Symptomatic Nonerosive Gastroesophageal Reflux Disease: 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DRAFT GUIDANCE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)

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Symptomatic Nonerosive Gastroesophageal Reflux Disease: Developing Drugs for Treatment Guidance for Industry[1]

I. INTRODUCTION

The purpose of this guidance is to help sponsors in the clinical development of drugs[2] for the treatment of symptomatic nonerosive gastroesophageal reflux disease (sGERD) in adults.

Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current recommendations on clinical trials for drugs intended for the treatment of sGERD 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 erosive esophagitis,[4] Barrett's esophagus, pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome), peptic ulcer disease, or sGERD 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 sGERD.

[4] See the draft guidance for industry *Erosive Esophagitis: Developing Drugs for Treatment* (September 2025) for recommendations.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

Symptomatic nonerosive gastroesophageal reflux disease 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). In patients with characteristic symptoms of GERD (e.g., heartburn, regurgitation), lack of evidence of injury to the esophageal mucosa on endoscopic evaluation is used to establish the diagnosis of sGERD. GERD affects males and females in nearly equal proportions; however, females experience sGERD more often than males.[5,6]

In patients with sGERD, the goal of therapy is reduction or resolution of symptoms. Management of sGERD includes diet, lifestyle, or behavioral modifications; pharmacological therapies; and endoscopic or surgical interventions. Surgical management is typically reserved for severe and intractable cases. Complications of untreated sGERD can include tooth decay and progression to erosive esophagitis.

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 treatment of sGERD should also consider the following:

1. Inclusion Criteria

- Trials evaluating drugs for the treatment of sGERD should enroll subjects who meet all of the following criteria:
  - Identify heartburn as their primary symptom
  - Have a history of heartburn episodes for 6 months or longer
  - Experience heartburn on at least 4 of the 7 days per week during the baseline assessment

[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.

- Have normal appearing esophageal mucosa during the baseline endoscopy

- Endoscopy should be performed as part of the baseline assessments to ensure that subjects meet endoscopic eligibility criteria (i.e., have not developed evidence of injury to the esophageal mucosa subsequent to a prior evaluation) before administration of the investigational drug.

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 GERD 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 treatment of sGERD should consider the following:

- Sponsors should conduct a randomized, double-blind, placebo-controlled trial design for trials of drugs for the treatment of sGERD. For sponsors that intend to demonstrate noninferiority or superiority to an approved therapy, we recommend a randomized, double-blind, active comparator trial design.[7]

- Sponsors should consider a treatment period of at least 8 to 12 weeks to assess the drug's benefit for the treatment of sGERD. The trial duration and timing of efficacy assessments 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 in the intended population. Additionally, sponsors should consider the duration of exposure necessary to inform the safety profile of the drug for its intended use and durability of treatment effect.

- Subjects should be instructed that diet, lifestyle, or behavioral modifications designed to mitigate symptoms of sGERD (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 used at baseline) throughout the duration of the trial.

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

C. Efficacy Considerations

Sponsors developing drugs for the treatment of sGERD should consider the following:

1. Efficacy Assessments

- Trials should assess a primary efficacy endpoint of 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, to establish efficacy for the relief of heartburn associated with sGERD.

- Sponsors may also 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

[7] 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.

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.[8]

2. Statistical Considerations

- Sponsors should analyze the primary endpoint for the treatment of sGERD (i.e., average proportion of 24-hour heartburn-free days) by evaluating the difference in the average proportion of heartburn-free days across treatment arms.

- Sponsors should adjust the statistical analyses 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.[9]

  - 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

[8] 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.

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

196 ▪ A composite strategy in which subjects who experience the intercurrent event are
197 considered to have an unfavorable outcome
198
199 • Sponsors should prespecify how missing data from patient-reported outcome instruments
200 will be handled in calculating 24-hour heartburn-free days. To ensure that the computed
201 proportion of 24-hour heartburn-free days is representative of a subject's outcome during
202 the assessment period, sponsors should prespecify a minimum number of non-missing
203 days needed for the proportion of 24-hour heartburn-free days to be non-missing in the
204 primary analysis.
205
206 • Sponsors should also prespecify sensitivity analyses to evaluate whether the results from
207 the primary and secondary analyses are robust to the missing data assumptions. These
208 sensitivity analyses should comprehensively explore the space of plausible assumptions.
209
210 **D. Safety Considerations**
211
212 Sponsors developing drugs for the treatment of sGERD should consider the following:
213
214 • Multiple potential risks have been identified with long-term acid suppression (e.g.,
215 *Clostridioides difficile* enteric infections, osteoporosis-related bone fractures, vitamin
216 deficiencies). Sponsors should consider these potential risks, as well as known adverse
217 events associated with the therapeutic class of the drug, to inform the overall extent and
218 duration of treatment provided in the program's overall safety database.
219
220 • Sponsors should consider a treatment period of at least 8 to 12 weeks to assess the drug's
221 benefit for the treatment of sGERD; however, the duration of the controlled treatment
222 period should be guided by the types and frequency of adverse events reported in
223 development, as well as what is known about the drug and drug class, to allow for
224 characterization of the safety profile.
225
226 • Drug-specific considerations may alter the minimum acceptable size of the safety
227 database and duration of exposure, including whether the drug in question is a new
228 molecular entity or has relevant supportive safety data from other populations, the known
229 and anticipated adverse events of the drug and drug class, and nonclinical findings.
230
231