DRUG DEVELOPMENT TOOL
LETTER OF INTENT DETERMINATION
DDT COA#000093

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Philadelphia, PA 19146-2305

Dear Drs. Tucker and Forrest:

We have completed our review of the Letter of Intent (LOI) for Drug Development Tool (DDT) COA #000093 received on June 10, 2019 by the CDER Clinical Outcome Assessments (COA) Qualification Program, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act.

The LOI is for the PROMIS Pediatric Crohn's Disease Short Form – Pain Interference, a patient-reported outcome (PRO) proposed for the assessment of interference from pain of any cause in the lives of pediatric patients age 8-17 years with Crohn's disease (CD).

We have determined that we are unable to accept your LOI because it is unclear how results from a general pain interference instrument would be interpreted within the type of clinical trials currently being conducted for development of drugs for pediatric CD. Currently, pediatric studies in CD rely on partial extrapolation of efficacy from adult data, and the clinical trials for pediatric CD typically do not include a placebo control arm. In the absence of a randomized, placebo-controlled study design, we are concerned that data from a general pain interference assessment may be challenging to interpret in terms of demonstrating a benefit from treatment. If you choose to submit a revised LOI, please address the following comments:

1. FDA has accepted abdominal pain intensity as a core symptom to measure in the CD patient population as abdominal pain intensity relates to the intestinal manifestations of the disease that are expected to improve with treatment. Conducting assessments of abdominal pain intensity and other efficacy endpoints at the same timepoints as they were collected in adult trials aids in interpretation of these data to support extrapolation of efficacy. It is unclear how a change in general pain interference would

be interpreted in the currently utilized pediatric study designs, nor how we could use such data as a primary or key secondary endpoint, to support an efficacy determination, as proposed. We recognize that a smaller proportion of patients with CD may also experience extra-intestinal pain (e.g., joint pain). General pain, however, might include painful symptoms of CD (i.e., both abdominal and extra-intestinal pain) as well as pain unrelated to CD (e.g., headache, injury, other illness, etc.), making general pain interference challenging to interpret.

2. Patients with CD present with symptomatic heterogeneity (i.e., present with varying degrees of abdominal pain, bowel symptoms, fatigue, etc.), and each of these symptoms, or a combination of symptoms, can affect the patient's ability to engage in activities of daily living. Given that other known symptoms of CD are expected to interfere with patients' activities of daily living, it is unclear whether children can validly and reliably attribute the interference in daily activities to general pain.

From a regulatory perspective, we agree that it may be valuable to measure disease impacts on activities of daily living. Therefore, we are open to well-designed measures of pediatric CD patients' daily functioning or activities of daily living, which could provide additional context regarding the effects of treatment on patients' lives, and thus could be considered for use as exploratory endpoints in pediatric CD clinical trials.

Please contact the CDER COA Qualification Program at COADDTQualification@fda.hhs.gov should you have any questions (refer to DDT COA #000093).

Sincerely,

Elektra J. Papadopoulos -S

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