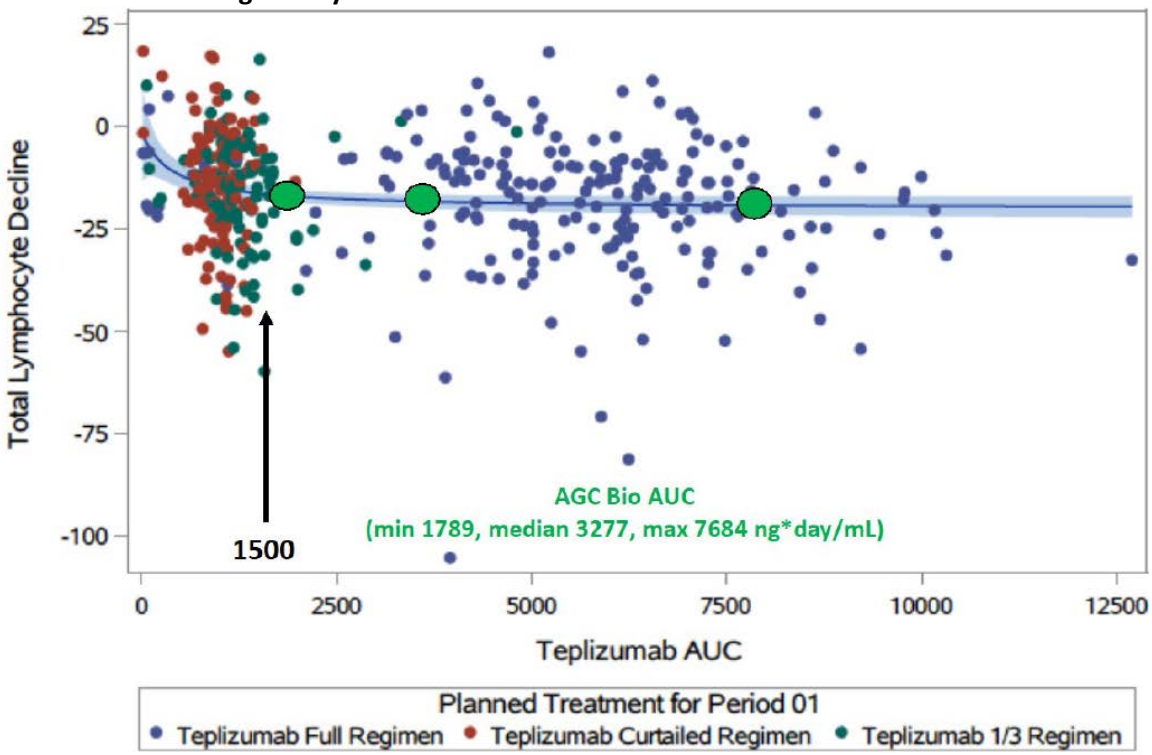
The studied exposure-response relationship did not include the data from Encore study population, which showed 49% higher teplizumab CL (with expected 49% lower exposure) in all arms compared to the Protégé study population (despite similar dosing regimen). An information request was issued to the applicant in order to include Encore study data, as a sensitivity analysis. The applicant replicated the analysis using the data from both Protégé and Encore studies. The results were similar to the Emax model analysis for Protégé study alone. The Emax for Protégé alone versus Protégé and Encore combined were 21.0 and 20.4 (10^3 cells*day/µL), respectively. Likewise, the EC50 was 306.5 and 361.9 ng*day/mL for Protégé versus Protégé and Encore combined, respectively (Table 19).

Table 19. Parameter Estimates from the Emax Model: Protégé and Encore Studies (Cycle 1)

Parameter	Estimate	Approximate Standard Error	Approximate 95% Confidence Limits	
E_0	-0.0804	6.2265	-12.3174	12.1565
Emax	20.3921	5.9828	8.6342	32.1501
EC_{50}	361.9	244.2	-118.1	841.8

Source: Applicant's Response to Request for Information-Part 2, Table 5, page 22.

Figure 30. Teplizumab AUCinf versus Total Lymphocytes Decline Relationship During the First 28 Days of Treatment: Protégé Study

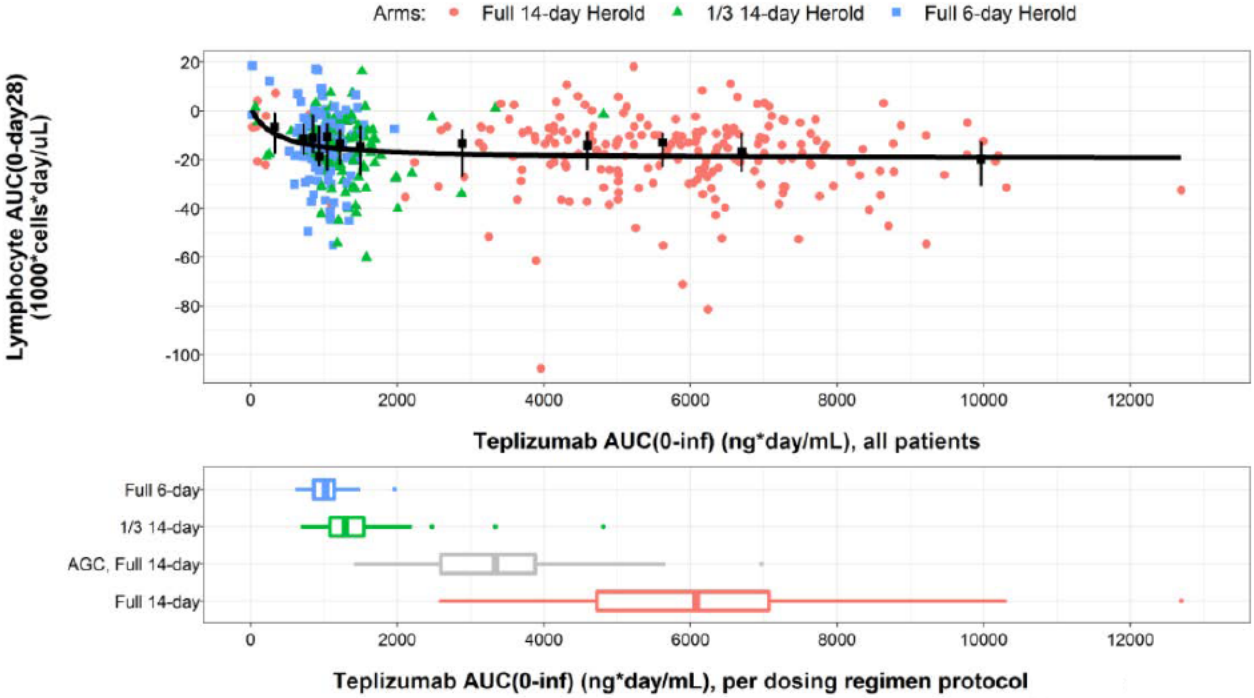


Source: Applicant's Companion Document to PRV-031-004 CSR, Figure 5, page 16.

Reviewer's Assessment on the exposure versus total lymphocyte decline relationship

- The exposure-response relationship is very shallow and the EC50 parameter of 306.5 ng*day/mL was not precisely estimated in the Emax model (asymptotic 95%CI included zero). This is likely due to the few exposure-PD observations and large variability in the PD outcome around the EC50 value as shown from Figure 30 and from the quantile plot in Figure 31.
- Figure 31 shows that almost all the observations from the 3 treatment arms are in the plateau of the Emax relationship.

Figure 31. Teplizumab AUCinf versus Total Lymphocytes Decline Relationship During the First 28 Days of Treatment and Expected Distribution of Teplizumab Exposure Under AGC biologics product (Lower Panel): Protégé Study Population



- In Figure 30, the sponsor overlaid the expected teplizumab exposure in the healthy subject from PRV-031-004 study receiving the full 14-day regimen, which may not be fully representative of the Protégé study population used to build the Emax model. The boxplots in Figure 31 provides the distribution of teplizumab AUCinf in patients from the Protégé study who received all their treatment doses. The grey boxplot represents the predicted exposure under the full 14-day regimen in the Protégé study patients if they were to receive the AGC Biologics product (AGC doses were estimated to be 55% of the Eli Lilly or MacroGenics doses, as previously predicted from the PRV-031-004 study PK model). Table 20 provides the estimated distribution of teplizumab AUC under the different dosing regimen, and Table 21 provides the expected percentage of maximum PD effect under various teplizumab exposure values. As shown from Figure 31, Table 20 and Table 21, the maximum or near maximum effect on total lymphocyte decline is reached under the exposures observed from the 3 different dosing regimens, with almost 70% of Emax reached with the minimum teplizumab exposure under

the reduced dose 14-day regimen (1/3 14-day regimen). The efficacy of the reduced dose in the delay of clinical T1D was not studied and the shallow exposure-lymphocyte decline relationship (i.e. absence of clear separation in effect between the full 14-day regimen and the other studied doses) does not allow to derive a margin of acceptance for PK difference and thus does not provide a compelling evidence to claim the bio comparability between products based on this PD marker.

Table 20. Summary of Teplizumab AUCinf from the Protégé Study, in Patients who Received All Treatment Doses

Dosing Regimens	Median (range) teplizumab AUCinf	25th percentile of teplizumab AUCinf	75th percentile of teplizumab AUCinf
Full 14-day	6076 (2562 - 12696)	4723	7066.2
AGC, Full 14-day	3336 (1407 - 6970)	2593	3879
1/3 14-day	1016 (604 - 1964)	859	1541.4
Full 6-day	1016 (684 - 4814)	859	1142

Table 21. Summary of Expected Percentage of Maximum PD Effect under Teplizumab Exposure from the Protégé Study, in Patients who Received All Treatment Doses

Dosing Regimen	Median (range) teplizumab AUCinf	25th percentile of teplizumab AUCinf	75th percentile of teplizumab AUCinf
	% of maximum effect on lymphocyte count decline		
Full 14-day	95 (89 - 98)	94	96
AGC, Full 14-day	92 (82 - 96)	89	93
1/3 14-day	81 (69 - 94)	78	83
Full 6-day	77 (66 - 87)	74	79

4.4.3.2 Exposure versus C-peptide change form baseline (at 2 years) relationship

Analysis on the relationship between the change from baseline in C-peptide at 2 years and teplizumab exposure was conducted from the Protégé study data.

For the analysis of C-peptide change from baseline at 2 years, data from a 4-hour mixed meal tolerance test (MMTT) was used. The natural-log transformed average C-peptide concentrations (computed as $AUC_{0\text{-}4hours}$ divided by the 4-hour time interval) was used as a measurement for the C-peptide level. The C-peptide levels used were collected at baseline and Day 728.

Teplizumab exposure (AUCinf) following the 2nd treatment course (cycle 2) of Protégé study was estimated from the final population PK model developed in T1D patients.

An Emax model (fixed Hill coefficient=1) was used to describe the relationship between C-peptide change from baseline and teplizumab exposure in subjects who received teplizumab (1/3 regimen, 6-day curtailed regimen, or full 14-day regimen).

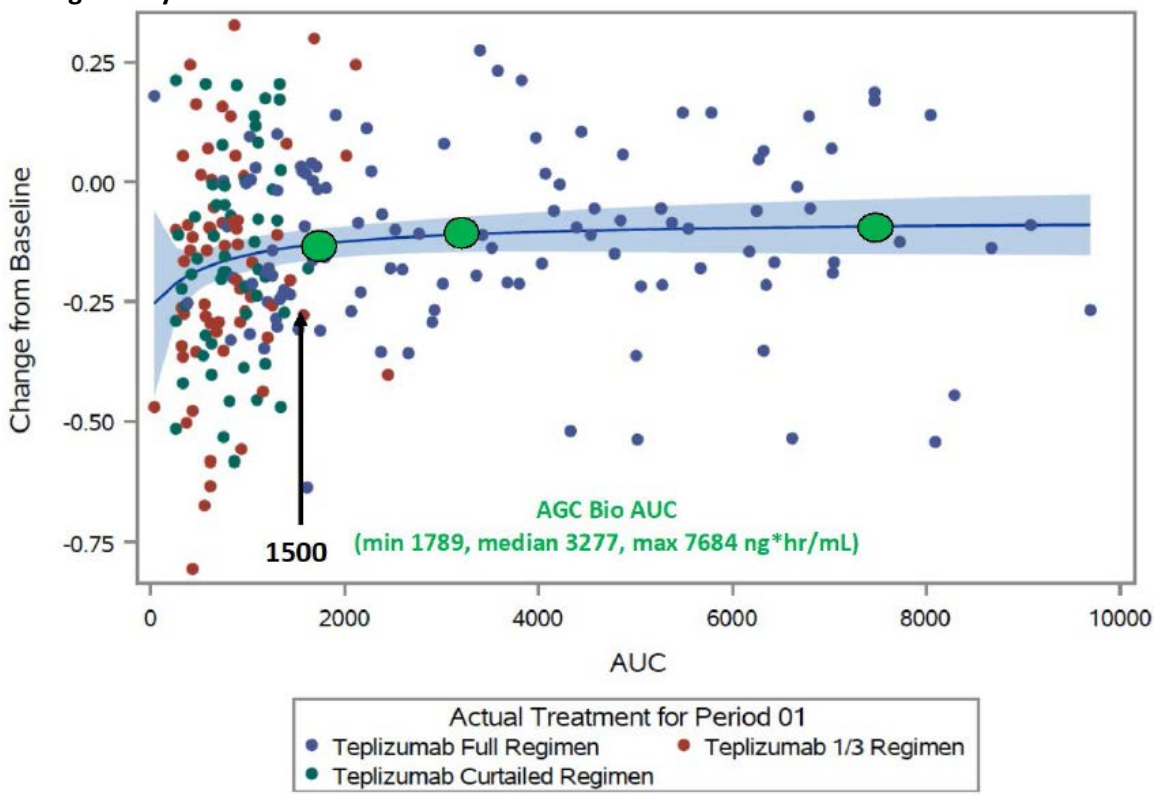
The parameter estimates are presented in Table 22 and the predicted C-peptide change at 2 years versus teplizumab AUCinf is presented in Figure 32. The Emax model showed that as the teplizumab AUCinf increased, the C-peptide decline decreased (C-peptide levels are better maintained with higher teplizumab exposure), until reaching a plateau. According to the model, teplizumab AUCinf responsible for half of the maximum effect (EC50) was estimated to be 677 ng*day/mL. The estimated EC80, EC90 and EC95 corresponded to teplizumab AUCinf of 2710, 6097 and 12871 ng*day/mL, respectively. The teplizumab AUCinf of 1,500 ng*day/mL, depicted in Figure 32, corresponded to EC69.

Table 22. Parameter Estimates from the Emax Model: Protégé Study (Cycle 2)

Parameter	Estimate	Approx Std Error	Approximate 95% Confidence Limits	
E0	-0.2637	0.1175	-0.4951	-0.0322
Emax	0.1860	0.1018	-0.0145	0.3866
EC50	677.4	1130.3	-1549.8	2904.5

Source: Applicant's Statistical Report of PK/PD/Efficacy Analyses, Table 4, page 5.

Figure 32. Teplizumab AUCinf versus C-peptide Change From Baseline (At 2 Years) Relationship: Protégé Study



Source: Applicant's Companion Document to PRV-031-004 CSR, Figure 9, page 22.

Reviewer's comment: the correct unit for AUCinf is ng*day/mL. The actual treatment period is period 2 (i.e. Cycle 2), not period 1.

Reviewer's Assessment on the exposure versus C-peptide change from baseline relationship

- The exposure-response relationship is very shallow. The Emax parameter (0.186 nmol/L) and the EC50 parameter (677.4 ng*day/mL) were not appropriately with a lack of precision for all parameters (asymptotic 95%CI included zero). This shallow relationship is in line with the applicant analysis from the protégé study comparing the change from baseline in C-peptide at week 104 (Day 728) between placebo and the different treatment arms (mga031-01-csr-body.pdf report, Table 30).
- The boxplots in Figure 33 shows that the distribution of teplizumab AUCinf, from cycle 2 dosing, overlapped between AGC product and Eli Lilly product under the full 14-day regimen. The lower range of exposure from the AGC product under the full 14-day regimen also overlapped with the upper range exposure from the curtailed (6-day) regimen and the reduced-dose (1/3) 14-day regimen.
  Table 23 provides the estimated distribution of teplizumab AUC under the different dosing regimen, and Table 24 provides the expected percentage of maximum PD effect under various teplizumab exposure values. The median and 75th percentiles of teplizumab exposure from the curtailed and reduced dose regimens provide at least 70% and 76% of the maximum effect of maintaining higher C-peptide levels. The 25th percentile and median teplizumab exposure from the AGC product under the

full 14-day regimen represent EC74 and EC86 respectively. As for the total lymphocyte count change from baseline, the shallow exposure-response relationship (i.e. absence of clear separation in effect between the full 14-day regimen and the other studied doses) does not allow to derive a margin of acceptance for PK difference and thus does not provide a compelling evidence to claim the bio comparability between products based on this PD marker.

- In addition, the studied exposure - C-peptide response relationship was performed in T1D patients (Stage 3 of the disease) and thus the exposure-response cannot be extrapolated to subjects at Stage 2 of the natural history of T1D progression, with preserved ability to produce C-peptide.

Figure 33. Teplizumab AUCinf versus C-peptide Change from Baseline (At 2 Years) Relationship and Expected Distribution of Teplizumab Exposure Under AGC biologics product (Lower Panel): Protégé Study Population

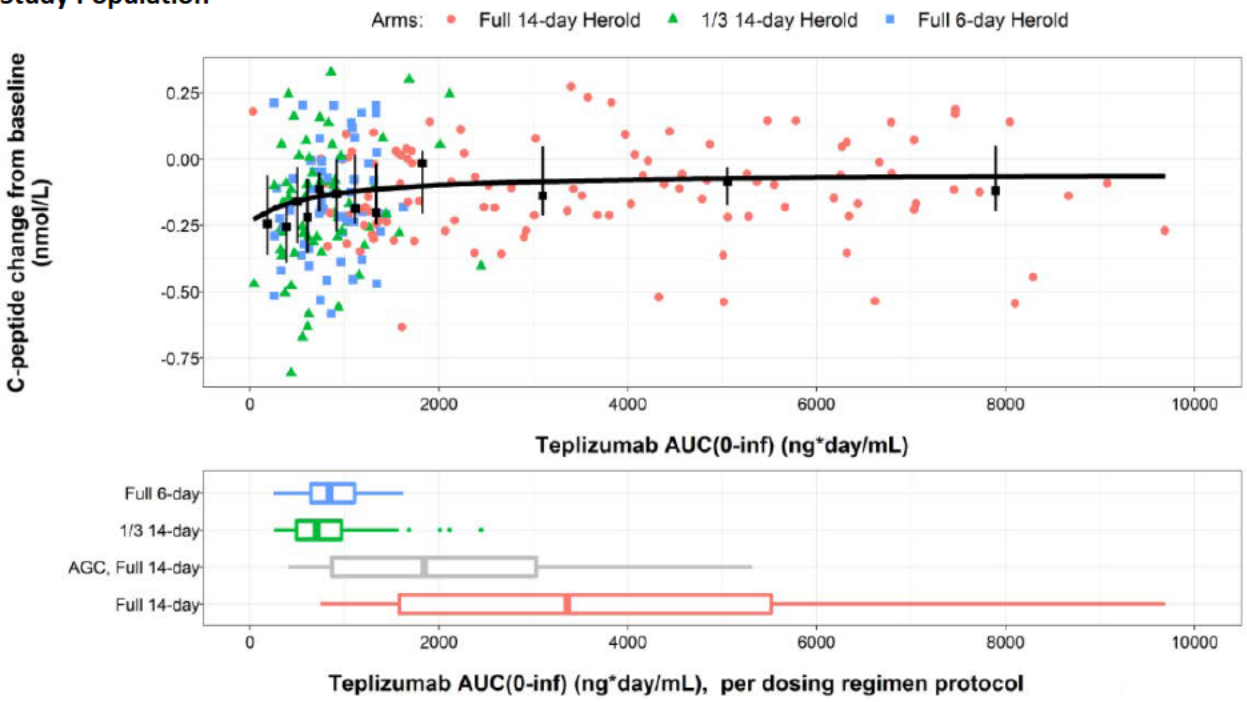


Table 23. Summary of Teplizumab AUCinf from the Protégé Study, in Patients who Received All Treatment Doses

Dosing Regimens	Median (range) teplizumab AUCinf	25th percentile of teplizumab AUCinf	75th percentile of teplizumab AUCinf
Full 14-day	3358 (745 - 9690)	1579	5517
AGC, Full 14-day	1844 (409 - 5320)	867	3029
1/3 14-day	707 (259 - 2446)	494	967
Full 6-day	841(255 - 1626)	646	1107

Table 24. Summary of Expected Percentage of Maximum PD Effect under Teplizumab Exposure from The Protégé Study, in Patients who Received All Treatment Doses

Dosing Regimen	Median (range) teplizumab AUCinf	25th percentile of teplizumab AUCinf	75th percentile of teplizumab AUCinf
	% of maximum effect on C-peptide change form baseline		
Full 14-day	92 (71- 97)	84	95
AGC, Full 14-day	86 (57- 95)	74	91
1/3 14-day	70 (46- 89)	62	76
Full 6-day	73 (45- 84)	68	78

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