
Gastroparesis: Clinical Evaluation of Drugs for Treatment Guidance for Industry

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
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Gastroparesis: Clinical Evaluation of Drugs for Treatment Guidance for Industry

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Gastroparesis: Clinical Evaluation of Drugs for Treatment Guidance for Industry¹

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 create 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 for the treatment of diabetic and idiopathic gastroparesis.² Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding clinical trial designs and clinical endpoint assessments to support development of gastroparesis drugs.

This draft guidance is intended to serve as a focus for continued discussions among the Division of Gastroenterology and Inborn Errors Products, pharmaceutical sponsors, the academic community, and the public.³ This guidance does not address detailed patient-reported outcome (PRO) instrument design. These issues are addressed in the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.⁴

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical*

¹ This guidance has been prepared by the Division of Gastroenterology and Inborn Errors Products in the Center for Drug Evaluation and Research (CDER) 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 gastroparesis.

⁴ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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33 *Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical*
34 *Trials*, respectively.

35
36 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
37 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
38 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
39 the word *should* in Agency guidances means that something is suggested or recommended, but
40 not required.

41
42

43 **II. BACKGROUND**

44

45 Gastroparesis is a disorder of the stomach characterized by delayed gastric emptying (DGE) in
46 the absence of mechanical obstruction; symptoms are chronic with episodic symptom
47 exacerbation (Parkman, Hasler, et al. 2004). It predominantly affects young adult females, and
48 the burden of this disease on the individual (morbidity and mortality) and society (health care
49 costs) is considerable (Jung, Cheung, et al. 2009). Although gastroparesis is frequently
50 associated with diabetes (diabetic gastroparesis), idiopathic gastroparesis of unknown cause
51 accounts for the greatest number of cases (Soykan, Sivri, et al. 1998; Karamanolis, Caenepeel, et
52 al. 2007). Diabetic gastroparesis likely occurs because of impaired neural control of gastric
53 motility and may involve the vagus nerve (Parkman, Hasler, et al. 2004). In addition, acute
54 hyperglycemia has the potential to slow gastric emptying and decrease the effects of prokinetic
55 drugs (Camilleri 2010). Therefore, uncontrolled hyperglycemia may affect observed clinical
56 trial outcomes for new drugs.

57

58 The core signs and symptoms of gastroparesis, reported by incidence, are nausea (92 to 96
59 percent), vomiting (68 to 88 percent), postprandial fullness (54 to 77 percent), early satiety (42 to
60 86 percent), and upper abdominal pain (36 to 85 percent) (Soykan, Sivri, et al. 1998;
61 Hoogerwerf, Pasricha, et al. 1999; Anaparthi, Pehlivanov, et al. 2009). Patients may experience
62 any combination of signs and symptoms with varying degrees of severity. Pain is more prevalent
63 in patients with idiopathic gastroparesis than diabetic gastroparesis. Patients with diabetic
64 gastroparesis may experience further derangement of glucose control because of unpredictable
65 gastric emptying and altered absorption of orally administered hypoglycemic drugs, which may
66 in turn affect measurement of core signs and symptoms. Severe signs and symptoms may cause
67 complications such as malnutrition, esophagitis, and Mallory-Weiss tears. Gastroparesis
68 adversely affects the lives of patients with the disease, resulting in decreased social interaction,
69 poor work functionality, and development of anxiety or depression (Soykan, Sivri, et al. 1998;
70 Parkman, Hasler, et al. 2004).

71

72 Because the signs and symptoms of gastroparesis overlap with other gastrointestinal conditions,
73 gastroparesis may be incorrectly diagnosed as bowel obstruction, functional dyspepsia, irritable
74 bowel syndrome, or peptic ulcer disease. In a patient with signs and symptoms suggestive of
75 gastroparesis, a finding of DGE in the absence of an obstruction or alternative diagnosis provides
76 critical support to the diagnosis of gastroparesis, and can be assessed using gastric emptying
77 scintigraphy (GES) or the Gastric Emptying Breath Test (GEBT). GES of a solid-phase meal
78 has been considered in the medical community to be the gold standard for diagnosing DGE.

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79 However, qualified personnel are needed to conduct this test, and scintigraphy induces a
80 significant radiation burden (Siegel, Wu, et al. 1983), which may limit its application in children,
81 fertile women, and subjects undergoing repetitive measurements of gastric emptying in a short
82 period of time.

83
84 The GEBT is a recently approved noninvasive test that aids in the diagnosis of gastroparesis.
85 The GEBT can determine how fast the stomach empties the meal by measuring the ratio of
86 carbon-13 (¹³C) to carbon-12 (¹²C) collected in breath samples at multiple time points after the
87 meal is consumed compared to baseline. The GEBT does not require specially trained health
88 care professionals to administer the test or to take special precautions related to radiation
89 emitting compounds. However, the GEBT should not be used in people with hypersensitivity to
90 Spirulina, egg, milk, or wheat allergens and should not be used in patients with certain lung
91 diseases or small bowel malabsorption. The advantages and disadvantages of each approach
92 should be considered when designing a clinical trial in gastroparesis and when identifying the
93 appropriate patient population for study.

94
95 There is an urgent medical need for development of drugs with a favorable risk-benefit profile to
96 treat patients with gastroparesis.

97
98
99 **III. ENDPOINTS AND TRIAL DESIGN FOR GASTROPARESIS CLINICAL**
100 **TRIALS**

101
102 Primary efficacy assessments for adequate and well-controlled trials must be well-defined and
103 reliable.⁵ Because gastroparesis is a symptomatic condition, a well-defined and reliable PRO
104 instrument that measures all the clinically important signs and symptoms of gastroparesis would
105 be the ideal primary efficacy assessment tool in clinical trials used to support labeling claims for
106 the treatment of gastroparesis.⁶ However, at the current time, we know of no measure of
107 clinically important gastroparesis signs and symptoms that would serve as the ideal primary
108 efficacy assessment tool. Until an appropriate PRO instrument for gastroparesis becomes
109 available, sponsors should consider the strategies discussed in the following sections when
110 designing gastroparesis clinical trials.

111
112 Sponsors may wish to explore new PRO instruments or novel diagnostic measures in early
113 development, and potentially correlate the results with dose-ranging trials. We encourage early
114 and regular discussions with the FDA regarding outcome assessments, endpoints, and trial design
115 to help ensure the use of adequate and interpretable assessments of treatment benefits that are
116 consistent with a drug's mechanism of action. Phase 2 studies represent an opportune time to
117 evaluate proposed outcome assessments to obtain data to support their use as prespecified

⁵ 21 CFR 314.126

⁶ See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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118 endpoints for phase 3 trials. These data can be discussed with the FDA in advance of the phase 3
119 trials.

120
121 Because gastroparesis manifests as more than one core sign or symptom, the effect of new drugs
122 intended to treat gastroparesis on each core sign and/or symptom should be assessed. It is
123 important to show that even drugs intended to treat only a subset of the core signs/symptoms,
124 based on the mechanism of the drug, do not worsen the remaining signs/symptoms of
125 gastroparesis. For example, a drug may be expected to improve gastroparesis-related nausea and
126 vomiting but not abdominal pain, based on its mechanism of action. In this scenario, clinical
127 studies should demonstrate not only improvement in nausea and vomiting, but also that the
128 treatment did not worsen abdominal pain in patients with gastroparesis.

129
130 The following sections provide recommendations regarding trial design, trial populations,
131 outcome assessment measures, and trial endpoints.

132
133 **A. Trial Design**

134
135 The trial design generally should consist of a randomized, double-blind, placebo-controlled trial
136 and should include a 1- to 2-week screening period. The screening period can be used to
137 establish the presence and persistence of trial entry criteria and for patients to gain experience
138 with the technical aspects of data collection of patient-reported signs and symptoms. The
139 screening period assessments of gastroparesis signs and symptoms can serve as the baseline
140 values used in the analyses of the primary endpoint; see section III.D., Trial Endpoints, for more
141 information. A baseline assessment period of at least 7 days is recommended. To be considered
142 evaluable for study, assessments should be available from at least 4 of the 7 days. The primary
143 endpoint should measure the change in signs and symptoms from baseline. The endpoint
144 assessment should be based on patients' daily reporting to avoid recall bias.

145
146 We recommend a treatment period of at least 12 weeks' duration, followed by a 2- to 4-week
147 randomized withdrawal period, to address the need for maintenance treatment to prevent sign or
148 symptom recurrence. Daily diaries should be collected throughout the entire study. In addition,
149 a placebo-controlled long-term safety study of 12 months' duration, with appropriate
150 prespecified provisions for rescue medications, is recommended as part of the development plan,
151 and should be conducted before submitting a new drug application.

152
153 **B. Trial Populations**

154
155 Idiopathic and diabetic gastroparesis patients should be studied in separate clinical trials.
156 Diabetic gastroparesis patients tend to experience the same core signs and symptoms as patients
157 with idiopathic gastroparesis, but individual signs and symptoms may occur more often in one
158 population compared to the other and the degree of diabetic control can also confound results.
159 To fully describe safety and efficacy in each group, separate trials are recommended. If
160 adequate safety and efficacy are demonstrated for both indications, one trial in patients with
161 idiopathic gastroparesis can cross-support another trial in patients with diabetic gastroparesis
162 and result in approval for both indications.

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164 We recommend that trial entry criteria include the following:
165

- 166 • The trial population should have a clinical diagnosis of diabetic or idiopathic
167 gastroparesis based on a demonstrable history of gastroparesis symptoms, exclusion of
168 other potential etiologies, and DGE (Abell, Camilleri, et al. 2008; Parkman, Hasler, et
169 al. 2004). To optimize the ability to demonstrate a treatment effect, the trial should
170 enroll patients with higher symptom severity (moderate to severe). Because there are
171 currently no accepted definitions of gastroparesis severity, the sponsor should provide
172 a justification for the severity index selected, including what defines moderate and
173 severe symptoms.
- 174
- 175 • Diabetic gastroparesis patients should have controlled and stable blood glucose levels.
176 Patients prone to acute hyperglycemic events may confound interpretation of the
177 therapeutic effect of the drug.
- 178
- 179 • Patients on opioids should be excluded because opioid use may affect gastrointestinal
180 motility.

181
182 **C. Outcome Assessment Measures**
183

184 Until a well-defined and reliable PRO instrument that measures all the clinically important signs
185 and symptoms of gastroparesis is available, we recommend that the five core signs and
186 symptoms of gastroparesis — nausea, vomiting, early satiety, abdominal pain, and postprandial
187 fullness — be evaluated in well-controlled clinical trials (Soykan, Sivri, et al. 1998;
188 Karamanolis, Caenepeel, et al. 2007; Hoogerwerf, Pasricha, et al. 1999; Anaparthi, Pehlivanov,
189 et al. 2009). All five should be measured, even in trials where a drug is intended to treat only a
190 subset of the core signs/symptoms, to ensure that treatment does not worsen the remaining
191 signs/symptoms. The sponsor should identify and empirically justify the questionnaire items
192 (and their wording) that will be used in the trial.

193
194 Piloting the instrument in phase 2 trials can provide an opportunity to evaluate the instrument’s
195 ability to detect change as well as to provide guidelines for interpretation of meaningful
196 inpatient change (e.g., responder definition). Therefore, the results from exploratory studies
197 (typically phase 2 studies) can further inform instrument design and plans for its implementation
198 in the phase 3 trials. Wording of the questionnaire items should be carefully thought out so the
199 items do not overlap in their measurement concepts (e.g., postprandial fullness and early satiety)
200 and are interpretable by patients (i.e., sponsors need to define in the questionnaire what is meant
201 by postprandial fullness, early satiety, or other terms that may vary in their definition and
202 interpretation between patients). The assessment of the effects of a pharmacological agent on
203 each of the core signs and symptoms should be separately measured and documented in the
204 clinical trial.

205
206 The sponsor should also specify the format that patients will use to record daily signs and
207 symptoms (e.g., interactive voice response, personal digital assistant, or paper diary). The signs
208 and symptoms should be recorded daily by patients to minimize inaccurate responses resulting

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209 from problems with patient recall (Revicki, Camilleri, et al. 2012; Revicki, Camilleri, et al.
210 2009).

211
212 All signs and symptoms except vomiting should be rated by severity. For example, item
213 responses can range from 0 for no symptoms to 4 for the most severe symptoms (0=none;
214 1=mild; 2=moderate; 3=severe; and 4=very severe) or a numerical rating scale from 0 to 10,
215 where 0 reflects the absence of symptoms and 10 reflects symptoms as bad as can be imagined.
216 We recommend that reporting of vomiting in a daily symptom diary be measured by frequency
217 rather than severity. The severity of nausea, early satiety, abdominal pain, and postprandial
218 fullness should be recorded based on the patient's worst experience over a 24-hour period.
219

220 **D. Trial Endpoints**

221
222 *1. Primary Endpoint*
223

224 A PRO measure of signs and symptoms should form the basis of the primary efficacy assessment
225 in therapeutic trials for diabetic and idiopathic gastroparesis. The primary endpoint should be
226 based on patients' core signs and symptoms or a subset of them. Based on currently available
227 data, the core signs and symptoms of gastroparesis include nausea, vomiting, postprandial
228 fullness, early satiety, and abdominal pain. If a proposed indication is based on improvement of
229 only a subset of the core signs and symptoms of gastroparesis, such as nausea or vomiting, the
230 results of the trial should also demonstrate that the drug does not cause a worsening of the other
231 core gastroparesis sign or symptoms. Gastric emptying time should not be used as a primary
232 efficacy endpoint because changes of gastric emptying time do not correlate with the changes of
233 the clinically important signs and symptoms in patients with gastroparesis.
234

235 The primary endpoint should measure change in signs and symptoms from baseline. The
236 analysis plan should include an evaluation of treatment effect throughout the 12-week study
237 period. As previously stated, the endpoint should be based on patients' daily reporting to
238 avoid recall bias. All signs and symptoms except vomiting should be rated by severity, and
239 vomiting should be measured by frequency. Scoring of the severity of nausea, postprandial
240 fullness, early satiety, and abdominal pain should be based on the worst experience over a 24-
241 hour period.
242

243 We recommend the use of an endpoint(s) that is based either on: (1) measuring each of the core
244 signs and symptoms separately, thereby producing individual sign and symptom scores with a
245 responder definition that incorporates each individual sign and symptom score change; or (2) a
246 summary score of the core signs and symptoms (excluding vomiting) with a responder definition
247 based on meaningful summary score change and vomiting frequency change. If sponsors
248 propose a summary score, they should evaluate item level responses to determine which item(s)
249 are driving the overall score. At this time, we do not have evidence to recommend one approach
250 over the other. Endpoint decisions should be discussed with the FDA early in drug development,
251 particularly since evidence will need to be generated (ideally in phase 2 studies) that supports the
252 specification of the responder definitions.
253

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254 Responder definitions should be based on actual data that establish that the change is clinically
255 important. There are two responder definitions of interest: one for a clinically important
256 improvement from baseline and one for a clinically important deterioration from baseline.
257 Depending on the proposed mechanism of action of the drug and study objectives, a proposed
258 responder definition can specify some level of improvement on each of the five core signs and
259 symptoms, or it can specify some level of improvement on a subset of those core signs and
260 symptoms with further specification that the other core signs and symptoms do not worsen.
261 Any responder definition should be well-justified. Similarly, a summary score used as a
262 primary endpoint should include only those signs and symptoms that are the targets of
263 treatment. In either case, the prespecified plan should address an analysis of the endpoints that
264 represent core signs and/or symptoms that are not expected to improve with the treatment
265 under study to document that these core signs and/or symptoms do not worsen.

2. *Secondary Endpoints*

268
269 The FDA recommends that changes from baseline in the individual signs and symptoms that are
270 not assessed as part of the primary endpoint be measured as secondary endpoints to understand
271 how each of the signs or symptoms are affected by the study treatment. Therefore, the primary
272 and secondary endpoints should include evaluation of changes from baseline in each of the five
273 core signs and symptoms: change from baseline in nausea, change from baseline in early satiety,
274 change from baseline in abdominal pain, change from baseline in postprandial fullness, and
275 change from baseline in vomiting frequency. Change in gastric emptying time also can be
276 measured as a secondary endpoint, if desired (Abell, Camilleri, et al. 2008).

277
278 Definitions of a responder for each of the individual signs and symptoms should be
279 prospectively described before the start of the study and should be based on actual data that
280 establish that the change is clinically important. There are two responder definitions of
281 interest: one for a clinically important improvement from baseline and one for a clinically
282 important deterioration from baseline.

3. *Defining Clinically Meaningful Changes in Sign and Symptom Scores*

283
284
285
286 Ideally, the amount of change that is meaningful to patients in a total summary score or in
287 individual sign and symptom scores should be established in advance of phase 3 trials so that
288 responder definitions may be prespecified. We recommend the use of both anchor-based and
289 distribution-based approaches, typically evaluated using phase 2 data, to justify a responder
290 definition for phase 3 trials. As part of an anchor-based approach to estimate meaningful
291 change, we recommend at a minimum using a global assessment of patients' ratings of
292 gastroparesis severity. It is also useful to include this type of global assessment as an
293 exploratory endpoint in phase 3 trials to provide further support for the responder definition
294 of the PRO assessment.

295
296 The global assessment should ask patients to evaluate only their current gastroparesis status and
297 not compare their current gastroparesis status to another point in time, such as baseline status.
298 The following question, which could be asked weekly of patients and at baseline, is an example
299 of such an assessment:

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300
301 “How would you rate your overall severity of gastroparesis signs and symptoms over the past
302 7 days?”

303
304 Sponsors can consider the following response options to this question: 0=no signs and
305 symptoms; 1=mild; 2=moderate; 3=severe; and 4=very severe.

306
307 **IV. CONCLUSION**

308
309 The proposed endpoints and trial design recommendations in this guidance are considered
310 appropriate for use in the evaluation of drugs for the treatment of idiopathic and diabetic
311 gastroparesis. These recommendations can assist companies in developing treatments to address
312 the needs of patients with gastroparesis while the important work of developing well-defined and
313 reliable PRO instruments for clinical trials of gastroparesis continues.

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