The Gastroparesis Clinical Research Consortium (GpCRC)

September 20, 2015

Stephen Ostroff, MD
Acting Commissioner
United States Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Gastroparesis: Clinical Evaluation of Drugs for Treatment; Draft Guidance for Industry; Availability (FDA-2015-D-2479-0001)

Dear Dr. Ostroff,

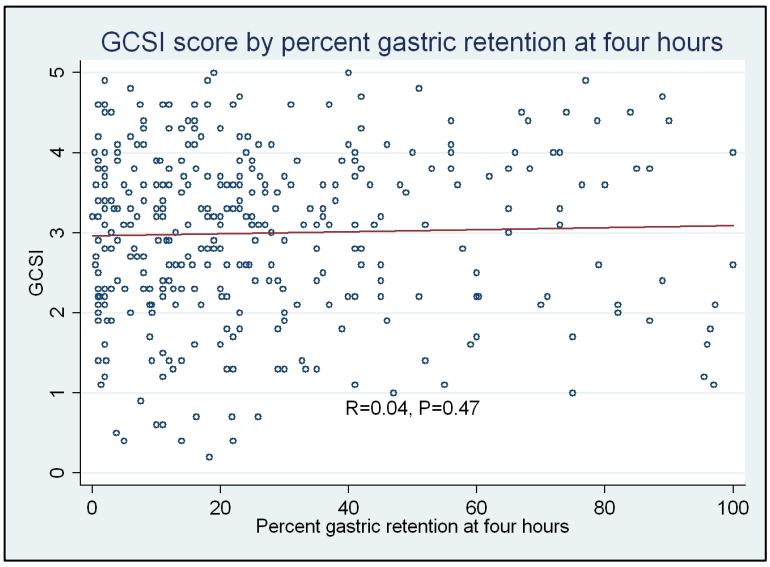
On behalf of the Gastroparesis Clinical Research Consortium (GpCRC) and the patients we serve, we wish to applaud the publication of the draft guidance, named above. This is a major step forward for the field and we are grateful to the FDA for providing clarity and the needed guidance to the Pharma Industry. Most importantly, this action provides hope and encouragement for patients who have suffered too long without adequate treatment of their symptoms.

By way of background, the GpCRC is a NIH/NIDDK-funded project, with seven clinical sites (Johns Hopkins, Temple, University of Michigan, Texas Tech, University of Louisville, Wake Forest, Stanford and California Pacific Medical Center), a center for histopathology and molecular investigation (Mayo Clinic) and a Data Coordination Center (Johns Hopkins Bloomberg School of Public Health). The principal investigators are gastroenterologists, members of the major professional societies (AGA, ACG and ANMS) and key opinion leaders in the field, having dedicated their careers to both research on gastroparesis and the care of patients suffering from this and related disorders.

The GpCRC has been actively studying patients with both gastroparesis and chronic unexplained nausea and vomiting for almost a decade. It has the largest prospectively collected database in the world with over 700 carefully and comprehensively phenotyped patients along with annotated bio-samples and physiological tests, including gastric emptying, wireless motility capsule testing, electrogastrography, liquid meal satiety testing, autonomic function testing and detailed immunohistochemical and electron microscopic analysis of full thickness biopsies as well as a growing repository of next generation sequencing data on gastric tissue samples for our patients. It represents the largest clinical and physiologic data repository for gastroparesis that has ever been assembled.

Through numerous publications and research presentations, the consortium has transformed our understanding of many aspects of gastroparesis.[1-13] As such, we believe our group has the perspective, expertise and knowledge to comment on elements of the guidance document, most of which we strongly endorse. In particular, we are very appreciative of the emphasis on symptomatic relief. We agree with the cardinal symptoms that the FDA has identified (nausea, early satiety, postprandial fullness, abdominal pain, and vomiting) and also agree with the need for agents that can relieve some, if not all of these symptoms. Chronic nausea, frequent vomiting, meal-related symptoms (satiety, fullness), and pain can all individually and collectively take a terrible toll with quality of life measures showing equivalent or worse status when compared to inflammatory bowel disease (IBD).[13] In our most recently published study, we reported on the outcome of 262 patients, seen every 16 weeks at our centers of excellence and treated according to the standard of care with prescribed medications or other therapies and followed for up to 4y (median, 2.1 y). Of these, only about one-fourth (28%) showed meaningful clinical improvement at 48 weeks or beyond regardless of the presence or absence of diabetes.[13] These findings attest to the chronic nature of gastroparesis has well as the relative ineffectiveness of current approaches.

As a corollary to the above, we also support the FDA's recommendation that improvement in gastric emptying ***not*** be considered a requirement for clinical trials in gastroparesis (apart from establishing the diagnosis). While a delay in gastric emptying is required to make the diagnosis and may underlie the development of some disease related symptoms, there is much literature to support the concept that in chronic gastroparesis gastric emptying and clinical symptoms are not linked. Therefore until we have therapeutic agents that target the underlying cellular and molecular defect, we should not require a change in gastric emptying for clinical trials aimed at alleviating the considerable symptom burden. As an example, the consortium, has shown no correlation between symptom severity and gastric emptying (Figure), using prospectively collected AND validated measures for both parameters (GCSI and 4-hour scintigraphy).[12]



There is also published evidence that drugs can improve symptoms (or at least some symptoms) without necessarily improving gastric emptying and the converse is also true, that is- drugs can improve gastric emptying without improving symptoms.[14-16]

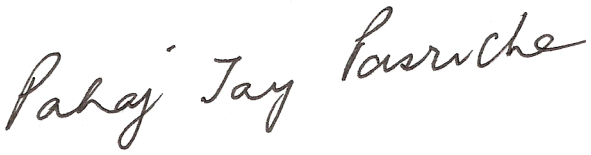
Gastroparesis is a complex, probably heterogeneous disorder and while gastric motility is definitely impaired, different regions of the stomach may each contribute in their own way to the symptom complex, along with changes in extrinsic innervation (including vagal, spinal and possibly sympathetics). Our recommendation therefore is that while there needs to be continued

investment in research, this should be separated from what needs to be a practical and responsive guidance for the relief of symptoms in our patients. We do not believe that we have to pursue a full understanding of the pathogenesis before these efforts can begin.

We also encourage the adoption of validated PROs to assess symptom burden of gastroparesis in addition to those suggested by in the guidance document. The American Neurogastroenterology & Motility Society Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD) is a validated outcome measure that has the characteristics that the FDA has suggested in this guidance document. It has been submitted to the FDA as a PRO ((COA DDT# 000020).

We do wish to point out that the FDA has set a very high bar for trials with respect to 12 month safety data compared to placebo. This is not practical given the chronic relentless nature of the symptoms (as described above)[13] and we would find it hard to justify to patients that they be included in a trial when no more than one quarter of whom will show any improvement during this period if on placebo (the placebo response rate in the NORIG trial conducted by the GpCRC was 21%).[8]

In conclusion, we are pleased with the overall direction and guidelines that the FDA has issued and concur with the substance and spirit in which they were formulated. We are grateful to the Administration for clarifying and facilitating the path for new treatments for patients with this debilitating disorder. As a group, we stand by to offer any further assistance that the FDA needs in this regard.



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