American Diabetes Association.
Connected for Life

May 26, 2021

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Via www.regulations.gov

Re: Docket No. FDA-2021-N-0270; Endocrinologic and Metabolic Drugs Advisory Committee Notice of Meeting; Establishment of a Public Docket; Request for Comments.

Dear FDA Regulators and Advisory Committee Members,

On behalf of the 34 million Americans living with diabetes, the American Diabetes Association (ADA) submits comments to the U.S. Food and Drug Administration's ("FDA" or "Agency") docket FDA-2021-N-0270, regarding the Federal Register notice, "Endocrinologic and Metabolic Drugs Advisory Committee Notice of Meeting: Establishment of a Public Docket; Request for Comments" which appeared in the Federal Register on April 1, 2021.

Type 1 Diabetes

Type 1 diabetes (T1D) is one of the most common chronic diseases in childhood and the incidence is increasing, especially in children less than 5 years of age. T1D is also diagnosed at an increasing rate in adults.[1] T1D is an autoimmune disease characterized by loss of insulin producing β-cells and reliance on exogenous insulin for survival. T1D is caused by immune-mediated destruction of insulin producing β-cells in the pancreas.[2] The destruction of β-cells results in insulin insufficiency, and patients can develop life-threatening hyperglycemia and diabetic ketoacidosis.

People with T1D require life-long insulin replacement therapy. In the United States, there are an estimated 1.6 million people with T1D,[3] and that number is expected to grow to 5 million by 2050.[1] More than 64,000 T1D are diagnosed each year in the U.S.[4] T1D is associated with high morbidity and mortality. Close to 50% of patients will develop a serious complication over the lifetime. Some will lose eyesight, and others will develop end-stage kidney disease. The disease

[1] Simmons KM, Michels AW. Type 1 diabetes: A predictable disease. *World J Diabetes*. 2015;6(3):380-390. doi:10.4239/wjd.v6.i3.380
[2] Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014;383:69–82.
[3] CDC National Diabetes Statistics Report, 2020. https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html. Accessed May 20, 2021.
[4] Rogers, M.A.M., Kim, C., Banerjee, T. *et al.* Fluctuations in the incidence of type 1 diabetes in the United States from 2001 to 2015: a longitudinal study. *BMC Med* 15, 199 (2017). https://doi.org/10.1186/s12916-017-0958-6

has no cure, and with time, the patient may develop premature coronary artery disease, neuropathy, foot ulcers, and vision loss.

Quality of Life and Unmet Needs

For a century, insulin has been front line therapy for T1D disease management. Although life-sustaining, insulin therapy has significant medical risks of hypoglycemia, and often people living with diabetes must spend an inordinate amount of their lives and psyche considering the many factors that affect blood glucose in order to strive for good glucose control. Additionally, the cost of insulin places high burdens on people living with diabetes and on the U.S. healthcare system as a whole.

People living with T1D must have insulin to survive, injected or infused exogenously. Too much insulin and a person living with diabetes can experience dangerous consequences of hypoglycemia, such as loss of confusion, seizures, and possible death. Insufficient insulin, and the associated hyperglycemia can lead to long-term complications such as kidney failure, vision loss, heart attacks, nerve damage from high blood glucose levels. Indeed, approximately 25% of people living with T1D will progress to end-stage kidney disease[5] (requiring dialysis or kidney transplant), and more than 50% show signs of diabetic retinopathy after 20 years.[6]

Even with the best tools available, insulin delivered exogenously has delays in action, and dosing is less precise than insulin secreted from β-cells. Management of T1D falls on the person living with diabetes and their family and requires 24-hour vigilance. People living with T1D have a decreased life expectancy impacted by both duration of their disease and HbA1c levels.[7] Researchers noted that even with diligent monitoring, many people with T1D in the United States do not achieve ADA-recommended HbA1c targets.[8,9]

The National Institute of Health's Diabetes Control and Complications Trial have shown that the development of diabetes-related complications are reduced and life is prolonged when people

[5] Bakis GL, Molitch M. Are all patients with type 1 diabetes destined for dialysis if they live long enough? Probably not. Diabetes Care. 2018 Mar; 41(3):389-390. Doi: 10.2337/dci17-0047. PMID: 29463664.
[6] Kyto JP, et al. Decline in the cumulative incidence of severe diabetic retinopathy in patients with type 1 diabetes. Diabetes Care. 2011 Sep;34(9):2005-7. Doi: 10.2337/dc10-2391. PMID: 21868777;PMCID: PMC3161282.
[7] Rawshani et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset; a nationwide, register-based cohort study. Lancet, 2018.
[8] Miller KM et al. T1D Exchange Clinic Network. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. Diabetes Care 2015;38:971-978 pmid:25998289
[9] The T1D Exchange Registry demonstrated that, within participating specialized diabetes clinics, approximately 4 in 5 children and 2 in 3 adults do not meet HbA1c targets.

living with T1D experience intensive blood glucose control.[10] However, maintaining euglycemia for a lifetime is associated with severe anxiety and depression; for many patients with T1D, the quality of life may be poor.[11]

Clinically Meaningful Therapy

T1D is a T-cell mediated autoimmune disease with selective destruction of β-cells. To date there are no available disease modifying therapies for T1D that impact the fundamental autoimmune defects that damage the β-cells in the pancreas and thus the body's ability to produce insulin. In addition, there are no immunological interventions which are directed at arresting the loss of β-cell function that will make it easier for people living with diabetes to control their glucose levels.[12]

To provide an individual a 2-year delay from the symptoms, sequalae, and burden of T1D is clinically meaningful, as there will likely be long-term benefits for glycemic control and the reduction in – or delayed, or decreased severity of – acute and long-term complications. Additionally, the quality of life significantly improves, not only for the person living with T1D, but also for their family. The 2-year delay in symptom onset also reduces the stress on young developing bodies and reduces the burden on the healthcare system.

FDA understands the need for disease-modifying therapy for the treatment of T1D and granted breakthrough therapy designation and priority review for teplizumab. Given the urgent need for a monoclonal antibody that modulates the response of the T-lymphocytes that mediate the destruction of the insulin-producing beta cells in the islets of the pancreas, ADA, on behalf of individuals living with T1D urges the FDA to promptly review and give serious consideration to rapid approval to this clinically meaningful treatment.

The American Diabetes Association thanks the FDA and the Advisory Committee for its consideration of these comments. Should you have any questions, please feel free to contact Emilia Lonardo, PhD at Elonardo@diabetes.org.

Kind regards,

Robert Gabbay, MD, PhD
Chief Scientific & Medical Officer

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[10] Diabetes Control and Complications (EDIC) Research Group, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. NEJM. 1993 Sep 30;329(14):977-86. Doi: 10.1056/NEJM199309303291401. PMID: 8366922.
[11] Lucier J, Weinstock RS. Diabetes Mellitus Type 1. [Updated 2020 Nov 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507713/
[12] Masharani UB, Becker J. Teplizumab therapy for type 1 diabetes. *Expert Opin Biol Ther*. 2010;10(3):459-465. doi:10.1517/14712591003598843