DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: April 23, 2015

ATTN: Steve Broadbent, MBA
Chief Operating Officer
Critical Path Institute
1730 E River Rd.
Tucson, Arizona 85718

Subject: Biomarker Letter of Support

Dear Mr. Broadbent:

We are issuing this Letter of Support to the Critical Path Institute's Polycystic Kidney Disease Outcomes Consortium (PKDOC) to encourage the further development of Total Kidney Volume (TKV), as measured by magnetic resonance imaging (MRI), computed tomography (CT), or ultrasound (US), and possibly in combination with other patient factors, as an exploratory prognostic biomarker for enrichment in clinical trials for autosomal dominant polycystic kidney disease (ADPKD).

ADPKD, the most common hereditary kidney disease, is characterized by progressive enlargement of the kidneys due to cyst growth and formation. In up to half of those diagnosed with the disease, progressive kidney dysfunction develops over decades, with a typical age of onset of end stage renal disease in the mid to late 50s among those who progress to kidney failure. Given the variable course of the disease and the extended time frame for disease progression, there is considerable interest in the identification of biomarkers that might support ADPKD drug development programs.

We support PKDOC's proposed study of TKV, as measured by MRI, CT, or US, in combination with patient age and estimated glomerular filtration rate (eGFR), as a prognostic biomarker to identify patients likely to experience a progressive decline in renal function, as characterized by a decline in eGFR or progression to end-stage renal disease (ESRD), over the course of clinical trials. Such application is consistent with the FDA's draft guidance "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products."[1] Greater experience with this prognostic imaging biomarker in clinical trials would be useful to determine its clinical utility for drug development decisions and study design considerations.

Several imaging modalities may be used to acquire images of the kidneys, and TKV may be determined using a variety of methods. No specific image-based TKV measurement method is endorsed by FDA at this time. Applying good scientific, laboratory, and quality control practices to image acquisition and analysis procedures to TKV is important. We recommend the use of standardized imaging acquisition protocols and standardized volume calculation methodologies to reduce uncertainty and facilitate future analyses across studies.

We encourage exploration of the use of baseline TKV as measured by MRI, CT, or US to enrich for patient subgroups which may be more likely to experience progression of their renal dysfunction over the course of

[1] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf.

clinical trials. When including this biomarker in clinical trials, sponsors are encouraged to employ consensus PKD Clinical Data Interchange Consortium (CDISC)[2] standards for data harmonization. We believe data sharing and integrating data across trials can foster an accelerated path for ADPKD drug development programs. If sponsors intend to include analyses of this biomarker to support regulatory decision making for a given IND drug development program, they should prospectively discuss the approach to these analyses with the Division of Cardiovascular and Renal Products at the Center for Drug Evaluation and Research (CDER).

Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Mr. Steve Broadbent (sbroadbent@c-path.org), the ADPKD point of contact for this project, or view the Critical Path Institute website.

Sincerely,

Janet Woodcock, M.D.

Director, CDER

U.S. Food and Drug Administration

[2] http://www.cdisc.org/therapeutic#polycystickidneydisease