Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to help sponsors develop antidiabetic drugs[2] for adults and children with type 1 diabetes mellitus (T1D) and/or type 2 diabetes mellitus (T2D). In this guidance, *antidiabetic drugs* refer to drugs intended to improve glycemic control, including drugs intended to reduce diabetes-related hyperglycemia (i.e., antihyperglycemic drugs) and drugs intended to mitigate iatrogenic hypoglycemia associated with diabetes management.

This guidance replaces, in part, the draft guidance for industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*, (73 FR 11420) published in February 2008. In March 2020, FDA withdrew the February 2008 draft guidance for industry because its recommendations for safety assessment were outdated. At the same time, FDA issued the draft guidance for industry *Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control*[3] March 10, 2020 (85 FR 13903). When finalized, this guidance will address the FDA's current recommendations regarding defining efficacy endpoints for clinical trials investigating antidiabetic drugs and replace the relevant sections in the withdrawn February 2008 draft guidance for industry.

This guidance does not address the following topics: endpoints related to clinical complications of diabetes (e.g., cardiovascular risk reduction), endpoints related to the prevention or delay of T1D, or the use of hypoglycemia efficacy endpoints in trials of conditions other than diabetes mellitus (e.g., hypoglycemia related to bariatric surgery, congenital hyperinsulinism).

[1] This guidance has been prepared by the Division of Diabetes, Lipid Disorders, and Obesity in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

In addition, general issues of statistical analysis or clinical trial design are outside the scope of this guidance and are addressed in the International Council for Harmonisation (ICH) guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998), *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021), and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001).

Recommendations regarding the evaluation of safety for drugs intended for patients with diabetes mellitus is also outside the scope of this guidance document. Additional information for trial design considerations related to safety can be found in the ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* (March 1995) and the draft guidance for industry *Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control* (March 2020).[4]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Diabetes mellitus, which affects more than 37 million people in the United States (Centers for Disease Control and Prevention, 2022), is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia as a result of defective insulin secretion, increased insulin resistance, or a combination of both. Most patients with diabetes mellitus have either T1D or T2D. T1D is characterized by autoimmune-mediated pancreatic beta cell destruction leading to failure in insulin production, and T2D is characterized by insulin resistance with variability in insulin secretory deficiency. Diabetes mellitus may also result from other etiologies, including genetic defects, endocrinopathies, pregnancy, pancreatic diseases, infections, and certain drugs.

Clinical manifestations of uncontrolled diabetes include short-term acute events, such as life-threatening diabetic ketoacidosis (primarily in T1D) or hyperglycemic hyperosmolar nonketotic coma, and long-term effects, such as microvascular (e.g., retinopathy, nephropathy, neuropathy) and macrovascular (e.g., coronary artery disease, peripheral vascular disease, stroke) complications. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive glucose lowering measured by change in hemoglobin A1c (A1C) in patients with T1D significantly reduced the development and progression of microvascular complications (DCCT Research Group et al. 1993). Data from the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated the same causal relationship in patients with T2D (UKPDS Group 1998). Consequently, the Agency considers reduction in A1C to be a validated surrogate

[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

endpoint for microvascular disease risk reduction adequate to support traditional drug approval and has approved drugs *to improve glycemic control* on the basis of demonstrated reductions in A1C, without a postmarketing requirement to confirm a clinical benefit associated with the observed change in A1C. Although there is no clinical requirement to confirm a clinical benefit associated with A1C reduction, microvascular endpoints (e.g., retinopathy, nephropathy) may be expected to be collected and analyzed as safety endpoints.

In clinical practice, glycemic goals are individualized and guided by multiple factors, including patient age, comorbidities, life expectancy, and risk of hypoglycemia. The overall goal of diabetes management is to achieve individualized glycemic control targets by correcting hyperglycemia and to avoid hypoglycemic events. Iatrogenic hypoglycemia, or low blood glucose levels caused by use of antihyperglycemic drugs (e.g., insulin, sulfonylurea), can result in significant, recurrent, and debilitating morbidity and mortality in patients with diabetes. Fear of hypoglycemia is often a significant barrier to achieving glycemic goals. For these reasons, FDA considers drugs that can meaningfully reduce iatrogenic hypoglycemia and maintain glycemic control beneficial to patients.

Therefore, FDA encourages sponsors to develop antidiabetic drugs that reduce hyperglycemia with low hypoglycemic risk as well as drugs that may be beneficial as an adjunct to other antihyperglycemic drugs — particularly insulin — to reduce the risk of iatrogenic hypoglycemia. Different clinical trial endpoints may be appropriate depending on the clinical goal for the proposed antidiabetic drug and the regulatory framework for demonstrating substantial evidence of effectiveness. For antihyperglycemic drugs, FDA continues to recommend showing reduction in A1C to demonstrate effectiveness. Additionally, FDA considers a reduction in the risk of hypoglycemia, accompanied by either a reduction or maintenance of an acceptable A1C, a clinically relevant efficacy endpoint for clinical trials in subjects with diabetes, especially for subjects using insulin.

III. EFFICACY ENDPOINTS

A. A1C

Change from baseline in A1C has been the accepted primary endpoint in clinical trials for sponsors seeking a glycemic-control indication. As discussed above, A1C is a validated surrogate endpoint for microvascular disease risk reduction and, therefore, an acceptable endpoint to support a glycemic-control indication.

To allow for the adequate interpretation of clinical trials utilizing an A1C endpoint, FDA recommends the following:

- Statistically significant reductions from baseline in A1C that are consistent across trials and relevant subgroups should be demonstrated. The magnitude of reduction may be weighed against risks. In general, statistically significant but small reductions in A1C may not overcome serious risks observed with a drug.

- Formal hypothesis testing in a controlled trial with type I error control is expected. Hypothesis testing for either noninferiority (NI) versus an active comparator (with adequate justification for the NI margin)[5] or superiority versus placebo or active comparator may be appropriate depending on the trial design.[6]

- A1C should generally be measured in a central laboratory using an assay certified by the NGSP.[7]

- A1C reflects a weighted average of blood glucose over the preceding 2 to 3 months. To allow adequate glycemic comparison between treatment arms, A1C should be measured after at least 12 weeks of stable dosing.

- For active comparator trials evaluating titratable drugs, the interpretation of efficacy is dependent on adequate titration of the trial drug and comparator, so that positive efficacy findings are not simply a result of insufficient titration of the comparator. Titration algorithms should ensure similar glycemic targets and allow for commensurate changes in dose in response to fasting or postprandial blood glucose.

- For most development programs, the primary efficacy endpoint should be change from baseline in A1C after 6 months of randomized treatment, with an additional descriptive assessment of change from baseline in A1C at 12 months to assess longer term durability of effect. A controlled trial designed to evaluate change from baseline beyond 6 months may be necessary for drug development programs in which there is a concern about durability of effect or in which efficacy is not expected to be evident in a 6-month period (e.g., the drug requires a long titration period, the drug has a delayed onset of effect on glycemic control).

- Responder analyses for A1C that provide an assessment of the proportion of subjects who achieve improvements in A1C based on clinically important cut points (e.g., less than 7 percent, less than 6.5 percent) are not recommended as the primary analysis of A1C because of limited interpretability (Holland 2002).

- The dosage of protocol-allowed concomitant glycemic-lowering drugs should be stable throughout the trial. Changes in dosage or initiation of concomitant glycemic-lowering drugs (e.g., for glycemic rescue, to prevent hypoglycemia) should be documented as an intercurrent event and accounted for appropriately in the statistical analysis.

- In the phase 3 program, sponsors should enroll a sufficient number of subjects to allow for the meaningful evaluation of the consistency of effects across subgroups based on sex, age, race, ethnicity, duration, and severity of diabetes (e.g., based on categories of A1C at baseline), and other relevant factors.

[5] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016).

[6] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness*.

[7] NGSP was originally called the *National Glycohemoglobin Standardization Program*.

B. Hypoglycemia

In contrast to the extensive experience with A1C as an efficacy endpoint, hypoglycemia endpoints have primarily been used to evaluate safety and (at the time of publication of this guidance) have only rarely been used as endpoints for comparative claims (i.e., efficacy, comparative safety). Use of hypoglycemia as an endpoint to support a claim has previously been limited by issues such as lack of consensus definitions of hypoglycemia linked to clinical outcomes and the lack of availability of fit-for-purpose measurement tools. If a sponsor seeks to demonstrate an advantage in terms of lower incidence of hypoglycemia versus an active comparator (i.e., comparative safety claim), such a comparative claim should be based on a level of evidence similar to when a sponsor uses hypoglycemia as an efficacy endpoint.

The following sections of this guidance discuss endpoint definitions, clinical trial considerations, and appropriate measurement tools to facilitate evaluation of a hypoglycemia-related drug claim.

1. Hypoglycemia Definitions

Hypoglycemia is defined and described by the American Diabetes Association (ADA) as follows (ADA 2023):

- Level 1: blood glucose levels less than 70 milligrams/deciliter (mg/dL) (3.9 millimoles/liter (mmol/L)) and greater than or equal to 54 mg/dL (3 mmol/L). This threshold is an alert value at which patients should take action to avoid continued decline in blood glucose.

- Level 2: blood glucose levels less than 54 mg/dL (3 mmol/L) regardless of the presence of hypoglycemia symptoms. At this threshold, adrenergic and/or neuroglycopenic symptoms typically begin. However, given that hypoglycemia unawareness is not uncommon, an event of level 2 hypoglycemia does not require adrenergic and/or neuroglycopenic symptoms to be captured.

- Level 3 (e.g., severe hypoglycemia): characterized by a severely altered mental and/or physical functioning, which if untreated may result in loss of consciousness, seizures, coma, or ultimately death. Hypoglycemia reversal necessitates the assistance of another person. Glucose measurements may not be available during an event, but neurological recovery attributable to the restoration of blood glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

For patients with diabetes mellitus, FDA considers level 3 and level 2 hypoglycemia acceptable endpoints in support of claims related to improvement in glycemic control and/or iatrogenic hypoglycemia risk reduction, depending on the trial design. Level 3 hypoglycemia is a direct measurement of how a subject feels, functions, or survives and is therefore a clinical endpoint. FDA considers level 2 hypoglycemia to be a surrogate endpoint for neuroglycopenia-related adverse events (e.g., cognitive impairment, incoordination) acceptable for traditional approval.

Sponsors should consider the following when seeking a new claim supported by hypoglycemia data:

- The preferred primary endpoint for a hypoglycemia-related claim is a reduction in the incidence of level 3 hypoglycemia. The rationale for this recommendation is not only related to the clinical importance of avoiding level 3 hypoglycemia but also because of the reliability of the endpoint. Level 3 hypoglycemia is less prone to bias from selective subject reporting. However, the incidence rate of level 3 hypoglycemia is expected to be low, so either more subjects or a longer trial would be needed to provide statistical power to detect a treatment difference based solely on level 3 hypoglycemia. Sponsors should consider enrichment strategies and/or adaptive designs to increase the ability to accrue events.

- In certain circumstances (e.g., when the incidence of severe hypoglycemia is expected to be very infrequent), the use of a composite primary endpoint of the incidence of level 2 and level 3 hypoglycemia, may be acceptable. However, clinical trials should capture a reasonable number of level 3 hypoglycemia events to ensure qualitative consistency between level 2 and level 3 treatment effect (i.e., evidence of reduction in both level 2 and level 3 events).

Sponsors should consult with FDA early in the drug development process to obtain agreement on proposed endpoints.

2. Trial Design Considerations for Hypoglycemia Endpoints

For trial designs aiming to demonstrate reduction of hypoglycemia events, FDA recommends the following for adequate interpretation of the hypoglycemia findings:

- Sponsors should use rigorous methods for the collection of level 3 hypoglycemia events and assess them by adjudication. If glucose measurements during the event are available, they should be included with the data presentation. As a biomarker endpoint, level 2 hypoglycemia events do not need to be adjudicated but still require rigorous methods for data collection (see section III. B. 3., Hypoglycemia Measurement).

- For all definitions of hypoglycemia, the proportion of subjects experiencing one or more events (incidence rate) should be used for the primary analysis. Analyses of total number of events/total patient-years of exposure (event rate) should also be reported.

- Because higher average serum glucose concentrations may correlate with fewer hypoglycemic episodes, similar average glycemic control between trial arms should be demonstrated. Demonstration of an NI finding in A1C using the commonly used margin of 0.3 percent is not sufficient by itself to obtain a reduction of risk of hypoglycemia claim. In addition to excluding the upper 95 percent confidence limit of 0.3 percent, the point estimate for the difference in change in A1C should be no greater than 0.1 percent.

- The hypoglycemia analysis should include the entire study period, including events that occurred during both the titration and maintenance periods with titratable drugs such as insulins. Supportive analyses may examine these time periods separately.

- The hypoglycemia analysis should include the entire 24-hour period for each day on treatment. Confounders, including pharmacodynamic characteristics of a drug (e.g., basal insulin peak) in relation to the timing of the drug administration, prandial insulin, recent exercise, and food consumption, may affect the timing of hypoglycemia risk.

3. Hypoglycemia Measurement

The accurate measurement of endpoints is fundamental to ensure confidence in the results from clinical trials. Nonsevere hypoglycemia (e.g., level 1 and level 2 hypoglycemia) is typically measured by medical devices, such as self-monitoring blood glucose (SMBG) test systems or by continuous glucose monitoring (CGM) systems, each of which has different strengths and weaknesses in the ability to ascertain hypoglycemic events. In addition, technical characteristics of specific devices vary. Sponsors should consult with the Agency early in the drug development program on how best to measure primary endpoints and provide justification for why the selected device methodology is appropriate for the assessment of the proposed hypoglycemia-based endpoint(s) within the context of the specific clinical development program.

a. SMBG test systems

In clinical trials, SMBG test systems have been used extensively to direct insulin dose titration and detect nonsevere hypoglycemia for safety monitoring. In addition, SMBG device performance (e.g., accuracy, precision) is generally considered acceptable; however, FDA encourages sponsors to obtain prior agreement on the acceptability of specific devices to be used in clinical trials. Limitations to SMBG test systems include the requirement for trial subjects to actively obtain a blood glucose sample (which may introduce the potential for differences in endpoint ascertainment across trial arms attributable to subject effort, particularly in an open-label trial), inadequate characterization of nocturnal hypoglycemia, and the potential for missed events in subjects with hypoglycemia unawareness. Sponsors should address how they intend to minimize the SMBG test system limitations in the design and analysis of their trials.

b. CGM systems

CGM systems continuously and passively collect glycemic data and can provide access to near real-time glucose data and trend information regarding rising or falling glucose levels throughout the day. There has been increasing use of CGM in clinical practice and, hence, interest in CGM utilization in clinical trials for the characterization of various aspects of glycemic control. Historically, there were technical performance concerns that were barriers to CGM adoption in clinical trials, but technology continues to improve. FDA recognizes that CGM systems have certain advantages over SMBG test systems for use in clinical trials to assess hypoglycemia as an efficacy endpoint. For example, CGM systems may be more likely to capture hypoglycemia events because of the continuous nature of glucose data collection. They also likely limit bias

due to subject effort in data collection and better capture nocturnal hypoglycemia and hypoglycemia events in patients with hypoglycemia unawareness.

Given that the use of CGM systems in the regulatory context is evolving and various uncertainties exist regarding the use of this technology in clinical trials, FDA highly encourages sponsors to engage with the Agency regarding the use of CGM and CGM-based hypoglycemia endpoints (e.g., number of occurrences of low glucose values captured by a CGM system in a defined time period), how data will be analyzed and submitted to the Agency, the intended population (e.g., pediatric or adult and CGM devices to be used). In general, FDA recommends that a sponsor use a single CGM device model, which is authorized for use in the United States and has acceptable device performance (i.e., accuracy, precision) in the hypoglycemic range, throughout clinical development.

C. Additional Efficacy Endpoints

There are several additional endpoints that are used supportively in clinical trials for antidiabetic drugs that may be appropriate for inclusion in drug labeling.

1. Fasting Plasma Glucose

Fasting plasma glucose is used as an additional indicator of glycemic control, although not sufficient evidence on its own for a glycemic control indication. The change from baseline in fasting plasma glucose is typically described in the CLINICAL STUDIES section of labeling. Fasting plasma glucose data should be measured in a central laboratory using a validated method. Results should be presented in United States units (mg/dL).

2. Postprandial Glucose

For certain drugs in which the mechanism of action is primarily due to an effect on postprandial glucose, assessments of postprandial glucose may be completed in dose-finding, proof-of-principle, short-term, oral glucose challenge studies. Although such demonstrations of pharmacodynamic activity are not sufficient evidence for a glycemic control indication, they may provide further understanding of the mechanism of the drug. The sponsor should collect postprandial glucose data for the entire dosing interval of the drug.

3. CGM-Based Metrics

Various CGM-based metrics have been proposed as clinical trial endpoints such as time in range (TIR), defined as the percentage of time spent in a patient's target glucose range (e.g., between 70 and 180 mg/dL (3.9 to 10 mmol/L)), time above range (time greater than 180 mg/dL), and time below range (time less than 70 mg/dL) (Danne et al. 2017). TIR is a biomarker that has not been established as a surrogate for a clinical outcome, and thus, TIR is not acceptable as the primary endpoint for a glycemic-control indication. FDA will consider including relevant CGM-based metrics results in the CLINICAL STUDIES section of labeling of drugs approved for a glycemic-control indication with efficacy demonstrated by change in A1C or an appropriate

hypoglycemia endpoint, provided that the performance characteristics of CGM devices, data collection, and analyses are adequate.

IV. OTHER CONSIDERATIONS

Sponsors can also propose other clinically meaningful endpoints for drugs intended for patients with diabetes. Examples include the removal of dependency on exogenous insulin or a reduction in the number of daily insulin injections in subjects with T1D; a reduction in insulin dose alone is not sufficient. If a sponsor seeks to demonstrate a clinically meaningful improvement with respect to a diabetes-related safety issue such as a decrease in diabetic ketoacidosis events versus an active comparator (i.e., comparative safety claim), such a comparative claim should be based on a level of evidence similar to that of an efficacy endpoint. Sponsors seeking to pursue a novel approach should discuss their plans with FDA early in the drug's development program.

Some drugs that were initially approved with a glycemic-control indication in a population with T2D have been subsequently shown to be effective in other clinically important macrovascular outcomes (e.g., cardiovascular risk reduction) or microvascular outcomes (e.g., chronic kidney disease), and FDA has granted new macrovascular- or microvascular-related indications, respectively. FDA supports the development of drugs seeking to prevent diabetic complications and comorbidities and encourages sponsors to request further advice from the relevant review division and consult other existing guidances that may apply. However, A1C continues to be a valid surrogate endpoint for microvascular risk reduction and an acceptable endpoint for glycemic-control trials.

There may be other effects of a drug besides its intended effect on glycemic control, such as changes in blood pressure, serum lipids, and body weight, that may be of clinical relevance to prescribers when selecting a drug for glycemic control because patients with diabetes often have comorbid conditions that contribute to excess cardiovascular risk. It may be appropriate to present these data from adequate and well-controlled trials in the CLINICAL STUDIES section of labeling upon review of the data.

REFERENCES

American Diabetes Association, 2023, 6. Glycemic Targets: Standards of Care in Diabetes—2023, Diabetes Care, 46(Suppl 1):S97–S110.

Centers for Disease Control and Prevention, 2022, National Diabetes Statistics Report website, accessed February 1, 2023, https://www.cdc.gov/diabetes/data/statistics-report/index.html.

Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, Devries JH, Garg S, Heinemann L, Hirsch I, Amiel SA et al., 2017, International Consensus on Use of Continuous Glucose Monitoring, Diabetes Care, 40(12):1631–1640, doi: 10.2337/dc17-1600.

Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, Rand L, and Siebert C, 1993, The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus, N Engl J Med,;329(14):977–86, doi: 10.1056/NEJM199309303291401.

Holland PW, 2002, Two Measures of Change in the Gaps Between the CDFs of Test-Score Distributions, J Educ and Behav Stat, 27(1):3–17.

UK Prospective Diabetes Study (UKPDS) Group, 1998, Intensive Blood-Glucose Control With Sulphonylureas or Insulin Compared With Conventional Treatment and Risk of Complications in Patients With Type 2 Diabetes (UKPDS 33), Lancet, 352(9131):837–853 (Erratum, 1999, Lancet, 354:602).