Eosinophilic Esophagitis: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability when published in the *Federal Register*.

For questions regarding this draft document, contact Erica Lyons at 301-796-8023.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2019
Clinical/Medical

Eosinophilic Esophagitis: Developing Drugs for Treatment

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2019
Clinical/Medical

TABLE OF CONTENTS

I. INTRODUCTION....1
II. BACKGROUND....1
III. TRIAL POPULATION....3
IV. DEVELOPMENT PROGRAM....4
A. Trial Design....4
B. Efficacy Considerations....4
C. Clinical Outcome Assessments....5
D. Safety Considerations....6
V. PEDIATRIC CONSIDERATIONS....7
REFERENCES....9

Eosinophilic Esophagitis: Developing Drugs for Treatment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

The purpose of this guidance is to assist sponsors in the clinical development of drugs and therapeutic biologics for the treatment of eosinophilic esophagitis (EoE).[2] Specifically, this guidance addresses the FDA's current recommendations regarding clinical trials for EoE drugs and the necessary attributes of patients for enrollment, efficacy assessments, safety assessments, and pediatric considerations.[3]

This guidance does not address the clinical development of drugs for the treatment of non-EoE, eosinophilic gastrointestinal disorders.

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

EoE is a chronic immune or antigen-mediated esophageal disease clinically characterized by signs and symptoms related to esophageal dysfunction and histologically characterized by eosinophil-predominant inflammation (Liacouras et al., 2011). Left untreated, EoE leads to an

[1] This guidance has been prepared by the Division of Gastroenterology and Inborn Error Products (the Division) 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] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of drugs to treat EoE.

increase in esophageal stricture, dysphagia, and risk of food impaction (Warners et al 2018). EoE has an estimated incidence of 5–10 cases per 100,000 persons per year and prevalence of approximately 50–100 cases per 100,000 persons (Dellon & Hirano, 2017). Clinical signs and symptoms vary with age of the patient. Infants and toddlers present with feeding difficulties, school-aged children are more likely to present with vomiting or pain, and adolescents and adults present with dysphagia and food impaction (Straumann & Katzka, 2018).

In patients with EoE, clinical features and histologic activity can vary independently. Patients can have a reduction or resolution in signs and symptoms despite ongoing histologic activity; conversely, patients can have histologic remission (defined as a change in peak eosinophils per high power field (HPF) from a count greater than or equal to 15 to less than or equal to 6) with persistent clinical symptoms (Dellon et al., 2013).

For these reasons, the treatment goals of EoE include resolution or reduction of the signs and symptoms of active disease to provide relief to the patient, and healing or control of the esophageal inflammation and its complications.

Fit-for-purpose clinical outcome assessments (COAs),[4] such as patient-reported outcome (PRO)[5] or observer-reported outcome (ObsRO)[6] instruments, for evaluation of treatment response in EoE for regulatory use are not yet widely available, and the variability of symptomatology across pediatric and adult populations creates challenges to the development of such instruments. Recommendations for sponsor development of COAs are discussed later in this guidance.

[4] A COA can be made through a report by a clinician, a patient, or a nonclinician observer or through a performance-based assessment. For more information on the four types of COAs (clinician-reported outcome, observer-reported outcome, patient-reported outcome, and performance outcome) see the glossary of the BEST (Biomarkers, EndpointS, and Other Tools) Resource available at https://www.ncbi.nlm.nih.gov/books/NBK338448/?report=reader.

[5] A PRO is a type of clinical outcome assessment that is a measurement based on a report that comes directly from the patient (i.e., trial subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others. See the glossary of the BEST Resource available at https://www.ncbi.nlm.nih.gov/books/NBK338448/?report=reader.

[6] An ObsRO is a type of clinical outcome assessment that is a measurement based on a report of observable signs, events, or behaviors related to a patient's health condition by someone other than the patient or a health professional. Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life and are particularly useful for patients who cannot report for themselves (e.g., infants, individuals who are cognitively impaired). An ObsRO measure does not include medical judgment or interpretation. See the glossary of the BEST Resource available at https://www.ncbi.nlm.nih.gov/books/NBK338448/?report=reader.

III. TRIAL POPULATION

Sponsors developing drugs for the treatment of EoE should consider the following for clinical trial populations:

- Patients should be sufficiently symptomatic to warrant clinical trial enrollment. Signs and symptoms to support eligibility should be documented in a standardized case report form for all patients within a trial. The severity of symptomatology needed for enrollment can be influenced by the anticipated risks of the drug. We recommend the sponsor 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 COA data appropriately.

- EGD is needed to establish a histologic diagnosis of EoE; this can be provided by historical record, although such patients should also undergo EGD during screening periods to ensure they meet histologic eligibility criteria at time of enrollment. Alternately, the diagnostic EGD can be performed during the screening period. Currently, histologic diagnostic criteria for EoE includes a peak count of greater than or equal to 15 eosinophils per HPF (400X). Two to four biopsies should be obtained from both the proximal and distal esophagus. Biopsies can be taken from the midesophagus for additional evaluation.

- To exclude patients who may respond to proton pump inhibitor (PPI) therapy alone, sponsors should give patients with EoE a 2-month trial of an adequate dose of a PPI therapy followed by esophagogastroduodenoscopy (EGD) with biopsies to determine if the patients are eligible for trial entry (Dellon et al., 2013; Straumann & Katzka, 2018). A historical record of a failed PPI therapy trial can be acceptable. Alternately, a PPI therapy trial can be done during the screening period.

- During the diagnostic EGD, biopsy specimens from the antrum and/or duodenum should be taken to rule out alternate etiologies in all pediatric patients. Biopsy specimens from the antrum and/or duodenum should also be obtained in adult patients with gross endoscopic abnormalities or clinical signs and symptoms that indicate that gastric or small intestinal conditions are possibilities.

- We recommend including patients with a history of mild to moderate strictures as they may respond to treatment. Sponsors should exclude patients with a history of severe strictures requiring dilation or those patients found to have strictures preventing the passage of a standard, diagnostic upper endoscope or any critical esophageal stricture that requires dilation at screening as these patients are not expected to respond to pharmacological therapy. Sponsors should consider stratified randomization based on the presence or absence of baseline strictures.

- Because dietary restriction is a known effective treatment for EoE and signs and symptoms may be highly dependent on eating behaviors (Hirano et al. 2017), patients should maintain a stable diet preceding enrollment and throughout the duration of the

trial period. Sponsors should consider potential inclusion of diet as a covariate in analysis models or other methods to address the potential effect of dietary restrictions.

- Patients should maintain stable doses of PPI therapies (other than a failed trial of PPI monotherapy at an adequate dose); leukotriene inhibitors; or nasal, inhaled, and/or orally administered locally or topically acting corticosteroid drugs for any condition (such as asthma or allergic rhinitis) preceding enrollment and throughout the duration of the trial period. The trial protocol should specify the statistical plan to account for patients who initiate treatment with systemic corticosteroid drugs during the trial period, as well as those patients who need rescue treatment with topical or locally acting corticosteroid drugs.

IV. DEVELOPMENT PROGRAM

A. Trial Design

Sponsors developing drugs for the treatment of EoE should consider the following for clinical trial design:

- We recommend a randomized, double-blind, placebo-controlled trial design with a prespecified screening period before randomization of patients to confirm eligibility criteria.

- 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, we recommend an initial treatment period of at least 24 weeks' duration to assess efficacy on both clinical and histologic endpoints, followed by an extension period to provide a total treatment period of at least 52 weeks' duration. These data should be available before application for registration to inform labeling.

- FDA strongly recommends, following initial assessment of efficacy, a randomized withdrawal design to characterize the persistence of treatment effect as well as the incidence of relapse and need for redosing.

B. Efficacy Considerations

Sponsors developing drugs for the treatment of EoE should consider the following regarding a drug's efficacy:

- Trials intended to support marketing approval of a drug for the treatment for EoE should evaluate a drug's effect on both signs/symptoms and the related underlying inflammation. Therefore, sponsors should assess coprimary endpoints in phase 3 trials as follows:

  – Assess significant improvement from baseline in signs and symptoms, compared to placebo, using a well-defined and reliable COA instrument.

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

    - To aid in the interpretation of the COA endpoint results, the sponsor 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 scale as an anchor), supplemented with empirical cumulative distribution functions (eCDF) using data pooled across trial arms.

    - Additionally, the sponsor should submit for review a supportive graph (i.e., eCDF) of within-patient change from baseline by treatment arm.

  – Document a histologic response of peak esophageal eosinophil per HPF count of less than or equal to 6 across all available esophageal levels at the final treatment period evaluation. Two to four biopsies should be obtained from both the proximal and distal esophagus. Biopsies can be taken from the midesophagus for additional evaluation.

C. Clinical Outcome Assessments

Sponsors developing drugs for the treatment of EoE should consider the following when using COA instruments, including PROs and ObsROs:

- 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.[7]

- Until a well-defined and reliable PRO or ObsRO instrument that measures the clinically important signs and symptoms of EoE is available and accepted, we recommend modifying or developing a PRO or ObsRO instrument based on patient or observer input regarding the relevant and meaningful signs and symptoms of EoE (e.g., food getting

[7] 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). 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/RegulatoryInformation/Guidances/default.htm.

stuck). Sponsors should use instruments with daily assessments (e.g., past 24-hour recall period or event log) that focus on these items.[8]

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

- An instrument that captures both patient-reported and observer-reported data can be explored if patients are able to report some, but not all, signs and symptoms. For example, some school-aged pediatric patients may be able to report on abdominal pain severity using a simple pictorial scale but may not be able to reliably and validly report other important signs and symptoms. An observer should not be asked to rate, as a proxy, unobservable aspects of the pediatric patient's condition (e.g., abdominal pain severity). Observers should only be asked to rate signs and behaviors that are observable or verbalizations made by the pediatric patient about how he or she is feeling.

- When modifying an existing or developing a new COA instrument, sponsors should consider that phase 2 trials should help inform finalization of scoring algorithms and endpoint definitions. Piloting the proposed COA 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 and confirm the endpoint definition. Pilot results can further inform plans for implementation of the proposed instrument in phase 3 trials.

- We recommend that the sponsor analyze COA endpoints as continuous or ordinal variables using baseline values as covariates. FDA does not recommend a responder analysis endpoint or a percent change from baseline endpoint unless the targeted response is complete resolution of signs and symptoms. The statistical analysis plan should include alternative approaches for analysis if extreme outliers occur, such as analyses based on ranks. These recommendations are different from the Division's previous recommendations related to COA endpoint analyses. Sponsors in phase 3 trials at time of this guidance's publication in final should discuss their COA endpoints with the Division.

D. Safety Considerations

Sponsors developing drugs for the treatment of EoE should consider the following regarding safety in clinical trials:[9]

[8] For additional recommendations, see the draft guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2018). 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/RegulatoryInformation/Guidances/default.htm.

[9] 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).

- For trials of orally administered locally or topically acting corticosteroid drugs, sponsors should consider the following:

  - Performing at every visit a physical examination that includes specific examination to identify signs of glucocorticoid excess.

  - Performing hypothalamic pituitary adrenal (HPA) axis testing at preestablished time points throughout the phase 2 and 3 trials, as well as during any extension trials (including at the end of treatment, either at the end of the trial or at drop-out) and 6 weeks after the trial.

  - Following closely patients with abnormal HPA axis tests or hyperglycemia until resolution.

- For trials of drugs, such as monoclonal antibodies, that have the potential to induce an immune response, sponsors should see recommendations in the guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014). Sponsors should include neutralizing capabilities in the evaluations for antidrug antibodies.

V. PEDIATRIC CONSIDERATIONS

Sponsors developing drugs for the treatment of EoE should consider the following when enrolling pediatric patients in clinical studies:[10]

- We encourage the inclusion of adolescents (patients 12–17 years of age inclusive) in registration clinical trials, provided that preliminary safety and efficacy data in adult patients support enrollment. These trials should include design elements to ensure that all enrolled pediatric patients have the opportunity for exposure to active treatment (e.g., open-label extension, cross-over design) and should be followed by trials in patients younger than 12 years of age.

- We recommend including at least 40 adolescent patients per study arm in clinical studies that will include both adult and adolescent patients.

- For trials utilizing orally administered locally or topically acting corticosteroid drugs, growth measurements for pediatric patients should be standardized and replicated. Tanner stage should be obtained, and the growth data should be analyzed by pubertal stage (i.e., pre- and post-puberty).[11]

[10] For nonclinical program recommendations, see the guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products* (February 2006).

[11] See the guidance for industry *Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children* (March 2007).

- For drugs with potential to affect bone mineralization, the sponsor should, early in development, discuss with FDA the plan for evaluating effects on bone mineral density and composition.

REFERENCES

Literature

Dellon, E. S., Gonsalves, N., Hirano, I., Furuta, G. T., Liacouras, C. A., Katzka, D. A., and American College of Gastroenterology, 2013, ACG Clinical Guideline: Evidenced Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE), Am J Gastroenterol, 108(5), 679–692.

Dellon, E. S., and Hirano, I., 2017, Epidemiology and Natural History of Eosinophilic Esophagitis, Gastroenterology, 154(2):319–332.

Hirano, I., Spechler, S., Furuta, G., and Dellon, E. S., 2017, White Paper AGA: Drug Development for Eosinophilic Esophagitis, Clin Gastroenterol Hepatol, 15(8):1173–1183.

Liacouras, C. A., Furuta, G. T., Hirano, I., Atkins, D., Attwood, S. E., Bonis, P. A., et al., 2011, Eosinophilic Esophagitis: Updated Consensus Recommendations for Children and Adults, J Allergy Clin Immunol, 128(1):3–20.

Straumann, A., and Katzka, D. A., 2018, Diagnosis and Treatment of Eosinophilic Esophagitis, Gastroenterology, 154(2):346–359.

Warners, M. J., Oude Nijhuis, R. A. B., de Wijkerslooth, L. R. H., Smout, A., and Bredenoord, A. J., 2018, The Natural Course of Eosinophilic Esophagitis and Long-Term Consequences of Undiagnosed Disease in a Large Cohort, Am J Gastroenterol, 113(6):836–844.

Guidances[1]

Draft guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2018)[2]

Guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014)

Guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products* (February 2006)

Guidance for industry *Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children* (March 2007)

[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/RegulatoryInformation/Guidances/default.htm.

[2] 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/RegulatoryInformation/Guidances/default.htm.

Guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009)

Guidance for industry *Premarketing Risk Assessment* (March 2005)

Guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (January 2014)