Accelerating the Drug Delivery Pipeline for Acute and Chronic Pancreatitis

Summary of the Working Group on Drug Development and Trials in Acute Pancreatitis at the National Institute of Diabetes and Digestive and Kidney Diseases Workshop

SUPPLEMENTAL DIGITAL CONTENT

Memorandum

Date:	December 26, 2017
Subject:	Critical Path Innovation Meeting: Outcome assessment in Acute Pancreatitis
Date of meeting:	October 26, 2017
Requestor:	Dr. Bechien Wu, Director, Center for Pancreatic Care, Kaiser Permanente Southern California

Note: Discussions at Critical Path Innovation Meetings are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants.

FDA Attendees

Center for Drug Evaluation and Research

Office of Translational Sciences (OTS), Immediate Office
Chekesha Clingman, Ph.D., M.B.A., Associate Director for Strategic Partnerships
Ameeta Parekh, Ph.D., Senior Advisor for Scientific Collaborations
Jacqueline Brooks-Leighton, Project Manager

OTS, Office of Clinical Pharmacology
Darrell Abernethy, M.D., Associate Director for Mechanistic Drug Safety

OTS, Office of Biostatistics
Scott Komo, M.D., Ph.D., Statistical Reviewer, Division of Biostatistics IV

Division of Gastroenterology and Inborn Errors Products (DGEIP)
Donna Griebel, Director
Anil Rajpal, Medical Officer/Team Leader
Marjorie Dannis, Medical Officer

Office of New Drugs (OND), Immediate Office Clinical Outcome Assessments (COA) Staff
Michelle Campbell, Ph.D., COA DDT Qualification Scientific Coordinator
Susan M. Pretko, M.P.H., B.C.P.S., Science Policy Analyst
Sarrit Kovacs, Ph.D., Acting Team Leader

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REQUESTER:

Consortium Meeting Attendees-remote participation	
Name	**Affiliation**
Dr. Georgios Papachristou	Professor of Medicine, University of Pittsburgh Medical Center
Dr. Dhiraj Yadav	Professor of Medicine, University of Pittsburgh Medical Center
Dr. James Buxbaum	Associate Professor, University of Southern California
Dr. Stephen Pandol	Professor of Medicine, Cedars Sinai Medical Center
Dr. Valerie Durkalski-Mauldin	Professor of Biostatistics, Medical University of South Carolina
Dr. Vikesh Singh	Associate Professor, Johns Hopkins University
Dr. Bechien Wu	Director, Center for Pancreatic Care, Kaiser Permanente Southern California

1. BACKGROUND

Acute pancreatitis is an increasingly burdensome disease, accounting for more than 200,000 hospitalizations in the United States annually. There are no effective treatments that have been shown to alter the natural history of acute pancreatitis. The lack of standardized outcome measures to assess treatment intervention at various stages of disease course has hindered the development of novel treatments for acute pancreatitis. Dr. Bechien Wu and his colleagues who are representing a consortium of academic investigators in the field of acute pancreatitis requested a CPIM to discuss their progress in developing a clinical outcome assessment instrument for acute pancreatitis.

2. DISCUSSION

FDA gave an overview of the FDA Clinical Outcome Assessment (COA) Qualification Program. FDA briefly discussed the new provisions to the Drug Development Tool (DDT) qualification process enacted under the 21st Century Cures Act, which formally establishes three submission milestones: the Letter of intent (LOI), Qualification Plan, and Qualification Package. Once a COA is qualified, it can be used in multiple drug development programs.

The consortium investigators discussed the development of their clinical disease activity instrument for acute pancreatitis titled, “Pancreatitis Activity Scoring System (PASS)” to assist in the measurement, study and management of acute pancreatitis. The PASS instrument development consisted of a

systematic review of literature and input from a panel of experts in the field to identify and optimize parameters to be included in the instrument. Five parameters were identified by consensus for inclusion in the PASS instrument: organ failure, systemic inflammatory response syndrome (SIRS), abdominal pain, morphine equivalent dose and tolerating solid diet. The literature review and expert consensus phases were followed by a validation phase during which the score was assessed in retrospective studies of patients hospitalized for acute pancreatitis in several health systems in Southern California. Results from the initial validation study indicate that the PASS instrument can be used to assess disease activity for patients with different degrees of acute pancreatitis severity. The consortium investigators discussed plans to further validate the PASS instrument in the context of a multi-center randomized controlled trial to investigate the impact of early fluid resuscitation strategies on outcomes in acute pancreatitis.

FDA encouraged the investigators to pursue qualification of the PASS instrument. FDA advised that careful consideration should be given to the various aspects related to the assessment. Examples include, but are not limited to, causes and sources of variability in the measurements and the importance of standardized assessments across patients, clinicians, and sites so that scores reflect changes in disease status, the role of natural history data for the qualification pathway, the rationale for any item weighting in the scoring algorithm as scoring algorithms should be simple and interpretable for the purpose of translation into labeling claims, and that item-level data should be submitted to the FDA in order to examine which items may be driving the scores and to ensure that not item scores are worsening.

The consortium investigators stated that they plan to collect abdominal pain data (using an 11-point NRS) from patients. However, FDA expressed concern that if the patient was not self-reporting these data but rather a clinician was interviewing patients to obtain these abdominal pain data, the clinician interviewer would need to be trained to not bias the patients' answers in any way. FDA recommended that the consortium investigators consider the importance of collecting open-ended input from patients matching the clinical trial eligibility criteria on what are the core symptoms they are experiencing that they would like treated (e.g., pain, nausea, vomiting), and what is most important to them in terms of how the feel and function in their daily lives. After collecting these data, patient-reported items and response options could be drafted and then cognitively tested them in a similar sample of patients to ensure that the instrument instructions, recall period, items, and response options are meaningful to patients and interpreted as expected, as well as asking patients about meaningful change in scores with regard to response options. FDA also recommended that the consortium investigators consider translation and cultural adaptation of the instrument for each context of use in drug development and regulatory application.

FDA noted that there are other consortia, such as the Critical Path Institute's PRO Consortium, engaged in the development and qualification of COAs. These groups may serve as resources for Dr. Bechien and his colleagues moving forward. In addition, FDA discussed the CDER process for staff engagement in public-private partnerships and consortia activities.

3. ADDITIONAL RESOURCES

- COA Qualification Program:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.

Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm

- Manual of Policies and Procedures (MAPP) 4100.2 *"CDER Staff Participation in PPP and Consortia"*

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