Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA Center for Drug Evaluation and Research (CDER)
Docket ID: FDA-2015-D-2479:
Gastroparesis: Clinical Evaluation of Drugs for Treatment Guidance for Industry
August 2019 Clinical/Medical Revision 1
FR Document: 2019-17463. Citation: 84 FR 40423
https://www.regulations.gov/docket?D=FDA-2015-D-2479

Date: September 23, 2019

Dear Sir/Madam,

The release of the recent FDA Guidance for Industry on Gastroparesis shows the continued interest of the FDA in helping to bring to availability new medications to treat patients with gastroparesis. This document provides much needed information for conducting clinical trials for pharmaceutical companies for drug approval for gastroparesis. In an analogous fashion, the document provides information for studying gastroparesis in general to clinician scientists. We write this letter from the NIH Gastroparesis Clinical Research Consortium to help enhance the document for clinical trials in gastroparesis.

We agree with many of the statements in this guidance document. We agree that gastric emptying, although important in patient selection and diagnosis, is not particularly relevant in the responses to treatment with agents for gastroparesis. We also agree with the use of the cardinal ("core") symptoms of gastroparesis to follow the response to treatment of patients.

The following are areas that are of concern to us as clinician-scientists who take care of patients as well as perform clinical research in the area of gastroparesis. These are areas that we feel need to be reviewed for either considering revision or at least further clarification.

1. The FDA is sending a conflicting message with regards to the use of a single symptom end-point. While recognizing the "urgent need" in these patients, the guidance states "The primary endpoint should not be limited to a single sign or symptom." Thus, improvement in nausea alone would be not considered a valid endpoint. We think this is not in the best interests of the patients. Some patients suffer from severe nausea and for behavioral or physiological reasons do not vomit. The GpCRC studies have clearly shown that nausea, independent of vomiting, remains the most debilitating symptom and one that interferes the most with quality of life. Currently, apart from metoclopramide, there are no anti-nauseants that are approved for patients with gastroparesis. These patients have to resort to using drugs on an off-label basis- these are either expensive and denied by their insurance carriers (such as 5-HT3 antagonists) or are non-specific and associated with sedation, dependency or other neurological effects (such as phenothiazines or antihistamines). Further, the different symptoms of gastroparesis probably stem from distinct pathophysiologies and there is no scientific basis to believe that targeting any one pathway will benefit others. In the absence of disease-modifying approaches, the least we can do is offer symptomatic relief and

arbitrarily raising the bar so as to exclude drugs that address the most important and debilitating symptom of gastroparesis (nausea) will not be in the best interests of our patients.

2. We are not sure it is realistic to do a *randomized controlled* trial of safety lasting for a year for ethical, practical and economic reasons. Considering there are no drugs for gastroparesis that we can give for 12 months (only metoclopramide for 3 months), it is unclear as to what is suggested as the comparing agent, unless the FDA is encouraging off-label use of drugs whose efficacy has not been established. The inclusion of this requirement in the guidance is therefore puzzling, especially given the consensus on the urgent need to develop effective medicines. Further, such guidance has not been applied to other conditions. Without a clear justification, the FDA is giving the appearance that it is disincentivizing smaller companies to enter the gastroparesis market and biasing the rules in favor or large corporations. Again, this measure is not in the best interests of patients.

3. We agree that regular opioid users should not be studied, as this brings in patients with predominant pain and the opioids can delay gastric emptying and produced GI symptoms. However, patients with gastroparesis can have abdominal pain, requiring intermittent uses of opioid analgesia. Thus, while we agree that patients with regular use of opioids should be excluded, occasional use (< three times a week) may be permissible (lines 164-65).

4. We agree with the need for a daily assessment of symptoms of gastroparesis (169-173). On the other hand, no mention is made of Gastroparesis Cardinal Symptom Index (GCSI). We have used the GCSI and GCSI-Daily Diary (GCSI-DD) in multiple studies and find that it provides the basis for much of our understanding of the severity of gastroparesis and how it correlates with multiple variables and how it changes over time or in response to multiple different interventions. Further validation of these scores are provided in REFS. The FDA should clearly state its issues with what is currently the "gold standard" (GCSI-DD) for measuring patient outcomes.

Our impression on reading the latest version of this guidance is that it would improve significantly by including the advice of clinical researchers and experts in gastroparesis. We therefore respectfully request that you address each of the above points to revise the FDA guidelines in order to help guide the field conducting achievable clinical trials which will allow much needed new treatments for our patients with gastroparesis.

Sincerely,

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