



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

Date: June 14, 2016

ATTN: Harald Mischak, Dr. Med. Habil, Ph.D.
Mosaiques-diagnostics GmbH
Rotenburger Str. 20
D-30659 Hannover
GERMANY

Subject: Biomarker Letter of Support

Dear Dr. Mischak,

We are issuing this Letter of Support to Mosaiques Diagnostics GmbH to encourage the further development of CKD273, a prognostic enrichment biomarker panel composed of 273 urinary peptides, to be used in combination with current measures (i.e., albuminuria, serum creatinine) in early phase clinical trials in diabetic kidney disease (DKD) to identify patients with early stage disease who may be more likely to progress. For a listing of the components of the CKD273 biomarker panel, please see Appendix 1.

Chronic Kidney Disease (CKD) is a major health problem, especially in type 2 diabetes. Many patients with DKD manifest progressive renal dysfunction, ultimately leading to end stage kidney disease. DKD is currently diagnosed by the presence of albuminuria and/or changes in serum creatinine indicating decline in estimated glomerular filtration rate (eGFR). However, risk assessment based on these and other available clinical parameters is insufficient, particularly in patients with early stages of disease. The proposed CKD273 panel is intended to be used to enrich clinical trials of early stage diabetic kidney disease with patients who are more likely to progress.

To date, published and non-published information submitted to FDA suggests that the individual peptide CKD273 biomarkers, specifically collagen fragments and alpha-1-antitrypsin fragments, may be linked to fibrosis and inflammation. These biological processes are assumed to be of relevance in the onset and progression of DKD. Based on experience with use of this biomarker panel classifier in several cross-sectional and longitudinal studies, some analyses suggest that the proteomic signature may provide added prognostic information when used with standard parameters, including albuminuria and eGFR. The prognostic value may be dependent on stage of disease since the submitted data suggests that the CKD273 signature does not appear to perform well in predicting progression to ESRD or doubling of serum creatinine in patients with more advanced disease. While the lack of correlation of the proteomic signature with clinical outcomes in late-stage DKD does not mean it cannot be predictive in early DKD, a biologic rationale for disease stage-specific prognosis, given the ongoing role of processes generating the biomarker signal in late-stage DKD, needs further consideration.

The proposed use of the CKD273 biomarker panel for prognostic enrichment is consistent with the FDA's draft guidance "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products". Greater experience with the use of CKD273 as a biomarker panel in DKD early phase clinical trials is needed to determine its clinical utility for prognostic enrichment, drug development decisions, and study design considerations. We further encourage the investigation of the proposed peptides in the biomarker panel, alone and in combination and potentially with the addition of novel peptides not currently represented, to determine the prognostic potential and to identify the combination that has greatest impact.

We understand the interest in evaluating the efficacy of drugs in early stages of DKD, in the belief that some drugs may be effective only in early stages of the disease. However, the more remote the clinical outcome of interest is, the more challenging and critical it becomes to predict these outcome events accurately since progressively fewer of the nominally at-risk population will go on to have these events. Further work needs to be done to identify surrogate endpoints that reliably predict treatment effects on long-term renal outcomes in early stage DKD and that can be used to establish the effectiveness of drugs intended to treat early (as opposed to later) stages of DKD disease.

Strong emphasis on applying good scientific, laboratory, and software development practices for quality control and validation of CKD273 is imperative. If, after further research, CKD273 is formally proposed as a biomarker panel for qualification, analytical validation of the tests measuring the 273 urinary peptides and validation of the algorithm that determines the panel score for CKD273 should be performed to support the clinical validation of CKD273 as a prognostic enrichment biomarker.

When including the CKD273 biomarker panel in early clinical studies, sponsors should prospectively discuss any proposed application of the clinical biomarker panel to decisions during the course of the study with the appropriate CDER review division.

Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Harald Mischak (mischak@mosaiques.de) or view Mosaiques Diagnostics' webpage (www.mosaiques.de).

Sincerely,



Janet Woodcock, M.D.
Director, CDER
U.S. Food and Drug Administration