Celiac Disease: Developing Drugs for Adjunctive Treatment to a Gluten-Free Diet

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
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Guidance for Industry[1]

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I. INTRODUCTION

The purpose of this guidance is to help sponsors in the clinical development of drugs[2] for the treatment of celiac disease (CeD) as an adjunct to a gluten-free diet in adults. Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current recommendations on clinical trials for drugs being developed under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR parts 312 and 314 and/or for biologics being developed under section 351 of the Public Health Service Act and 21 CFR part 601 for the treatment of CeD as an adjunct to a gluten-free diet in adults. This guidance also addresses considerations for eligibility criteria, trial design features, efficacy evaluations, clinical outcome assessments, and safety assessments.

This guidance does not address the clinical development of drugs intended to prevent signs and symptoms of CeD or treatment of CeD as monotherapy (i.e., treatment replacing a gluten-free diet). In addition, this guidance does not address the clinical development of drugs to treat CeD in asymptomatic patients or patients with minimal to no histologic inflammation who continue to experience symptoms.

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[1] This guidance has been prepared by the Division of Gastroenterology (the Division) in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) in 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.

II. BACKGROUND

CeD is an autoimmune condition in which dietary gluten triggers small bowel inflammation and villous atrophy, causing malabsorption and gastrointestinal symptoms. The only treatment for CeD is a strict, lifelong gluten-free diet (Green 2007). CeD affects about 1% of the U.S. population with a female preponderance (Rubio-Tapia 2012).

Malabsorption results in gastrointestinal signs and symptoms, including diarrhea, abdominal pain, bloating, vomiting, weight loss, anemia, and micronutrient deficiencies. Patients with CeD may also have extraintestinal symptoms such as fatigue, headaches, depression, difficulty concentrating, skin rashes, and arthralgias. Some patients with CeD are asymptomatic (Green 2007).

CeD is diagnosed based on a patient's medical history, physical examination, serologies (e.g., serum tissue transglutaminase IgA), and histologic findings on small bowel biopsies. Proper biopsy technique is important to confirm the diagnosis. Multiple histologic scoring systems have been developed that incorporate assessments of villous atrophy, crypt hyperplasia, and intraepithelial lymphocytes to identify and classify severity of small bowel inflammation.

The goals of treatment in patients with CeD include resolution of intestinal inflammation and associated clinical signs and symptoms. For many adults, strict adherence to a gluten-free diet will result in improvement in both histologic findings and signs and symptoms; however, some adults may not be able to achieve normalization of the mucosa (Wahab 2002; Rubio-Tapia 2010). In addition, intentional and inadvertent dietary digressions can lead to disease exacerbation. Complications of CeD include poor growth, osteoporosis, tooth enamel defects, neuropathy, and vitamin deficiencies. Although rare, serious complications such as small intestinal lymphoma and adenocarcinoma can occur in patients with CeD (Green 2007; Catassi 2005).

III. DEVELOPMENT PROGRAM

A. Trial Population

Sponsors developing drugs to treat CeD as an adjunct to a gluten-free diet should consider the following:

- A diagnostic esophagogastroduodenoscopy with multiple biopsies of the duodenum is needed to establish a diagnosis of CeD. One or two biopsies of the duodenal bulb and at least four biopsies of the distal duodenum should be obtained to confirm diagnosis (Rubio-Tapia 2013). The diagnostic endoscopy can be provided by historical record or performed during the screening period.

- A screening esophagogastroduodenoscopy with biopsy should be performed to ensure patients meet histologic eligibility criteria at time of enrollment. We encourage sponsors to use a central reader to ensure consistent histologic evaluations.

  - Relying solely on symptomatic assessment without histologic evidence of active CeD at baseline may result in inclusion of patients whose symptoms are not caused by CeD (e.g., functional gastrointestinal disorders) (Drossman 2016), given that signs and symptoms of CeD are heterogeneous and can overlap with those of other gastrointestinal disorders.

  - We recommend that sponsors assess the mucosa with a clinically accepted histologic scale, which incorporates evaluation of villous atrophy, crypt hyperplasia, and intraepithelial lymphocytic infiltration (e.g., modified Marsh-Oberhuber classification) (Oberhuber 2000). Sponsors should reach agreement on the approach to the histologic assessment before trial initiation.

- Patients should be sufficiently symptomatic at baseline, based on prespecified enrollment criteria, to allow for observation of improvement caused by treatment during the trial.

  - Investigators should document in a standardized case report form the type and severity/frequency of signs and symptoms to support eligibility.

- The celiac serologies (e.g., anti-tissue transglutaminase or antigliadin antibodies) can be used in conjunction with clinical and histologic findings to aid in the diagnosis of CeD; however, celiac serology assays have not been cleared by the Center for Devices and Radiological Health to monitor disease progression or indicate disease stability or remission.[3]

- Because strict adherence to a gluten-free diet is a known effective treatment for CeD, patients should maintain a stable gluten-free diet preceding enrollment for a prespecified duration (e.g., 1 year) and throughout the duration of the trial. Dietitians experienced in CeD management should evaluate patients during the screening period to assess for adherence to the gluten-free diet.

- Sponsors should enroll patients who reflect the characteristics of clinically relevant populations, including with regard to race and ethnicity, and should consider clinical trial sites that include geographic locations with higher proportions of racial and ethnic minorities to recruit a diverse study population.[4]

[3] Available at https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm.

[4] For additional recommendations, see the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020). We update guidances periodically. 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.

B. Trial Design

Sponsors developing drugs to treat CeD as an adjunct to a gluten-free diet should consider the following:

- We recommend a randomized, double-blind, placebo-controlled trial design.

- We recommend that sponsors include a screening period before randomization of the patients to confirm histologic eligibility criteria, document persistence of clinical signs and symptoms, and train patients and/or care providers to collect the clinical outcome assessment (COA) data appropriately.

- The trial duration and timing of efficacy assessments should be guided by the goal of therapy, mechanism of action of the drug and its expected onset of action, and the time frame in which a clinical benefit is expected to be observed.

- For drugs intended to be administered chronically as adjunctive treatment to a gluten-free diet, we recommend a placebo-controlled treatment period of at least 52 weeks' duration to allow for characterization of the safety profile and durability of response. Patients should continue the gluten-free diet throughout the 52-week duration.

  - The primary efficacy assessment on both clinical and histologic endpoints may be evaluated at week 24.

  - An esophagogastroduodenoscopy with biopsy should be performed at week 52 to assess for durability of response. Durability of response is especially important for diseases, such as CeD, that may result in serious clinical sequelae if untreated or inadequately treated over time. Persistent and/or worsening underlying histologic inflammation at week 52 would be inconsistent with the expected clinical benefit and will be taken into account when evaluating the benefit and risk.

  - Data from the entire controlled period (i.e., 52 weeks total) should be included at time of submission of an application for registration.

  - Sponsors should discuss with the appropriate review division the number of patients exposed to the to-be-marketed dosing regimen for a minimum of 1 year that should be available at the time of application submission.

- Sponsors should include an assessment of patient adherence to the gluten-free diet during the treatment period.

  - We acknowledge the limitations of incorporating daily diet logs, as patients may modify behavior by adhering more or less strictly to the gluten-free diet in the setting of a clinical trial. At a minimum, we recommend that patients record any intentional or suspected inadvertent gluten exposure during the trial.

- We recommend that dietitians experienced in CeD management be involved in evaluating patients for the adherence to the gluten-free diet during the treatment period.

- The following considerations are relevant for trial designs that incorporate a gluten challenge:

  - Sponsors should justify the need for gluten challenge in the proposed trial.

  - The amount and duration of gluten exposure during a gluten challenge should be justified.

  - Patients with known history of severe hypersensitivity reactions or anaphylaxis to gluten should be excluded from participation in gluten challenges.

  - Histologic evaluations should be incorporated both before and after a gluten challenge to evaluate the response to gluten exposure.

C. Efficacy Considerations

Sponsors developing drugs to treat CeD as an adjunct to a gluten-free diet should consider the following:

1. Efficacy Assessments

- Trials intended to support marketing approval should evaluate a drug's effect on both signs and symptoms and the related underlying mucosal inflammation. Therefore, sponsors should include coprimary endpoints[5] in phase 3 trials that assess improvement or resolution from baseline in the following:

  - Clinically important signs and symptoms, using a well-defined and reliable COA instrument.

  - Histology using a clinically accepted scale (e.g., Marsh-Oberhuber classification).

- The primary endpoint to assess symptomatic improvement should be based on prespecified core signs and symptoms of CeD and not be limited to a single sign or symptom.

- We recommend a prespecified secondary endpoint to assess the proportion of patients who achieve improvement in both signs and symptoms and mucosal inflammation.

[5] Demonstrating treatment effects on both distinct endpoints is necessary to establish clinical benefit for this indication. See the draft guidance for industry *Multiple Endpoints in Clinical Trials* (January 2017). 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.

- We acknowledge that improvement of signs and symptoms and mucosal inflammation may not occur simultaneously. To inform timing of the endpoint assessments, sponsors should consider the duration of time in which improvement or resolution of signs and symptoms and mucosal inflammation are expected to occur based on the mechanism of action of the drug and the patient population.

2. Clinical Outcome Assessments

Sponsors developing drugs to treat CeD as an adjunct to a gluten-free diet should consider the following:

- FDA encourages sponsors to seek FDA input as early as possible and at important milestones throughout the drug development process to meet the challenges of COA development in this patient population.[6] We also encourage sponsors to obtain patient input early in the drug development process to identify what matters most to patients regarding burden of disease and burden of treatment.[7,8]

- Until a well-defined and reliable patient-reported outcome (PRO) instrument that measures the clinically important signs and symptoms of CeD is available and accepted for regulatory use, we recommend modifying an existing instrument or developing a new instrument based on patient input regarding the relevant and important signs and symptoms of CeD.[7,8] For measurement of core signs and symptoms, sponsors should use instruments with daily assessments (e.g., past 24-hour recall period, event log) in which patients complete the instruments at the same time each day (e.g., evening before bedtime) or at the time of event.

- Items assessing symptom severity (e.g., abdominal pain) should ask patients to rate their worst experience of a specific symptom over the past 24 hours. For example, item response options can be based on either a verbal rating scale (e.g., ratings are none, mild, moderate, severe, and very severe scored 0-4) or an 11-point (i.e., 0 to 10) numeric rating scale, where 0 reflects the absence of the symptom and 10 reflects the worst possible symptom experience.

- Items assessing event-related signs and symptoms (e.g., diarrhea, vomiting) should ask patients to report each occurrence of a specific sign or symptom. Frequency should be reported as the exact number of episodes over a 24-hour period, and a clear definition of what is considered *one episode* should be provided to patients to ensure consistency both

[6] For general recommendations regarding PRO assessments (as well as information relevant for other COAs) and the documents to be provided to FDA for review, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

[7] For additional recommendations, see the guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020).

[8] For additional recommendations, see the draft guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Methods to Identify What Is Important to Patients* (October 2019). When final, this guidance will represent the FDA's current thinking on this topic.

within and between patients in reporting the number of episodes a sign or symptom has occurred.

- Sponsors also can assess as secondary or exploratory endpoints, once identified, the important and common impacts of CeD signs or symptoms on patients' daily lives using a separate score from the core signs and symptoms.

- We recommend that sponsors, when modifying an existing PRO instrument or developing a new PRO instrument, use data obtained in phase 2 trials to help inform finalization of scoring algorithms and endpoint definitions. Piloting the proposed PRO instrument in phase 2 trials can provide the sponsor an opportunity to evaluate the instrument's psychometric properties and performance (reliability, validity, and ability to detect change) as well as provide guidelines for interpretation of clinically meaningful within-patient change in scores and confirm the endpoint definition. Pilot results can further inform plans for implementation of the proposed instrument in phase 3 trials.

3. Statistical Considerations

Sponsors developing drugs to treat CeD as an adjunct to a gluten-free diet should consider the following:

- Efficacy analyses should include all randomized patients.

- To support efficacy, the trial results should demonstrate statistical significance for both primary endpoints (clinical endpoint and histologic endpoint).

To gain precision in the evaluation of overall treatment effects, we recommend statistical analyses adjust for patient characteristics at baseline that may impact efficacy outcomes, such as age, duration of disease, disease severity, duration of prior adherence to gluten-free diet, etc.

- Given that adherence to a gluten-free diet could impact efficacy outcome, sponsors should conduct analyses of adherence to a gluten-free diet.

- Sponsors should prespecify a primary estimand of interest for each endpoint and justify that it is meaningful and that it can be estimated with minimal and plausible assumptions with the proposed analysis.[9] All clinically important intercurrent events, such as treatment discontinuation, should be considered when defining an estimand. Potential strategies for handling intercurrent events include the following:

  - A treatment policy strategy in which outcomes are collected after the intercurrent event and used in analyses.

[9] For additional recommendations, see the International Council for Harmonisation harmonized guideline *E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials* to the guideline on *Statistical Principles for Clinical Trials*, available at https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf.

- A composite strategy in which patients who experience the intercurrent event are considered to have an unfavorable outcome (e.g., to have not achieved clinical or histologic improvement).

- Sponsors should continue to follow patients after the occurrence of all intercurrent events, regardless of the strategy used in the primary analysis, to facilitate important analyses using a treatment policy strategy. The protocol should distinguish between reasons for treatment discontinuation and reasons for study withdrawal and should include plans to follow patients for collection of relevant data after treatment discontinuation and use of rescue therapies.

- Sponsors should prespecify sensitivity analyses to evaluate whether the results from the primary and secondary analyses are robust to the missing data assumptions. These sensitivity analyses should comprehensively explore the space of plausible assumptions.

We recommend sponsors analyze COA endpoints as continuous or ordinal variables using baseline values as covariates. For COA endpoints, FDA does not recommend a percentage change from baseline endpoint.

- Small but statistically significant group-level mean differences in the COA endpoint may not establish whether the effect is clinically meaningful.

  - To aid in the interpretation of the COA endpoint results, sponsors should propose an appropriate range of within-patient score change that patients consider to be clinically meaningful using anchor-based methods (e.g., patient global impression scales as anchors) supplemented with empirical cumulative distribution function curves using data pooled across trial arms.

  - Additionally, sponsors should submit for review empirical cumulative distribution function curves by treatment arm and supportive descriptive analyses of within-patient changes from baseline.

D. Safety Considerations

Sponsors developing drugs to treat CeD as an adjunct to a gluten-free diet should consider the following:

- Given that the therapeutic benefit of an investigational drug is unknown during conduct of clinical trials, it is critical that patients understand the importance of adhering to the gluten-free diet, and risks of nonadherence should be communicated in the informed consent form.

- For drugs intended for long-term treatment, such as for CeD, a sufficient number of patients should be exposed to the to-be-marketed dosing regimen for at least 52 weeks to characterize the safety profile of the drug.[10]

- For trials of therapeutic protein products, such as monoclonal antibodies, sponsors should consider recommendations in the guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014). Sponsors should evaluate neutralizing capabilities of antidrug antibodies and their impact on clinical efficacy and safety.

- Sponsors should prospectively plan for safety analyses to compare treatment groups with respect to risk (e.g., with a risk difference, relative risk, rate ratio, or hazard ratio) along with a confidence interval for the chosen metric to help quantify the uncertainty in the treatment comparison. Sponsors should stratify by study any analyses of integrated data from multiple studies.

[10] For recommendations regarding duration of exposure and number of patients to be included in the safety database, see the guidance for industry *Premarketing Risk Assessment* (March 2005).

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Guidances[1]

Draft guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Methods to Identify What Is Important to Patients* (October 2019)[2]

Draft guidance for industry *Multiple Endpoints in Clinical Trials* (January 2017)[3]

Guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020)

[1] 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.

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