

---

# Gastroparesis: Clinical Evaluation of 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## *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (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 that publishes in the *Federal Register*.

For questions regarding this draft document contact Ruyi He at 301-796-0910.

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

**July 2015  
Clinical/Medical**

# **Gastroparesis: Clinical Evaluation of 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*

*Tel: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov)  
<http://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)**

**July 2015  
Clinical/Medical**

## TABLE OF CONTENTS

<b>I.</b>	<b>INTRODUCTION.....</b>	<b>1</b>
<b>II.</b>	<b>BACKGROUND .....</b>	<b>2</b>
<b>III.</b>	<b>ENDPOINTS AND TRIAL DESIGN FOR GASTROPARESIS CLINICAL TRIALS.....</b>	<b>3</b>
	<b>A. Trial Design .....</b>	<b>4</b>
	<b>B. Trial Populations.....</b>	<b>4</b>
	<b>C. Outcome Assessment Measures .....</b>	<b>5</b>
	<b>D. Trial Endpoints .....</b>	<b>6</b>
	1. <i>Primary Endpoint</i> .....	6
	2. <i>Secondary Endpoints</i> .....	7
	3. <i>Defining Clinically Meaningful Changes in Sign and Symptom Scores</i> .....	7
<b>IV.</b>	<b>CONCLUSION .....</b>	<b>8</b>
	<b>REFERENCES.....</b>	<b>9</b>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32

# Gastroparesis: Clinical Evaluation of Drugs for Treatment Guidance for Industry<sup>1</sup>

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.<sup>2</sup> 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.<sup>3</sup> 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*.<sup>4</sup>

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*

---

<sup>1</sup> 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.

<sup>2</sup> For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

<sup>3</sup> 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.

<sup>4</sup> 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>.

***Contains Nonbinding Recommendations***  
***Draft — Not for Implementation***

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.

***Contains Nonbinding Recommendations***  
***Draft — Not for Implementation***

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 (<sup>13</sup>C) to carbon-12 (<sup>12</sup>C) 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.<sup>5</sup> 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.<sup>6</sup> 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

---

<sup>5</sup> 21 CFR 314.126

<sup>6</sup> 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>.

*Contains Nonbinding Recommendations*  
*Draft — Not for Implementation*

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.

163

*Contains Nonbinding Recommendations*  
*Draft — Not for Implementation*

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

***Contains Nonbinding Recommendations***  
***Draft — Not for Implementation***

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

## *Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

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:

***Contains Nonbinding Recommendations***  
***Draft — Not for Implementation***

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.

*Contains Nonbinding Recommendations*  
*Draft — Not for Implementation*

**REFERENCES**

- 314  
315  
316 Abell TL, Bernstein RK, Cutts T, Farrugia G, Forster J, Hasler WL, McCallum RW, Olden KW,  
317 Parkman HP, Parrish CR, Pasricha PJ, Prather CM, Soffer EE, Twillman R, and Vinik AI, 2006,  
318 Treatment of Gastroparesis: A Multidisciplinary Clinical Review, *Neurogastroenterol Motil*  
319 18:263-283.  
320  
321 Abell TL, Camilleri M, Donohoe K, Hasler WL, Lin HC, Nauer AH, McCallum RW, Nowak T,  
322 Nusynowitz ML, Parkman HP, Shreve P, Szarka LA, Snape WJ, and Ziessman HA, 2008,  
323 Consensus Recommendations for Gastric Emptying Scintigraphy: A Joint Report of the  
324 American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine, *Am*  
325 *J Gastroenterology*, 103:753-763.  
326  
327 Anaparthi R, Pehlivanov N, Grady J, Yimei H, and Pasricha PJ, 2009, Gastroparesis and  
328 Gastroparesis-Like Syndrome: Response to Therapy and its Predictors, *Dig Dis Sci*, 54(5):1003-  
329 10.  
330  
331 Bjorkman D, Moore J, Klein P, and Graham D, 1991, 13C-bicarbonate Breath Test as a Measure  
332 of Gastric Emptying, 1991, *Am J Gastroenterol*, 86(7):821-3.  
333  
334 Bolondi L, Bortolotti M, Santi V, Colletti T, Gaiani S, and Labo G, 1985, Measurement of  
335 Gastric Emptying by Real-Time Ultrasonography, *Gastroenterology*, 89:752-759.  
336  
337 Braden B, Adams S, Duan L, Orth K, Maul F, Lembke B, et al., 1995, The 13C-acetate Breath  
338 Test Accurately Reflects Gastric Emptying of Liquids in Both Liquid and Semisolid Test Meals,  
339 *Gastroenterology*, 108:1048-1055.  
340  
341 Brown BH, Barber DC, and Seagar AD, 1985, Applied Potential Tomography: Possible Clinical  
342 Applications, *Clin Phys Physiol Meas*, 9:499-507.  
343  
344 Camilleri M, 2010, Treatment of Delayed Gastric Emptying, In: *UpToDate*, Talley, NJ (Ed),  
345 *UpToDate*, Waltham, MA.  
346  
347 Ghos Y, Maes B, Geypens B, Mys G, Hiele M, Rutgeerts P, et al., 1993, Measurement of  
348 Gastric Emptying Rate of Solids by Means of a Carbon-Labeled Octanoic Acid Breath Test,  
349 *Gastroenterology*, 104:1640-1647.  
350  
351 Hawkyard CV and Koemer RJ, 2007, The Use of Erythromycin as a Gastrointestinal Prokinetic  
352 Agent in Adult Critical Care: Benefits Versus Risks, *J Antimicrob Chemother*, 59:347-358.  
353  
354 Hejazi R, McCallum R, and Sarosick I, 2012, Prokinetics in Diabetic Gastroparesis, *Curr*  
355 *Gastroenterol Rep*, 14:297-305.  
356  
357 Hoogerwerf WA, Pasricha PJ, Kalloo AN, and Schuster MM, 1999, Pain: The Overlooked  
358 Symptom in Gastroparesis, *Am J Gastroenterol*, 94:1029-1033.  
359

*Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

- 360 Jung HK, Cheung RS, Locke GR 3rd, Schleck CD, Zinsmeister AR, Szarka LA, Mullan B, and  
361 Talley NJ, 2009, The Incidence, Prevalence, and Outcomes of Patients with Gastroparesis in  
362 Olmsted County, Minnesota, from 1996 to 2006, *Gastroenterology*, 136:1225-33.  
363
- 364 Karamanolis G, Caenepeel P, Arts J, and Tack J, 2007, Determinants of Symptom Pattern in  
365 Idiopathic Severely Delayed Gastric Emptying: Gastric Emptying Rate or Proximal Stomach  
366 Dysfunction? *Gut*, 56:29-36.  
367
- 368 McClelland GR and Sutton JA, 1985, Epigastric Impedance: A Non-invasive Method for the  
369 Assessment of Gastric Emptying and Motility, *Gut*, 26:607-614.  
370
- 371 Parkman HP, Hasler WL, and Fisher RS, 2004, American Gastroenterological Association  
372 Technical Review on the Diagnosis and Treatment of Gastroparesis, *Gastroenterology*,  
373 127(5):1592-1622.  
374
- 375 Parkman HP, Yates K, Hasler WL, Nguyen L, Pasricha PJ, Snape WJ, Farrugia G, Koch KL,  
376 Calles J, Abell TL, McCallum RW, Lee L, Unalp-Arida A, Tonascia J, and Hamilton F, 2011,  
377 Similarities and Differences Between Diabetic and Idiopathic Gastroparesis, *Clin Gastroenterol*  
378 *Hepatol*, 9:1056-1064.  
379
- 380 Revicki D, Camilleri M, Kuo B, Norton N, Murray L, Palsgrove A, and Parkman H, 2009,  
381 Development and Content Validity of a Gastroparesis Cardinal Symptom Index Daily Diary,  
382 *Aliment Pharmacol Ther*, 30:670-680.  
383
- 384 Revicki D, Camilleri M, Kuo B, Szarka L, McCormack J, and Parkman H, 2012, Evaluating  
385 Symptom Outcomes in Gastroparesis Clinical Trials: Validity and Responsiveness of the  
386 Gastroparesis Cardinal Symptom Index-Daily Diary (GCSI-DD), *Neurogastroenterol Motil*,  
387 24:456-63, e216.  
388
- 389 Revicki DA, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, and Tack J, 2004,  
390 Gastroparesis Cardinal Symptom Index (GCSI): Development and Validation of a Patient  
391 Reported Assessment of Severity of Gastroparesis Symptoms, *Qual Life Res*, 13(4):833-44.  
392
- 393 Rossi M and Giorgi G, 2010, Domperidone and Long QT Syndrome, *Curr Drug Saf*, 5:257-62.  
394
- 395 Schwizer W, Fried M, Siebold K, Macke H, and Stalder G, 1990, Magnetic Resonance Imaging  
396 (MRI): A New Tool to Measure Gastric Emptying in Man, *Gastroenterology*, 98:A389.  
397
- 398 Siegel J, Wu R, Knight L, Zelac RE, Stern HS, and Malmud LS, 1983, Radiation Dose Estimates  
399 for Oral Agents Used in Upper Gastrointestinal Disease, *J Nucl Med*, 24:835-837.  
400
- 401 Soykan I, Sivri B, Sarosiek I, Kierran B, and McCallum RW, 1998, Demography, Clinical  
402 Characteristics, Psychological Profiles, Treatment and Long-Term Follow-Up of Patients with  
403 Gastroparesis, *Dig Dis Sci*, 43:2398-2404.