CONSULTING REVIEW

Date: March 2, 2015

To: Biomarker Qualification Review Team for Total Kidney Volume (TKV)

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Subject: **Baseline Total Kidney Volume (TKV) as a prognostic biomarker for clinical trial enrichment in Autosomal Dominant Polycystic Kidney Disease (ADPKD)**

Submitter: **Polycystic Kidney Disease Outcomes Consortium**

I. Summary

Qualification of total kidney (TKV) for the proposed context of use should be independent of the imaging modality and method used to assess total kidney volume. However, various imaging methods may be more or less accurate and reproducible. Reducing variability in the imaging modality method may help to reduce the uncertainty in the clinical enrichment model. Voxel-based counting methods (quantitative stereology or boundary tracing) using MRI or CT should provide improved accuracy and reproducibility compared to ellipsoid calculation methods based on ultrasound images.

II. Background and scope

The Polycystic Kidney Disease Outcomes Consortium (PKDOC) has submitted a biomarker qualification package for total kidney volume (TKV) as a prognostic biomarker for use in clinical trials evaluating patients with autosomal dominant polycystic kidney disease (ADPKD).

The scope of this review is the imaging techniques used to acquire the total kidney volume measurements.

III. Context of Use

General Area

Clinical trial enrichment in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Target Population for Use:

Patients with ADPKD

Stage of Drug Development for Use

All clinical stages of ADPKD drug development, including proof of concept, dose-ranging, and confirmatory clinical trials.

Intended Application

Baseline TKV can be applied as a prognostic biomarker that, in combination with patient age and baseline estimated Glomerular Filtration Rate (eGFR), can be used to help identify those ADPKD patients who are at the greatest risk for a substantial decline in renal function defined as (1) 30% worsening of

eGFR, (2) 57% worsening of eGFR (equivalent to doubling of serum creatinine), or (3) End-Stage Renal Disease (ESRD, defined as dialysis or transplant). This biomarker will be used as an inclusion criterion in clinical trials to identify patients likely to show a clinically relevant decline in kidney function during the duration of the trial. Data are provided showing the calculated risk of each of these outcomes of declining renal function depending on age, total kidney volume, and baseline eGFR. Tables will be used by clinical trial researchers to determine the inclusion criteria to help select patients who are likely to reach the clinical endpoint of interest within a timeframe practical for the trial. These criteria include the optimum age, TKV, and eGFR for selecting subjects to be enrolled in the clinical trial.

Kidney volume can be measured by Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, or ultrasound (US) imaging, and the volume calculated by a standard methodology, such as an ellipsoid volume equation (for ultrasound), or by quantitative stereology or boundary tracing (for CT/MRI).

IV. Imaging methodology

In general, imaging techniques should be suitable for the intended task for which they are used. All quantitative metrics (such as distance, size, volume, T1-values, blood flow, etc.) have uncertainty associated with the measurand. Many tasks and assessments involving imaging may be capably performed with high variability in the measurand. Therefore, the acceptable uncertainty in the total kidney volume (TKV) measurand depends on the use of that measurand in the clinical study. In this instance, the biomarker is the prognostic value of TKV in addition to eGFR for patient population enrichment. The degree of enrichment will depend on the specific statistical model used by the future applicant and the impact of the variability in the measurand (TKV) may depend, in part, on the statistical model employed for the specific trial. In general, reducing the variability of the measurement should improve the utility of the statistical model used for trial enrichment.

The submitter has included three image acquisition modalities in the context of use: magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound (US).

Variability in measurements derived from radiological imaging of humans may be generally separated into four categories: physiologic/pathologic, image acquisition, image analysis, and image interpretation. Physiologic or pathologic variability describes the variability in the measurement across the population. Image acquisition variability is the uncertainty caused by noise in the image acquisition system hardware, patient positioning, operator error, and any inherent limitations of the image acquisition technique. Image analysis variability is variability introduced when the investigator derives the quantitative metric from the images and includes software algorithm errors, software implementation errors, image analyst variability where manual image processing steps are required. Image interpretation includes the intra- and inter-reader variability in decision making and clinical evaluation based upon the same quantitative information. Image acquisition and image analysis are discussed below in the context of total kidney volume (TKV).

Image acquisition and analysis

Magnetic resonance images provide 3D information based upon the proton density, T1 relaxation, and T2 relaxation of the tissue under investigation. Computed tomography images provide 3D information about the absorption of x-rays of the tissue imaged. Both of these image acquisition methods permit volumetric analysis by boundary tracing or quantitative stereology. These post-processing methods (quantitative stereology and boundary tracing) are forms of voxel-counting and determine total volume by summing the voxels of known dimensions (voxel size) determined by the image analyst to be part of the kidney. These MRI-based or CT-based methods of calculating TKV tend to have less than 1% average measurement errors.

Ultrasound has been included to measure TKV using an ellipsoid volume measurement that assumes a simple shape of the kidney. This method of volume measurement tends to produce less accurate and reproducibility results compared with MRI or CT and could introduce additional variability into the enrichment model. The kidney is not ellipsoid. Furthermore, the precision and accuracy of this ultrasound technique depend, in part, upon the ultrasound operator or technologist. The error for TKV by ellipsoid

formal may be significant even for small kidneys (95% limits of agree of -120.0 cm^3 and +138.3 cm^3 for kidneys less than 500 mL compared to CT [Mancini et al. 2006]). Measurements of normal kidney volume in vivo have shown relatively poor accuracy and reliability as compared to CT and MRI (Sargent 1997, Bakker 1998, Bakker 1999). Furthermore, inter-observer variation may increase with renal volume (Sargent 1997). The submitter provided a discussion of ultrasound and MRI methods of assessing TKV from the CRISP studies also noting the increased variability in ultrasound measurements of TKV (O'Neill et al. 2005). Variability between sonographers reading the same images ranged 18 – 42%. By comparison, reproducibility of MR from a study of 4 patients was 1.7% coefficient of variation as presented by the sponsor. In the submitter's assessment of variability of CT, average inter-observer variability for CT was 0.97% with inter-reader variability of 1.57%. Measures of average variability TKV with Gadolinium (Gd) and without Gd were similar with intra-reader variability of 0.97% (with Gd Emory), 0.88% (with Gd Mayo Clinic) and 0.98% (without Gd Mayo Clinic) and inter-reader variability of 0.99% (with Gd Emory), 0.95% (with Gd Mayo), and 1.32% (without Gd).

Three-dimensional ultrasound may provide another alternative to CT or MRI and improve accuracy over ellipsoid-based ultrasound methods, but none of the data presented by the submitter used this methodology.

Recommendation about imaging modalities for measuring TKV

MRI without the use of Gadolinium would be the most-preferred method of TKV assessment as the method is more accurate and reproducible than ultrasound methods, does not use ionizing radiation, and has similar performance to MRI with Gadolinium without the risks associated with contrast agent use. CT and MRI with Gadolinium are preferred over ultrasound because of the reliability and accuracy of the TKV measurements compared to ultrasound using the ellipsoid or sequential transverse image techniques. Three-dimensional ultrasound may provide an additional alternative without ionizing radiation or risks associated with contrast agent use, but the submitter did not provide any performance data (accuracy and reproducibility) concerning 3D ultrasound for TKV measurement

V. References

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O'Neill WC, Robbin ML, Bae KT, Grantham JJ, Chapman AB, Guay-Woodford LM, Torres VE, King BF, Wetzel LH, Thompson PA, Miller JP. Sonographic assessment of the severity and progression of autosomal dominant polycystic kidney disease: the Consortium of Renal Imaging Studies in Polycystic Kidney Disease (CRISP). Am J Kidney Dis. 2005 Dec;46(6):1058-64.

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VI. Signatures

Digital Signature Concurrence Table	
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