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Response to Miner *et al.*

Mark G. Currie, PhD¹, Steven J. Shiff, MD²,
Harvey A. Schneier, MD³ and
Jeffrey M. Johnston, MD¹

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To the Editor: We read with interest the phase 3 trial publication by Miner *et al.* (1) for the second FDA-approved GC-C agonist, plecanatide, in *American Journal of Gastroenterology*. While encouraged that the trial's results appear to further support use of this pharmacologic class in treating patients with chronic idiopathic constipation (CIC), we are concerned that the authors did not disclose non-standard adverse event (AE)-reporting methods employed in this trial.

Both linaclotide and plecanatide act locally on the luminal surface of the intestinal tract to activate GC-C and are minimally absorbed with negligible systemic exposure. Diarrhea is an expected AE given the pro-secretory characteristics of this pharmacologic class. In linaclotide clinical trials, all spontaneously reported AEs and AEs reported in response to non-leading questions (including diarrhea) were recorded as verbatim terms. Thereafter, qualifiers such as bothersome/annoying were used to grade the severity of these AEs, but were not used to rule out recording of events (2). It appears that a different approach to reporting of AEs was applied in the plecanatide phase 3 CIC trials. According to the FDA's summary basis of approval for plecanatide, patient reports of diarrhea were recorded only if the events were considered "bothersome":

"Since an increase in the number of BMs from baseline was an expected

pharmacodynamic effect of plecanatide and would be coded as diarrhea, sites were instructed to only record an AE of diarrhea if the patient reports that it was bothersome [e.g., watery/mushy stool (Bristol Stool Form Scale [BSFS] score of 6 or 7), with a sense of urgency, etc.] or if the event required treatment or hospitalization." (3)

This description of the methodology used for diarrhea AE collection is not completely clear and raises questions, including:

- If the patient reported diarrhea, but did not specify whether it was bothersome, was the patient further questioned about the event, or was it simply not recorded?
- If the sites determined bothersomeness, how was this done?
- Did a reportable diarrhea event require specific BSFS values and/or a sense of urgency?

In the spirit of good scientific exchange, we ask the authors to provide, in a response letter for *American Journal of Gastroenterology*, answers to these questions, as well as the specific instructions given to sites for determining which diarrhea events were to be recorded as AEs. If diarrhea and diarrhea-like events deemed "non-bothersome" were collected, the overall (i.e., with and without "bothersomeness") diarrhea rates should also be provided.

CONFLICT OF INTEREST

Guarantor of the article: Jeffrey M. Johnston, MD.

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Potential competing interests: Mark G. Currie is an employee of and owns stock/stock options in Ironwood Pharmaceuticals. Jeffrey M. Johnston is a consultant for Ironwood Pharmaceuticals and owns stock/stock options in the company. Steven J. Shiff is an employee of and owns stock/stock options in Allergan plc. Harvey A. Schneier has served as a consultant to Allergan, plc.

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¹Ironwood Pharmaceuticals, Cambridge, Massachusetts, USA; ²Allergan plc, Jersey City, New Jersey, USA; ³HASMD Consulting, LLC., New York, New York, USA. Correspondence: Mark G. Currie, PhD, Ironwood Pharmaceuticals, Cambridge, Massachusetts, USA. E-mail: jjohns5ton@gmail.com

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