Memo to the File

From:	Michael Davis, MD, PhD Acting Director Center for Drug Evaluation and Research (CDER)
To:	Biologics License Application (BLA) 761183-Supplement 010
Applicant's original proposed Indication:	(b) (4) indicated to delay the progression of Stage 3 T1D in adults and pediatric patients 8 years of age and older recently diagnosed with Stage 3 T1D.
Revised indication following discussions with the FDA review team:	To delay the decline in endogenous insulin production in pediatric patients aged 8 to 17 years recently diagnosed with Stage 3 T1D. This indication is approved under accelerated approval based on evidence of reduced C-peptide decline *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
Subject:	Documentation of concurrence with Division recommendation

The purpose of this memo is to document my concurrence with the Division of Diabetes, Lipid Disorders and Obesity's (DDLO) recommendation that CDER approve BLA 761183, Supplement 010 without holding a public discussion before an advisory committee.

Background

BLA 761183 for Tzield (teplizumab-mzwv) injection was approved on November 17, 2022, under traditional approval for the delay of onset of Stage 3 Type 1 diabetes (T1D) in adults and pediatric patients 8 years of age and older with Stage 2 T1D.[1] On July 21, 2025, the Applicant submitted a supplemental BLA (sBLA) requesting approval under accelerated approval for the proposed indication:

[1] This indication was expanded with the approval of an sBLA on April 20, 2026, to delay the onset of Stage 3 T1D in pediatric patients between 1 to 8 years of age with Stage 2 T1D

(b) (4)

indicated to delay the progression of Stage 3 T1D in adults and pediatric patients 8 years of age and older recently diagnosed with Stage 3 T1D.

The Applicant requested a priority review designation for the sBLA. The application was designated as a priority review application and filed on July 21, 2025, with a user fee goal date of January 21, 2026. The goal date was extended to April 21, 2026, after receipt of a major amendment.

By letter dated October 24, 2025, FDA communicated to the Applicant that the sBLA was selected for the FDA Commissioner's National Priority Voucher (CNPV) pilot program[2], on the basis that the Tzield injection for recently diagnosed Stage 3 T1D sBLA met pilot program criteria based on its alignment with critical U.S. national health priorities.

Before May 2026, following a presentation and a preliminary recommendation by the primary review team, applications reviewed under the CNPV were discussed internally before a select group (the CNPV Review Council) within FDA who voted on the application review issues brought before them, such as the benefits/risks of the drug product covered by the application. This supplement was discussed before the CNPV Review Council three times: on October 28, 2025, April 1, 2026, and April 8, 2026. Each of those meetings concluded with a vote from the CNPV Review Council. A separate non-voting briefing was also held on February 2, 2026; this meeting included only a small group from the application review team, former FDA Commissioner Dr. Marty Makary, former acting CDER Director Dr. Tracy Beth Hoeg, and former CBER Director Dr. Vinay Prasad.

During each of these meetings, the review team presented its position that the pivotal study (PROTECT) showed a statistically significant effect of teplizumab-mzwv on C-peptide, a surrogate endpoint considered reasonably likely to predict clinical benefit to support accelerated approval.[3] The review team also presented safety data related to risks of diabetic ketoacidosis (DKA), Epstein-Barr Virus (EBV) reactivation, infections, and cancer, and their conclusion was that these risks were unlikely related to

[2] On June 17, 2025, FDA announced the Commissioner's National Priority Voucher (CNPV) pilot program intended to shorten review time "from approximately 10-12 months to 1-2 months following an applicant's final drug application submission." On October 16, 2025, FDA announced that this sBLA was among nine recipients of a CNPV. Neither the Applicant nor the review division requested that this application be reviewed under the CNPV pilot program.

[3] Section 506(c) of the FD&C Act codified the accelerated approval program which provides a pathway for approval of drugs for serious conditions that fill an unmet medical need based on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit.

teplizumab-mzwv; or if related, the risks did not outweigh the benefits of teplizumab-mzwv if used as directed in labeling, including with a narrowed indication and recommendations to mitigate risks. In addition, the review team stated that the Applicant's agreed-to confirmatory trial to verify clinical benefit was already underway and would continue as a post-marketing requirement (PMR).[4] A PMR to conduct an observational registry study to assess long-term safety of teplizumab-mzwv to evaluate cytokine release syndrome, serious infections, hypersensitivity reactions, lymphoproliferative disorders (LPD) and malignancy is ongoing. Long-term safety data are also being collected as a PMR for an additional 42 months in participants who complete the PROTECT study.[5]

At each CNPV Review Council meeting, Dr. Hoeg voiced objection to approval of this application. She disagreed with the review team's view that the product's benefits outweighed its risks, including the risks of DKA, EBV reactivation, or cancer. She met with the Division review team, the Office Deputy Director, and the Office of New Drugs (OND) Director on April 9, 2026, stating that she could not approve the application. On April 21, 2026, the Applicant was informed that the Agency was going to miss the PDUFA goal date for the application in order to hold a public advisory committee meeting to discuss the benefits and risks of this product for its proposed indication.

Materials Reviewed

As the current acting Center Director, I reviewed the many documents provided by the multi-disciplinary review team to understand the benefits and risks of this product for this specific indication. These documents included:

1. Statistical Review, finalized October 20, 2025
2. Statistical Review, finalized March 5, 2026
3. Office of Oncology Drugs, Division of Hematologic Malignancies 2 consult dated January 9, 2026
4. Office of Infectious Diseases, Division of Antivirals consult dated January 9, 2026
5. Office of Infectious Diseases, Division of Antivirals consult dated March 30, 2026
6. Clinical Review from the Division of Diabetes, Lipids and Obesity (DDLO) and the Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN), finalized March 19, 2026
7. Office of Surveillance and Epidemiology (OSE) consult dated April 14, 2026
8. OSE DPV review dated April 30, 2026

[4] Section 506(c) of the FD&C Act, as amended by the Consolidated Appropriations Act, 2023, gives FDA authority to require, as appropriate, that a confirmatory trial be underway prior to accelerated approval or within a specified time period after the data of accelerated approval.

[5] As per the applicant's Annual Status Report received on January 15, 2026, and reviewed by FDA on March 31, 2026, both of these PMRs are ongoing.

Dr. Hoeg is no longer at the FDA; however, it is important to consider the safety concerns that she voiced on each of the occasions discussed above before determining whether the course of action previously directed by her should be followed. Dr. Hoeg did not provide any written review in the administrative record discussing her analyses of the safety findings, her consideration of the Division's recommendation, including labeling changes, or her consideration of the multiple consults provided to the Division; thus, there is no discussion of a counter-perspective of her concerns in this document. However, upon my independent review, I believe the multiple reviews and consult reviews, including one requested by Dr. Hoeg, provide evidence of a very thorough review performed by career FDA scientists with expertise in endocrinology, infectious disease, oncology/hematology, biostatistics, and epidemiology. Below, I summarize the conclusions from these reviews:

- The clinical and statistical reviews concluded that the applicant was able to demonstrate robust and superior effectiveness of teplizumab-mzwv in preserving C-peptide area under the curve (AUC) compared to placebo among pediatric patients 8 to 17 years of age.
- The clinical and statistical reviews provided very detailed reviews and analyses of DKA and serious infections, concluding that the totality of evidence, including individual review of cases, suggests that the occurrence of DKA or serious infections in the PROTECT study is unlikely to be related to teplizumab-mzwv.
- Two consult reviews from the Division of Antivirals and one consult from the Division of Hematologic Malignancies 2 on the cases of EBV reactivation, including risk of LPDs, acknowledged the biologic plausibility of EBV reactivation which is similar to other immune modulator drugs and recommended labeling to strengthen the warnings for this risk, including the addition of a Boxed Warning.
- The OSE consult, conducted at the request of Dr. Hoeg, to evaluate the risks for neoplasms, including EBV-associated LPD, provided a thorough review of five cases of neoplasm and a summary of a literature review performed by OSE. The consult review concluded that, based on available information, it is not possible to implicate teplizumab-mzwv as having a direct effect on the development of reported neoplasms. The consult recommended labeling changes regarding viral reactivation, continued pharmacovigilance, and fulfillment of PMRs.
- Another OSE review of all U.S. serious cases submitted to the FDA's Adverse Event Reporting System (FAERS) in pediatric patients under 18 years of age from November 17, 2022, to March 9, 2026, identified no new safety signals, no increased severity of any labeled adverse events, and no deaths directly associated with teplizumab-mzwv. This review concluded that no new pediatric

safety concerns for teplizumab-mzwv were identified at this time and that routine pharmacovigilance monitoring should continue.

All of these reviews led to consistent conclusions that the Applicant demonstrated a significant effect on an accepted endpoint to support accelerated approval, and that the risks identified did not outweigh this efficacy and could be further mitigated through labeling, required post-marketing studies, and postmarket pharmacovigilance to ensure the benefit-risk profile of this product for this indication remains favorable. None of these reviews stated that an advisory committee meeting would be useful for the regulatory decision.

Conclusion

Delegation of signatory authority for marketing applications is assigned to the OND Clinical Office Director (or deputy) for new molecular entity (NME) new drug applications (NDAs) or BLAs and the OND Division Director (or deputy) for non-NME NDAs or BLAs and supplemental applications to an approved NDA or BLA. The signatory authority for BLA 761183-Supplement 010 rests with the Director (or Deputy) of DDLO.

After reading the finalized reviews and consults and meeting with the review team, I believe the multi-disciplinary review team has carefully considered the available efficacy and safety data and reached reasonable, scientifically justified conclusions about the benefit/risk profile of this drug product for its proposed indication (with appropriate labeling and PMRs). I support their unanimous recommendation to approve teplizumab-mzwv under the accelerated approval pathway to delay the decline in endogenous insulin production in pediatric patients aged 8 to 17 years, recently diagnosed with Stage 3 T1D.

I also agree with the review team that an advisory committee meeting to discuss the pending application, as requested by former acting Center Director Dr. Hoeg, is not warranted here. Except in limited circumstances that are not applicable to this application, FDA is not required to convene an advisory committee meeting to discuss a pending drug application before taking action on the application. Although advisory committee meetings can be helpful in providing independent expert advice to FDA on FDA-regulated products, taking a pending drug application to an advisory committee for discussion and recommendations can add significant time to the drug review process and can require significantly more Agency and sponsor resources. Thus, FDA typically does not convene an advisory committee meeting to discuss a pending drug application unless the relevant Center determines that obtaining the advisory committee's non-binding advice on one or more scientific topics may be important to inform the Center's review and final decision on the application. For the reasons explained above, that is not the case here. Thus, CDER will not convene an advisory committee meeting to

discuss the application; instead, the review team will proceed to approve the application under accelerated approval with appropriate labeling and PMRs.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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