Erosive Esophagitis: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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

September 2025
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Erosive Esophagitis: Developing Drugs for Treatment 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 erosive esophagitis (EE) in adults.

Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current recommendations on clinical trials for drugs intended for the healing of EE and maintenance of healed EE in adults, including considerations for eligibility criteria, trial design features, efficacy evaluations, and safety assessments.[3]

This guidance does not address the development of drugs for the treatment of symptomatic nonerosive gastroesophageal reflux disease,[4] Barrett's esophagus, pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome), peptic ulcer disease, or the development of drugs for healing of EE and maintenance of healed EE in pediatric patients.

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

[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 *drug or drugs* include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and therapeutic biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262) that are regulated as drugs.

[3] In addition to consulting guidances, sponsors are encouraged to contact the Division to discuss specific issues that arise during the development of drugs for the treatment of EE.

[4] See the draft guidance for industry *Symptomatic Nonerosive Gastroesophageal Reflux Disease: Developing Drugs for Treatment* (September 2025) for recommendations. 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.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

EE is caused by reflux of acidic stomach contents into the esophagus and is included in the spectrum of acid-related disorders known as gastroesophageal reflux disease (GERD). EE is defined as the presence of superficial esophageal erosions on endoscopic evaluation in patients with or without the typical symptoms of GERD (e.g., heartburn, regurgitation). GERD affects males and females in nearly equal proportions; however, males develop EE more often than females.[5,6] Complications of untreated EE include the development of esophageal strictures, perforation, and progression to Barrett's esophagus.

In patients with EE, the goals of therapy include healing of erosions and maintenance of healed erosions. Accordingly, pharmacologic therapy for EE typically has two phases: an initial treatment period to heal existing erosions, followed by continued treatment to ensure healing is maintained (i.e., erosions do not recur).

III. DEVELOPMENT PROGRAM

A. Trial Population

Sponsors should enroll subjects who are representative of the population that will use the drug if approved and should consider clinical trial sites that facilitate this goal. Sponsors developing drugs for the healing of EE and maintenance of healed EE should also consider the following:

1. Inclusion Criteria

- Trials evaluating drugs for the healing of EE and maintenance of healed EE should enroll subjects with EE, as defined by the Los Angeles (LA) classification system (see Appendix)[7] at the baseline endoscopy, to ensure subjects meet endoscopic eligibility criteria and establish disease severity before administration of the investigational product.

- Trials should enroll subjects across the whole spectrum of disease severity (i.e., LA Grade A-D).

[5] Antunes, C, A Aleem, and SA Curtis, 2021, "Gastroesophageal Reflux Disease" in StatPearls [Internet], Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 28722967.

[6] Yamasaki, T, C Hemond, M Eisa, S Ganocy, and R Fass, 2018, The Changing Epidemiology of Gastroesophageal Reflux Disease: Are Patients Getting Younger? J Neurogastroenterol Motil, 24(4):559–569.

[7] Lundell, LR, J Dent, JR Bennett, AL Blum, D Armstrong, JP Galmiche, F Johnson, M Hongo, JE Richter, SJ Spechler, GNJ Tytgat, and L Wallin, 1999, Endoscopic Assessment of Oesophagitis: Clinical and Functional Correlates and Further Validation of the Los Angeles Classification, Gut, 45(2):172–180.

- Subjects should have documentation of healed EE (i.e., no erosions present) on endoscopy at the end of the healing phase of the trial to be eligible for enrollment in the maintenance of the healed EE phase of the trial.

2. Exclusion Criteria

- Subjects who test positive for *Helicobacter pylori* during screening should be excluded. However, subjects with a history of *H. pylori* who have received treatment and who have negative confirmatory testing may be included if they continue to meet the inclusion criteria after *H. pylori* eradication.

- Subjects with the following should also be excluded:

  - Evidence of Barrett's esophagus and/or definite dysplastic changes on endoscopic evaluation of the esophagus

  - History of dilation of esophageal strictures, other than a Schatzki's ring (i.e., a ring of mucosal tissue near the lower esophageal sphincter)

  - Presence of gastric or duodenal ulcers

  - Coexisting diseases affecting the esophagus (e.g., eosinophilic esophagitis, esophageal varices, scleroderma, viral or fungal infection, esophageal stricture)

  - History of radiation therapy, cryotherapy, sclerotherapy, or other caustic, thermal, or physiochemical trauma to the esophagus

3. Concomitant Medications

- With the exception of protocol-specified rescue medications, concomitant use of acid-reducing medications (e.g., proton pump inhibitors, histamine H2-receptor antagonists) or other drugs found to be effective for the treatment of GERD or other acid-related conditions (e.g., sucralfate, prokinetics, misoprostol) should not be permitted.

- As drugs with significant anticholinergic effects (e.g., tricyclic antidepressants, antispasmodics) may impact the occurrence of reflux of stomach contents through their action on the lower esophageal sphincter, subjects who require treatment with these drugs should maintain stable doses for at least 4 weeks before screening and throughout the duration of the trial.

B. Trial Design

Sponsors developing drugs for the healing of EE and maintenance of healed EE should consider the following:

- Sponsors should conduct a randomized, double-blind, active comparator trial design for trials of drugs for the healing of EE and maintenance of healed EE to demonstrate noninferiority or superiority to an approved therapy.[8]

- Sponsors should discuss their proposed noninferiority margin(s) with the Division. The characteristics of the trial population (e.g., disease severity by LA grade) and choice of active comparator may affect the suitability of a noninferiority margin.

- Sponsors seeking to conduct a placebo-controlled trial of their drug should discuss the specifics of the proposal (e.g., population, eligibility criteria, trial design, clinical and laboratory monitoring, escape criteria) with the Division.

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

  - If healing is anticipated to occur before the time point identified for primary efficacy assessment (i.e., completion of the healing phase of the trial), trials may include prespecification of an additional endoscopic assessment at an earlier time point.

    - If a subject's EE is observed to have healed before the prespecified primary efficacy assessment, they may be considered to have completed the healing phase and be eligible for direct rerandomization into the maintenance phase.[9]

    - If the subject's EE has not healed at an earlier assessment, they should continue in the healing phase, and eligibility for the maintenance phase should be determined by the results of endoscopic evaluation at the completion of the healing phase.

- Subjects who have achieved complete healing of erosions during the healing phase should undergo rerandomization into the maintenance phase to either study drug or the comparator for a treatment duration of at least 6 months to assess maintenance of healed EE.

- Subjects should be instructed that diet, lifestyle, or behavioral modifications designed to mitigate symptoms of EE (e.g., avoiding caffeine, eating smaller portions, elevating the head of the bed) should not be altered (i.e., initiated, discontinued, or modified from those utilized at baseline) throughout the trial.

[8] For additional recommendations and considerations for noninferiority clinical trial designs, see the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016). 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.

[9] Sponsors should consider how entrance into the maintenance of healed EE treatment period for subjects who have achieved healing before completion of the healing phase may impact prespecified noninferiority margins.

- Permitted rescue medications and their administration schedule should be protocol-specified and standardized.

C. Efficacy Considerations

Sponsors developing drugs for the healing of EE and maintenance of healed EE should consider the following:

1. Efficacy Assessments

Sponsors should consider the following to establish efficacy for the healing of EE:

- A primary efficacy endpoint of complete healing (i.e., no erosions present) on endoscopic evaluation

- Secondary efficacy endpoints of the following:

  - Complete healing of EE in subjects with LA Grade A or B at baseline

  - Complete healing of EE in subjects with LA Grade C or D at baseline

  - Relief of heartburn associated with EE, as assessed by the proportion of heartburn-free days during the prespecified assessment period, where a heartburn-free day is defined as a 24-hour period with no heartburn

Sponsors should consider the following to establish efficacy for the maintenance of healed EE:

- A primary efficacy endpoint of the maintenance of complete healing of all erosions (i.e., no erosions present) on endoscopic evaluation

- Secondary efficacy endpoints of the following:

  - Maintenance of complete healing of EE in subjects with LA Grade A or B at baseline

  - Maintenance of complete healing of EE in subjects with LA Grade C or D at baseline

  - Relief of heartburn associated with EE, as assessed by the proportion of heartburn-free days during the prespecified assessment period, where a heartburn-free day is defined as a 24-hour period with no heartburn

Sponsors should also consider the following:

- Sponsors can explore the effects of a drug on additional symptoms identified by patients as important (e.g., regurgitation), when present, using a fit-for-purpose patient-reported outcome measure.

- Sponsors should use patient-reported outcome instruments with a maximum recall period of the past 24 hours for all symptomatic assessments (e.g., heartburn, regurgitation). Respondents should complete the instruments at the same time each day (e.g., evening before bedtime).

- Additional information and recommendations regarding the assessment of clinical outcomes in drug development through patient-reported outcome assessments are included in FDA's patient-focused drug development guidance series.[10]

2. Statistical Considerations

- Sponsors should analyze the primary endpoint for the healing of EE phase (i.e., complete healing of EE) and the primary endpoint for the maintenance of healed EE phase (i.e., maintenance of complete healing of EE) by evaluating the difference in the proportions across treatment arms.

- Sponsors should analyze the secondary endpoint of the relief of heartburn associated with EE by evaluating the difference in the average proportions of heartburn-free days across treatment arms.

- Statistical analyses should adjust for patient characteristics at baseline that may impact efficacy outcomes (e.g., advancing age, obesity, smoking, alcohol and caffeine consumption) to gain precision in evaluating overall treatment effects. Sponsors should also consider exploring subgroup analyses and potential treatment interactions based on these factors.

- Sponsors should prespecify the approach to ensure strong control of the type I error rate when testing multiple endpoints (i.e., primary and secondary endpoints) that are clinically meaningful and for which labeling claims may be of interest. If an endpoint will be tested for both noninferiority and superiority, each test should be prespecified in the multiple testing procedure and appropriate methods should be used to control the type I error rate across both tests.

- 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. The estimand is a precise description of the treatment effect, reflecting the clinical question posed by a given clinical trial objective.[11]

[10] The FDA patient-focused drug development guidance series consists of a series of four methodological patient-focused drug development guidance documents. These guidance documents represent the FDA's current thinking and may be accessed at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

[11] See the ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021).

- The important intercurrent events that should be considered when defining the estimand include treatment discontinuation and use of rescue medication.

- Potential strategies for defining and handling intercurrent events include the following:

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

  - A composite strategy in which subjects who experience the intercurrent event are considered to have an unfavorable outcome (e.g., to have not achieved complete healing of EE)

- Sponsors should prespecify how missing data from patient-reported outcome instruments will be handled in calculating 24-hour heartburn-free days. To ensure that the computed proportion of 24-hour heartburn-free days is representative of a subject's outcome during the assessment period, sponsors should prespecify a minimum number of non-missing diary days needed for the proportion of 24-hour heartburn-free days to be non-missing in the primary analysis.

- Sponsors should also 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.

D. Safety Considerations

Sponsors developing drugs for the healing of EE and maintenance of healed EE should consider the following:

- Multiple potential risks have been identified with long-term acid suppression (e.g., *Clostridioides difficile* enteric infections, osteoporosis-related bone fractures, vitamin deficiencies). Sponsors should consider these potential risks, as well as known adverse events associated with the therapeutic class of the drug, to inform the overall extent and duration of treatment provided in the program's overall safety database.

- A sufficient number of subjects should be exposed to the to-be-marketed dosing regimen(s) for healing of EE, as well as for maintenance of healed EE, during controlled treatment periods of sufficient duration (e.g., at least 8 weeks for healing of EE, at least 24 weeks for maintenance of healed EE) to characterize the safety of the drug for healing of EE and for maintenance of healed EE.

- Drug-specific considerations may alter the minimum acceptable size of the safety database and duration of exposure, including whether the drug in question is a new molecular entity or has relevant supportive safety data from other populations, the known and anticipated adverse events of the drug and drug class, and nonclinical findings.

APPENDIX

Table 1. Los Angeles Classification of Esophagitis

Grade	Definition
A	One (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds
B	One (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds
C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but which involves less than 75% of the esophageal circumference
D	One (or more) mucosal break which involves at least 75% of the esophageal circumference

Source: Adapted from Lundell, LR, J Dent, JR Bennett, AL Blum, D Armstrong, JP Galmiche, F Johnson, M Hongo, JE Richter, SJ Spechler, GNJ Tytgat, and L Wallin, 1999 Endoscopic Assessment of Oesophagitis: Clinical and Functional Correlates and Further Validation of the Los Angeles Classification, Gut, 45(2):172–180.