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DRAFT GUIDANCE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
Center for Drug Evaluation and Research (CDER)

July 2015
Clinical/Medical

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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This draft guidance is intended to serve as a focus for continued discussions among the Division of Gastroenterology and Inborn Errors Products, pharmaceutical sponsors, the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.

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

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

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

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

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

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

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

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

III. ENDPOINTS AND TRIAL DESIGN FOR GASTROPARESIS CLINICAL TRIALS

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

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

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

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

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

A. Trial Design

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

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

B. Trial Populations

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

We recommend that trial entry criteria include the following:

- The trial population should have a clinical diagnosis of diabetic or idiopathic gastroparesis based on a demonstrable history of gastroparesis symptoms, exclusion of other potential etiologies, and DGE (Abell, Camilleri, et al. 2008; Parkman, Hasler, et al. 2004). To optimize the ability to demonstrate a treatment effect, the trial should enroll patients with higher symptom severity (moderate to severe). Because there are currently no accepted definitions of gastroparesis severity, the sponsor should provide a justification for the severity index selected, including what defines moderate and severe symptoms.

- Diabetic gastroparesis patients should have controlled and stable blood glucose levels. Patients prone to acute hyperglycemic events may confound interpretation of the therapeutic effect of the drug.

- Patients on opioids should be excluded because opioid use may affect gastrointestinal motility.

C. Outcome Assessment Measures

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

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

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

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

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

D. Trial Endpoints

1. Primary Endpoint

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

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

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

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

2. Secondary Endpoints

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

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

3. Defining Clinically Meaningful Changes in Sign and Symptom Scores

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

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

"How would you rate your overall severity of gastroparesis signs and symptoms over the past 7 days?"

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

IV. CONCLUSION

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

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