

Category

Best Pharmaceutical Product

General Information**Company Name ***

Sanofi-Aventis U.S. LLC

Product/Solution Name *

Tzield® (teplizumab-mzwv)

Compound/Tech Name*

teplizumab

Trade Name *

Tzield® (teplizumab-mzwv)

Corporate Name ***Date of Approval ***

2022-11-17

Indications *

Tzield® (teplizumab-mzwv) is a CD3-directed antibody indicated 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.

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Therapeutic Areas *

Stage 2 T1D, also known as 'at risk' or 'pre-symptomatic' T1D.

Stage 2 T1D is characterized by the presence of two or more T1D-related autoantibodies and dysglycemia and a life-time risk approaching 100% of developing clinical, insulin-dependent, T1D.

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Background information and need for drug / device

(please be as specific as possible in your description; limit 500 words)

Tziel® is the first disease-modifying therapy to be approved for Type 1 Diabetes (T1D), an acutely life-threatening autoimmune disease characterized by auto-reactive T cell-driven destruction of the pancreatic beta cells responsible for the production of insulin. The loss of endogenous insulin production leads to life long, daily dependence on injected insulin with reduced quality of life and increased morbidity and mortality, especially among children. T1D is diagnosed in over 60,000 Americans every year (Rogers et al 2017), and there are 1.8 million people living with T1D in the US according to JDRF International. T1D is typically sporadic and can be diagnosed from the first year of life to the 9th decade. Patients diagnosed before 10 years of age have an average of 16 years lost in life expectancy. Severe, life-shortening complications stem from the disease (serious acute and long-term micro- and macrovascular complications) and from the insulin therapy itself (life-threatening episodes of severe hypoglycemia).

Scientific advances in recent years have shown that T1D progresses through 3 stages (Insel et al 2015):

- Stage 1: asymptomatic stage with emergence of 2 or more T1D-related autoantibodies and normoglycemia (44% risk of progression to Stage 3 in 5 years and lifetime risk approaches 100%).
- Stage 2: pre-symptomatic stage with persistence of 2 or more T1D-related autoantibodies and dysglycemia (abnormal blood glucose control revealed in an oral glucose tolerance test or other metabolic assessments; 75% risk of progression to Stage 3 in 5 years and lifetime risk approaches 100%).
- Stage 3: symptomatic or clinical T1D, when remaining beta cell capacity is insufficient to maintain glucose control and exogenous insulin is needed to maintain life.

The emergence of T1D-related autoantibodies in Stage 1 reflects the initiation of the autoimmune process and thus the beginning of the disease. As the autoimmune process continues, destruction of beta cells and the appearance of dysglycemia signal entry into Stage 2. Further loss of beta cell function in Stage 2 ultimately leads to Stage 3 disease, when beta cell capacity is insufficient to maintain glucose homeostasis. Once individuals develop 2 or more T1D-related autoantibodies, the lifetime risk of progressing to Stage 3 T1D approaches 100% (Insel et al 2015). Beta cell function can be measured by C peptide levels, which reflect endogenous insulin production and are critical to describing beta cell reserve. The majority of patients with asymptomatic Stage 2 T1D are undiagnosed until they become symptomatic and hyperglycemic and enter Stage 3 disease. Once diagnosed with clinical, Stage 3, T1D, lifelong insulin therapy -requiring multiple daily injections or administered via an insulin pump- is instituted along with intermittent or continuous glucose monitoring. In addition to a restricted dietary regimen, life becomes very different, often extremely difficult and burdensome for these patients, especially those in the pediatric age group, and their caregivers. Patients and families often describe T1D as a "24/7 disease" from which they get no respite.

Prior to the approval of Tziel® (teplizumab-mzwv) in the US for Stage 2 T1D, the only available therapies for T1D were those initiated at the time of diagnosis of Stage 3 T1D to treat the symptomatic metabolic consequences of the disease, without any effect on the underlying autoimmune process. In other words, while existing therapies treat end-stage disease or disability (loss of insulin), Tziel® addresses the disease pathophysiology.

Tziel® is an anti-CD3 monoclonal antibody designed to incapacitate auto-reactive T lymphocytes by inducing a state of deactivation (anergy), leading to exhaustion and functional elimination of the cells responsible for beta cell destruction. Tziel® does not impair (and even increases) regulatory T cells and results in a net increase in the regulatory/autoreactive T cell balance. This leads to control of

autoimmunity and preservation of beta cells and beta cell function, thus delaying the progression of T1D. Importantly, the immune 'resetting' action of Tziel® induces long-lasting responses after a short 14-day course of drug. When administered to Stage 2 T1D patients, Tziel® leads to a substantial 2.7-year median delay of the onset of Stage 3 T1D, with some patients experiencing delays of up to 10 years.

When Tziel® was approved in the US on November 17, 2022 (100 years after the discovery of insulin), it became the first-ever and only approved disease-modifying drug in T1D. In addition, Tziel® is the first-ever and only non-chronic T cell immune modulator approved in any autoimmune disease. These are both major advances in diabetes and immunology in general, and a paradigm shift in how chronic immune diseases are managed. Delay of the onset of a disease provides healthy years and requires screening of asymptomatic/pre-symptomatic subjects, a challenge, but undoubtedly one of the trends in the future of Medicine.

Prior to its evaluation under Priority Review and ultimately US approval, Tziel® had received Breakthrough Therapy designation in the US, as well as PRIME designation in the EU and Innovation Passport designation in the UK, in recognition of its potential to significantly improve efficacy or safety in the treatment of a serious condition.

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History of the development of the solution/product *
(please be as specific as possible in your description; 500 words)

Tziel® has been under development for over 20 years by academic researchers and four pharmaceutical companies, a testament to the challenges to bring about the first-ever disease-modifying drug in Type 1 Diabetes (T1D), and specially the paradigm-changing nature of treating patients with pre-symptomatic disease before irreversible tissue damage. This type of work requires 1) a thorough understanding of the natural course of the disease, 2) robust biomarkers identifying patients with pre-symptomatic disease at high risk of progression to end-stage disease, and 3) well-tolerated and effective interventions given the lack of symptoms in the target subject population.

Pioneering studies on the natural course of T1D took two decades to be completed and required international consortia. Three of these consortia (TrialNet; Diabetes Prediction and Prevention study, DIPP; and The Environmental Determinants of Diabetes in the Young, TEDDY) have screened a combined 850,000 people for risk of T1D, following those with predisposition to map the triggers and course of disease.

The discovery and validation of the five major T1D-associated autoantibodies which enable screening, early diagnosis and disease course prediction also took decades of efforts by academic labs and diagnostic companies.

Finally, the trials were also very lengthy. The pivotal TN-10 clinical trial which led to the FDA approval of Tziel® took 8 years to be completed.

In all, half a decade of pre-clinical research was followed by a decade of phase 1-2 studies in T1D and the 8 years of TN-10.

The development of Tzield® is the result of an extraordinary collaborative effort by the entire T1D community, which has been waiting 100 years for a disease-modifying treatment option: the patient community (Breakthrough T1D, formerly known as JDRF, funded TrialNet and Provention Bio), the US government (National Institute of Diabetes and Digestive and Kidney Diseases, NIDDK, funded TN-10) and hundreds of academic researchers. Two of them deserve special mention: Dr. Jeffrey Bluestone (U. Chicago, UCSF, Immune Tolerance Network) and Dr. Kevan Herold (U. Chicago, Yale), whose tireless work ultimately allowed Provention Bio to take Tzield® through the Biologics License Application successfully. After acquiring Provention Bio, Sanofi is now committed to maximizing access to this 'miracle of science' for those people in need, and to deploy its resources to expand use into future indications, first and foremost newly-diagnosed T1D (results of the pivotal PROTECT study are expected in the summer of 2023).

The development history of Tzield® includes the following major events:

- The initial studies were focused on preserving remaining beta cell function in newly diagnosed patients with Stage 3 T1D and were conducted by academic investigators (Study 1, AbATE [Autoimmunity blocking Antibody for Tolerance in Recently Diagnosed Type 1 Diabetes], Delay) and a prior sponsor, MacroGenics (Protégé and Encore). These studies showed preservation of beta cell function as measured by slower decline in C-peptide levels and lower exogenous insulin use in Tzield®-treated patients.
- Provention Bio, a Sanofi company since May 2023, acquired Tzield® in 2018 to continue the clinical development program and is currently conducting the Phase 3 PROTECT study in newly diagnosed patients with Stage 3 T1D (NCT03875729). The primary objective in PROTECT is to demonstrate preservation of beta cell function (maintained C-peptide levels).
- The pivotal TN-10 study, initiated in 2011, was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and conducted by TrialNet, which is an international network of leading academic institutions with primary focus on T1D research. The objective of the study was to evaluate the effect of a single 14-day treatment course of Tzield® in delaying or preventing the onset of Stage 3 clinical T1D in patients with Stage 2 T1D (defined as those with at least 2 T1D-related autoantibodies and dysglycemia). The primary analysis of the TN-10 study was conducted in 2018, and results were available in 2019:
 - Efficacy: The efficacy results from the TN-10 study supported the proposed indication for Tzield® for the delay of progression to Stage 3 clinical T1D in patients with Stage 2 T1D. Efficacy was further supported by confirmatory evidence in the form of a meta-analysis of C-peptide levels, which demonstrated preservation of beta cell function in newly diagnosed Stage 3 patients, as requested by and agreed upon with Food and Drug Administration (FDA), signifying Tzield®'s effect on the underlying pathophysiology of the disease.
 - Safety: In the TN-10 study, a single 14-day treatment course of Tzield® showed no new safety signals beyond those observed in the prior Stage 3 studies. The most commonly reported adverse events in the Tzield® group were transient lymphopenia, rash, and leukopenia. Cytokine release was observed in a small percentage of patients and was generally mild or moderate. Liver enzyme abnormalities seen in a subset of patients were reversible upon completion of dosing. The safety findings from nearly 800 patients exposed to Tzield® with approximately 1,500 patient-years of follow up in the Stage 2 and Stage 3 T1D studies provide adequate population follow-up to support the safety profile of Tzield® for the proposed indication.

There have been significant challenges during Tzield® development. Since Stage 2 T1D is asymptomatic, the obstacle of identifying trial participants for the TN-10 study needed to be overcome

by working with highly skilled international T1D study networks. In addition, TN-10 study design involved a long event-driven endpoint that required waiting for sufficient cases of clinical T1D be accrued before unblinding. There were also unexpected challenges in comparability when a single low-dose trial in normal healthy volunteers resulted in lower exposure for the Tzield® product manufactured by Provention Bio for intended commercial use with respect to the product manufactured by Lilly a decade prior. This led to a Complete Response Letter by FDA in response to the Biologics License Application (BLA). Provention Bio predicted that this issue would be ameliorated when using Tzield® in the clinical dosing regimen of 14 consecutive days, as the clearance mechanisms would be partly saturated. Provention Bio then conducted a pharmacokinetic (PK)/pharmacodynamic (PD) study in patients with newly-diagnosed T1D. Robust PK modeling proved the prediction to be correct, enabling resubmission of the BLA and ultimately the approval of a modelled dose of Tzield® to ensure adequate exposure. This enabled the FDA to provide licensure for Tzield®, the first time FDA approved a first indication of a drug with a dosing regimen based on PK modeling.

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Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition *

Virtually all patients with Stage 2 T1D who do not receive intervention will progress to Stage 3 clinical T1D, resulting in lifelong insulin dependence implying the need of 24/7 lifestyle adjustment. Prior to Tzield®, therapies for T1D were directed at Stage 3 disease; there were no treatments approved for Stage 2 T1D nor any medicine to address the underlying autoimmune process. Tzield® ushers in a new era in T1D and in Immunology, by disrupting the causative autoimmune mechanism of T1D, preserving functioning beta cells, leading to the delay of progression to dependence on injected insulin. The beneficial impact on patients who get years of normalcy in their lives, as well as on their families cannot be overemphasized.

In the TN-10 study, a single 14-day course of teplizumab resulted in a 2-year median delay in the progression to Stage 3 clinical T1D in patients with Stage 2 T1D. The results were highly statistically significant. The benefits of the observed minimum 2-year delay in the median time to diagnosis of clinical Stage 3 T1D and potential prevention of the onset of T1D in at-risk patients are clinically meaningful. Based on self-reported treatment preferences, families with children at high risk of developing Stage 3 T1D indicated their willingness to accept side effects of a novel treatment for a delay of 2 years before becoming insulin dependent (DiSantostefano et al 2020). A delay of 2 or more years lessens the amount of time that young people will experience the clinical implications and complications of Stage 3 T1D during their teenage or young adult years - a time in life when glycemic control is particularly difficult, likely due to reduced compliance with the complex demands of insulin therapy (Dayan et al 2019; Miller et al 2015; Wood et al 2013). It is now well established that exposure to hyperglycemia is the dominant factor in the etiology of microvascular complications (blindness, loss of renal function, neuropathy) in T1D and that an agent that reduces the duration and level of glycemia will have long term clinical benefits (Palmer et al 2004). Finally, it has been reported that patients diagnosed with clinical T1D early in life experience greater loss of life expectancy (Rawshani et al 2018).

Thus, a treatment that delays the onset of clinical T1D beyond the childhood years could have considerable long-term impact.

The efficacy data from the TN-10 study was supported by the preservation of beta cell function as demonstrated by the statistically significant results of meta-analyses of C peptide levels in Stage 3 patients. Lower mean insulin use over time from the individual studies further supported the C-peptide findings. Together, these data provided evidence that Tziel® protects beta cells throughout the disease continuum.

Based on the experience to date in Stage 2 and Stage 3 T1D, the main risks with Tziel® are mechanism-based, predictable and transient with no evidence of increased risk of infections or malignancies. A 7-year follow-up of Tziel®-treated Stage 3 or newly diagnosed patients in the AbATE study showed no increased risk of infections and no malignancies were observed (Perdigoto et al 2019).

In another innovation, Tziel® can be administered not only in outpatient settings staffed by healthcare providers, but also at the patients' homes, by providers experienced in the administration of biologics and the management of potential adverse reactions.

Broad implications for future research include the dawn of a new era in T1D immunotherapy, with Tziel® as the backbone of disease modifying approaches deployed throughout the natural history of the disease, from Stage 1 to 3. Sequential and combination therapies with agents such as antigens, beta cell-targeting agents and regenerative medicine approaches are very likely to follow. Tziel® has shown POC in the improvement of outcomes of pancreatic islet transplant (Hering et al 2004, Bellin et al 2012) and offers tremendous promise to protect novel beta cell replacement strategies, with the dream of a cure for patients with long-standing T1D in the horizon.

These concepts are also applicable to other T cell-mediated immune disorders. Tziel® has achieved POC in renal and pancreatic transplantation (Woodle et al 1998, Woodle et al 1999) and in psoriatic arthritis (Utset et al 2012) with further studies planned in other autoimmune indications.

The approval of Tziel® represents a transformational shift in what can be offered to patients with T1D, and in Medicine. The Press Releases by FDA and JDRF summarized the importance:

- FDA Press Release: <https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-can-delay-onset-type-1-diabetes>
 - o "Today's approval of a first-in-class therapy adds an important new treatment option for certain at-risk patients," said John Sharretts, M.D., director of the Division of Diabetes, Lipid Disorders, and Obesity in the FDA's Center for Drug Evaluation and Research. "The drug's potential to delay clinical diagnosis of type 1 diabetes may provide patients with months to years without the burdens of disease."
- JDRF Press Release: <https://www.jdrf.org/press-releases/fda-approves-tziel-teplizumab-mzwv-a-drug-that-can-delay-the-onset-of-type-1-diabetes-for-approximately-2-years/>
 - o "This is a watershed moment for the T1D community. For the first time in history, there is now a therapy to address the underlying autoimmunity responsible for T1D. With breakthroughs in disease-modifying therapies-treatments that can slow, halt, or reverse the course of the disease, like Tziel and others in the pipeline-people at risk of T1D, who already have the markers of the disease, will be able to delay the onset of the disease for years. That means potentially years without blood-sugar

monitoring, insulin administration, and the fear of short- and long-term complications. This also gives these individuals the opportunity to learn more about disease management and enables next-generation treatments and technologies, which are in clinical trials now, to get to regulatory review."

o "We thank the FDA for their thorough review of the evidence, data, clinical benefits, and future impact of Tzield. Tzield and multiple other potential disease-modifying therapies that JDRF has invested research into put us on the critical pathway to finding cures and, one day, preventing T1D entirely."

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Please provide appropriate references (PubMed, Abstract, Website) *

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