
Eosinophilic Esophagitis: Developing Drugs for Treatment Guidance for Industry

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

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Clinical/Medical**

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TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	BACKGROUND	1
III.	DEVELOPMENT PROGRAM	3
	A. Trial Population	3
	B. Trial Design	4
	C. Efficacy Considerations	4
	1. <i>Efficacy Assessments</i>	<i>4</i>
	2. <i>Clinical Outcome Assessments</i>	<i>5</i>
	3. <i>Statistical Considerations</i>	<i>6</i>
	D. Safety Considerations	7
IV.	PEDIATRIC CONSIDERATIONS	8
	REFERENCES	10

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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 FDA's current thinking regarding clinical trials and development programs for EoE drugs, including recommendations for the necessary attributes of patients for enrollment, trial designs, efficacy considerations, 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

¹ This guidance has been prepared by the Division of Gastroenterology (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.

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esophageal stricture, dysphagia, and risk of food impaction (Warners et al. 2018). Furthermore, treatment cessation can lead to a recurrence of EoE clinical symptoms and histologic activity (Dellon et al. 2019). 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 and Hirano 2017). Clinical signs⁴ 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 often present with dysphagia and food impaction (Straumann and 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.

The variability of symptomatology across pediatric and adult populations creates challenges to the development of fit-for-purpose clinical outcome assessments (COAs),⁵ such as patient-reported outcome (PRO)⁶ or observer-reported outcome (ObsRO)⁷ instruments, for evaluation of treatment response in EoE for regulatory use. Recommendations for sponsor development of COAs are discussed later in this guidance.

⁴ For the purposes of this guidance, the term *sign* is used to describe both observable behaviors and findings on clinical examination unless otherwise specified.

⁵ 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>.

⁶ A PRO is a type of COA 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>.

⁷ An ObsRO is a type of COA 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>.

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III. DEVELOPMENT PROGRAM

A. 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 patient 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 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 COA data appropriately.
- Esophagogastroduodenoscopy (EGD) is needed to establish a histologic diagnosis of EoE; this can be provided by historical record, although such patients should also undergo EGD to ensure they meet histologic eligibility criteria at time of enrollment. Currently, histologic diagnostic criteria for EoE include a peak count of greater than or equal to 15 eosinophils per HPF (400X). Two to four biopsies should be obtained from the proximal esophagus and two to four biopsies should be obtained from the distal esophagus. Biopsies can be taken from the midesophagus for additional evaluation. To decrease potential variability across sites, the area of the HPF should be recorded (in mm² or μm²), and eosinophil density per mm² should be included in the report. We encourage the use of a central reader to ensure consistent histological evaluations.
- During the diagnostic EGD, biopsy specimens from the stomach and/or duodenum should be taken to rule out alternate etiologies in all pediatric patients. Biopsy specimens from the stomach 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. Adult and pediatric patients with abnormal biopsy specimens from the stomach and/or duodenum should be excluded from enrollment, if appropriate, as this may support an alternative diagnosis.
- Sponsors should provide justification for the inclusion or exclusion of patients with strictures. We recommend including patients with a history of strictures if there are existing data or a compelling scientific rationale to suggest that these patients may respond to the proposed treatment. Patients with esophageal strictures that require dilation at the initial endoscopy should undergo additional screening to document persistence of clinical signs and symptoms following dilation to confirm eligibility.
- 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.

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- Patients should maintain stable doses of proton pump inhibitor therapies; leukotriene inhibitors; or nasal, inhaled, and/or orally administered locally or topically acting corticosteroid drugs for comorbid conditions (e.g., asthma, allergic rhinitis) before enrollment and throughout the duration of the trial period.

B. 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, the 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 a treatment period of at least 24 weeks' duration to assess efficacy for both clinical and histologic endpoints, followed by an extension period to provide a total treatment period of at least 52 weeks' duration to ensure adequate exposure to allow for characterization of the safety profile and the durability of response. Long-term data from the treatment and extension period should be available before the submission of an application for registration. Sponsors should discuss with the Agency the number of patients with a minimum exposure of 1 year that will be available at the time of application submission.
- When scientifically appropriate, the inclusion of a randomized withdrawal design following the initial demonstration of efficacy may help to inform the incidence of relapse and need for redosing. FDA does not recommend a randomized withdrawal design for trials of therapeutic protein products (see section III. D., Safety Considerations).

C. Efficacy Considerations

1. Efficacy Assessments

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 of EoE should evaluate a drug's effect on signs and symptoms and the related underlying inflammation.

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Therefore, sponsors should include coprimary endpoints⁸ in phase 3 trials that assess the following:

- Signs and symptoms, using a well-defined and reliable COA instrument, assessed on a continuous or ordinal scale.
- 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 the proximal esophagus, and two to four biopsies should be obtained from the distal esophagus. Biopsies can be taken from the midesophagus for additional evaluation.
- We encourage the systematic collection of additional data on endoscopic findings (e.g., edema, rings, exudates, furrows, strictures) and histologic features of EoE (e.g., eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, lamina propria fibrosis).

2. Clinical Outcome Assessments

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

- 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.⁹
- Until a well-defined and reliable PRO or ObsRO instrument that measures the clinically important signs and symptoms of EoE is available and accepted for regulatory use, 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 stuck). Sponsors should use instruments with daily assessments (e.g., past 24-hour recall period, event log) in which respondents complete the instruments at the same time each day (e.g., evening before bedtime) that focus on these items.¹⁰

⁸ Demonstration of 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>.

⁹ For general recommendations regarding PRO instruments (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).

¹⁰ For additional recommendations, see the guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020).

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- Sponsors also can assess, once identified, important and common effects of EoE signs and symptoms on patients' daily lives. If adequately captured, this information could be included as a distinct endpoint from the core signs and symptoms.
- Capturing 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 on how he or she is feeling.¹¹
- When modifying an existing or developing a new COA instrument, FDA recommends that sponsors use data obtained in phase 2 trials to 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. These results can further inform plans for implementation of the proposed COA instrument in phase 3 trials.

3. *Statistical Considerations*

FDA recommends the following statistical considerations for sponsors developing drugs for the treatment of EoE:

- Sponsors should prespecify a primary estimand of interest for each endpoint and justify that it is meaningful and can be estimated with minimal and plausible assumptions with the proposed analysis.¹²

The proposed estimand should discuss how important intercurrent events will be handled such as the following:

- Initiation of treatment with systemic corticosteroid drugs for comorbid conditions during the trial period
- Use of rescue medications or emergency dilation
- Change in diet and adaptive eating behaviors

¹¹ The analysis plan for programs including both patient- and observer-reported data should be discussed with the Agency early in development as it may not be appropriate to integrate the data into a combined analysis.

¹² For additional recommendations, see the International Council for Harmonisation draft guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum on Estimands and Sensitivity Analysis in Clinical Trials* (October 2017). When final, this guidance will represent the FDA's current thinking on this topic.

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- To gain precision in the evaluation of overall treatment effects, we recommend that statistical analyses adjust for patient characteristics at baseline that may affect efficacy outcomes (e.g., presence of strictures, dietary restrictions).
- We recommend that the sponsor analyze COA endpoints as continuous or ordinal variables using baseline values as covariates. For COA endpoints, FDA does not recommend a percent change from baseline endpoint, or a responder analysis endpoint, unless the targeted response is complete resolution of signs and symptoms.
- 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, 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 function (eCDF) curves using data pooled across trial arms.
 - Additionally, the sponsor should submit for review eCDF curves by treatment arm and supportive descriptive analyses of within-patient changes from baseline.
- FDA recommends that the sponsor analyzes the histologic coprimary endpoint (i.e., a binary endpoint defined as a peak esophageal eosinophil per HPF count of less than or equal to 6 across all available esophageal levels) by evaluating the difference in the proportions of responders across treatment arms.

D. Safety Considerations

Sponsors developing drugs for the treatment of EoE should consider the following regarding safety in clinical trials:¹³

- For trials of corticosteroid drugs, sponsors should consider the following:
 - A physical examination to identify signs of glucocorticoid excess should be performed at every visit.
 - FDA recommends that hypothalamic pituitary adrenal (HPA) axis suppression potential be assessed by an adrenocorticotropic hormone (ACTH) stimulation test. The ACTH stimulation test should be performed at preestablished time points throughout the phase 2 and 3 trials as well as during any extension trials (including at

¹³ 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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the end of treatment, either at the end of the trial or at drop out) and 6 weeks after the completion of the trial.

- Patients showing signs of HPA axis suppression or having abnormal ACTH stimulation test results at the end of treatment should be followed closely until complete resolution.
- For trials of therapeutic protein products, such as monoclonal antibodies, 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.

IV. PEDIATRIC CONSIDERATIONS

Sponsors developing drugs for the treatment of EoE should consider the following when enrolling pediatric patients in clinical studies:^{14, 15}

- We encourage the inclusion of adolescent patients (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) and should be followed by trials in patients younger than 12 years of age. Trial design for studies in pediatric patients younger than 12 years of age should be informed by the safety and efficacy results in the adolescent and adult populations.
- EGD is necessary to evaluate the histologic diagnostic criteria for EoE, as well as for assessment of response of a therapeutic intervention. For trials including pediatric patients, repeated procedures, such as EGD, should be conducted in accordance with the standard of care for the individual patient (i.e., not for research purposes only).
- The number of adolescent patients included in adult studies may be guided by disease prevalence; however, a sufficient number of adolescent patients should be included to allow for a reliable estimate of the event of interest and the uncertainty about this estimate to support the determination of safety and efficacy.
- For trials utilizing corticosteroid drugs, growth measurements for pediatric patients should be made using stadiometry and recorded to the nearest 10th of a centimeter. The stadiometric measurement protocol should be specific (e.g., no socks, shoes, or hats; three reproducible measurements; calibration frequency). Tanner stage should be obtained, and the growth data should be analyzed by pubertal stage (i.e., pre- and post-

¹⁴ For nonclinical program recommendations, see the guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products* (February 2006).

¹⁵ See 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations.

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puberty).¹⁶ Additionally, the potential of these therapies to cause HPA suppression should be evaluated independently in the pediatric population (see section III. D., Safety Considerations).

- 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.

¹⁶ See the guidance for industry *Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children* (March 2007).

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Guidances¹

Draft guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (December 2019)²

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

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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