Polycystic Kidney Disease Outcomes Consortium

(PKDOC)

Total Kidney Volume (TKV) as a Prognostic Biomarker for Use in Clinical Trials Evaluating Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

PKDOC Response to European Medicines Agency (EMA) 3rd List of Issues

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Introduction

The purpose of this document is to provide the PKDOC written responses to EMA's 3rd List of Questions (dated 20 May 2014) in advance of the meeting with the Agency scheduled on 7 July 2014.

Issue 1 – External Validity of the Population

Please substantiate the external validity of the population included in this exercise.

PKDOC Response:

The population consists of those patients who presented to three nephrology clinics and a small subset of participants from a National Institute of Health (NIH) sponsored observational study, and is representative of those who would enroll in clinical trials. Several aspects of the generalizability of the population are discussed in more detail on pages 14 – 15 and 17 - 18 of the Briefing Book. All patients who entered the clinics during the timeframe of data collection and had a diagnosis of ADPKD are included in the database, unless they were already on dialysis or had a transplant. All of the studies underwent national recruitment efforts and included all races and ethnicities. The admitting policies for each institution are detailed below. Patients in the database were only excluded from analysis if they did not have sufficient data to be included; for instance, they did not have a sufficient number of TKV images or estimate glomerular filtration rate (eGFR) measurements.

The subjects represent a wide range in age (Briefing Book, page 78), year of study entry (page 78), age at mortality (page 79), age at end stage renal disease (ESRD) (page 80), age at first eGFR (page 81), and distribution of PKD1/PKD2 genotype when available (86% PKD1; 14% PKD2, page 83).

University of Colorado and Emory University Admittance Policy (Eligibility Criteria):

The data submitted to the PKDOC database were derived from the IRB-approved Natural History study. There were no restricted entry criteria (such as age, renal function, presence of PKD related symptoms, race or ethnicity) beyond diagnosis of ADPKD; thus patients represent a complete spectrum of disease progression from diagnosis to end-stage renal disease. All consecutive subjects consenting to the study were included. Many families were included in this study and multiple family members were clinically evaluated. Many of these individuals were first diagnosed through participation in the study further emphasizing the diversity of disease progression represented by the dataset.

Mayo Clinic Admitting Policy (Eligibility Criteria):

The data submitted to the PKDOC data from Mayo Clinic were derived from the IRB-approved Mayo PKD database. This database includes all the patients with a diagnosis of ADPKD who have been seen at the Mayo Clinic since 1984. Accuracy of ADPKD diagnosis is confirmed prior to entering the demographic, clinical, and laboratory data into the database. There are no additional criteria (such as age, renal function, presence of PKD related symptoms, race or ethnicity) for entry into the database. Therefore, this population is representative of the patients clinically diagnosed with ADPKD in the United States.

CRISP Inclusion and Exclusion Criteria:

The 241 subjects included in the Consortium of Radiological Imaging Studies of Polycystic Kidney Disease (CRISP) cohort had specific inclusion or exclusion criteria. Their ages were between 15 and 46; Cockcroft-Gault creatinine clearance >70 ml/min; 2/3 had hypertension or greater than 300 mg/day urinary protein excretion that are known clinical characteristics associated with progression of renal disease. These inclusion and exclusion criteria create a group of patients that have a risk for progression, but also those who may be at low risk for progression given that individuals were required to have relatively intact kidney function.

Summary:

Data from multiple, longitudinal, well-characterized observational registries maintained by leading PKD investigators at leading American academic medical institutions extending over seven decades were utilized. For comparison purposes and as an indicator of the generalizability of the US data above, Figure 2 on page 15 of the Briefing Book provides age of ESRD for nine European countries. The mean age of ESRD for the European registries, the United States Renal Data System (USRDS), and our study population is similar, further supporting that the registry populations are representative of the overall ADPKD population.

Issue 2 – Subgroup Analysis and Missing Registry Information

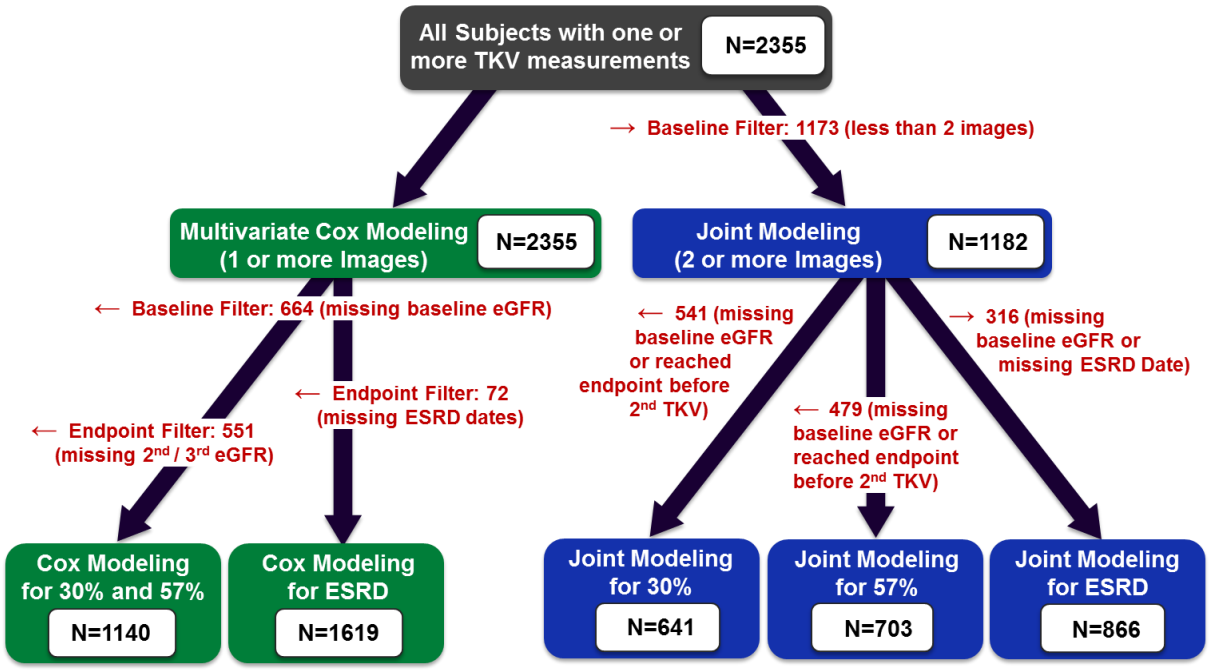
Please justify why some of the analyses have been conducted in subgroups of the total dataset. Also comment on the large amount of missing information in the registries, especially the unavailability of eGFR is a surprise.

PKDOC Response:

The inclusion of subjects into subgroups, and hence the size of those subgroups, is determined solely by the availability of appropriate data points at baseline and post-baseline. This is covered in the Briefing Book on pages 18 – 19, and Section 4.4 (page 104). The various rules applied for the inclusion of baseline and post-baseline measurements are explained below for the multivariate Cox analysis and Joint modeling.

- **TKV Requirement:** A single TKV measurement was required for Cox analyses. Since the joint modeling simultaneously assessed the trajectory of TKV, at least two TKV measurements (separated by at least 6 months) was required for the analysis. As a result, not all patients that were used in the Cox analysis could be used in the joint modeling.
- **Baseline Requirements:** Baseline TKV was defined as the first TKV measurement available in the dataset. Corresponding baseline eGFR measurements were required within one year after the baseline TKV measurement. Overall, we believe that these rules resulted in the cleanest baseline dataset by only including measurements collected within one year after the baseline TKV. The number of subjects excluded from the multivariate Cox and joint modeling according to missing baseline eGFR and other covariate are presented in Figure 1.
- **Endpoint Requirements:** As requested by the US Food and Drug Administration (FDA), patients must have one post-baseline eGFR measurement showing that the subject had reached the endpoint in question (i.e., 30% or 57% decline in eGFR), and a subsequent measurement to confirm the original decline. The confirmatory data point was used, as requested by the FDA, to ensure that reaching the endpoint was not a transient event. This was defined as the "restricted" definition of the 30% or 57% decline in eGFR endpoint. This reduced the number of patients included in the analysis when compared to the dataset that required only one data point achieving the endpoint (defined as the "non-restricted" endpoint). Confirmed ('true') transients were removed from both the "restricted" and "non-restricted" analyses.

Figure 1: Number of Subjects for each Analysis Dataset



As shown in Figure 1, subjects were eliminated from the analysis for one or more of the following reasons:

- They were not included in the analysis if they did not have a baseline eGFR measurement corresponding to the baseline TKV measurement.
- They were not included in the analysis for 30% and 57% decline in eGFR if they did not have at least 2 eGFR measurements beyond the baseline.
- They were not included in the analysis for ESRD if the date on which they reached ESRD was not available.
- They were not included in the joint modeling if they did not have at least two TKV measurements at least six months apart.
- They were not included in the joint modeling if they reached the endpoint before the second TKV measurement was taken. This is the primary reason why these three datasets are different in size.

In order to determine the significance that the restrictive definition had on the results, several additional analyses were performed. Table 1 below shows the effects of the "restrictive" rule on the number subject who reached the endpoints for the 30% and 57% decline in eGFR (for the multivariate Cox analyses only).

Table 1: Effect on the number of subjects using the more restrictive definition of the endpoints

Description (for the Multivariate Cox Modeling)	30% Decline of eGFR	57% Decline of eGFR
1. Number of events under the original submission (where no confirmation was required)	**576**	**210**
2. Number of events retained under the new FDA rule (events confirmed by a subsequent reading, i.e., "restrictive")	**361** (62.7%)	**115** (54.8%)
3. Analysis of removed events. Total number removed:	**215** (37.3%)	**95** (45.2%)
a. Number of 'true transient' events (confirmed by a subsequent reading) that were removed	**62** (10.8%)	**16** (7.6%)
b. Number of 'unconfirmed' events (no subsequent reading was available) that were removed	**153** (26.5%)	**79** (37.6%)

In addition, Kaplan-Meir curves and hazard ratio plots were generated, and the predictive values of the models ROC at 1 and 5 years were calculated using both the "non-restrictive" and "restrictive" definitions and the results were compared. The results for 30% worsening of eGFR are given in Figures 2 and 3, and the results for 57% decline in eGFR are given in Figures 4 and 5. The results using the "restrictive" definition were used in the final analysis presented in the

briefing book by request of FDA. The "non-restrictive" definition yielded similar results as shown below.

Figure 2: 30% Decline in eGFR (Kaplan-Meier Curves)

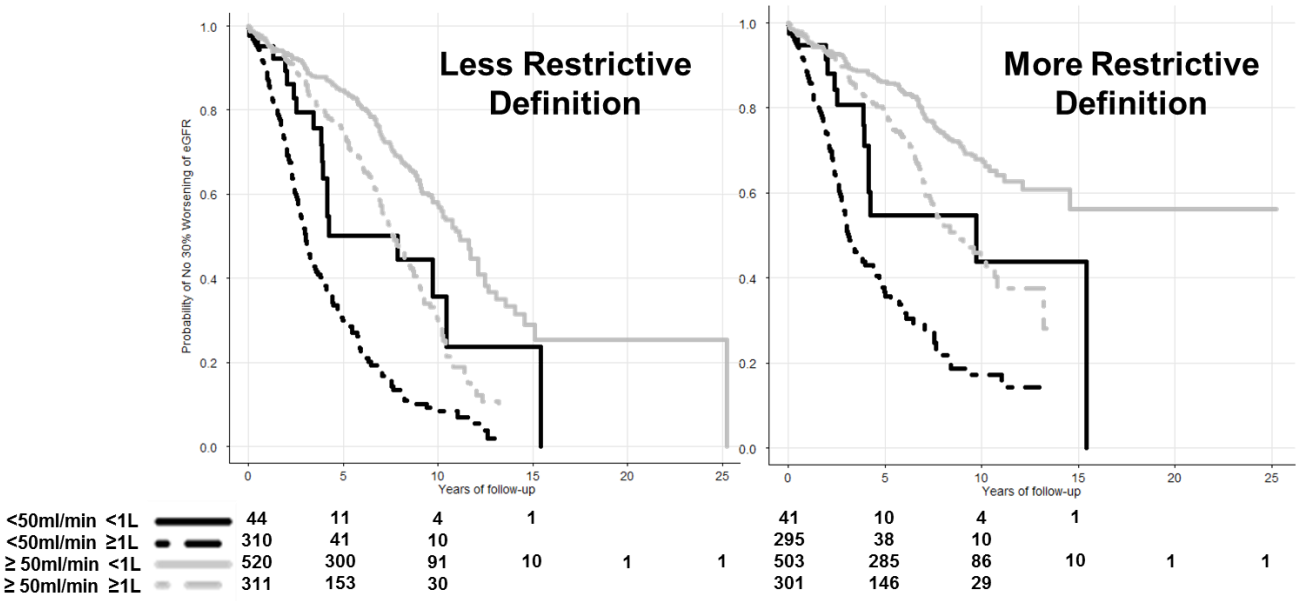
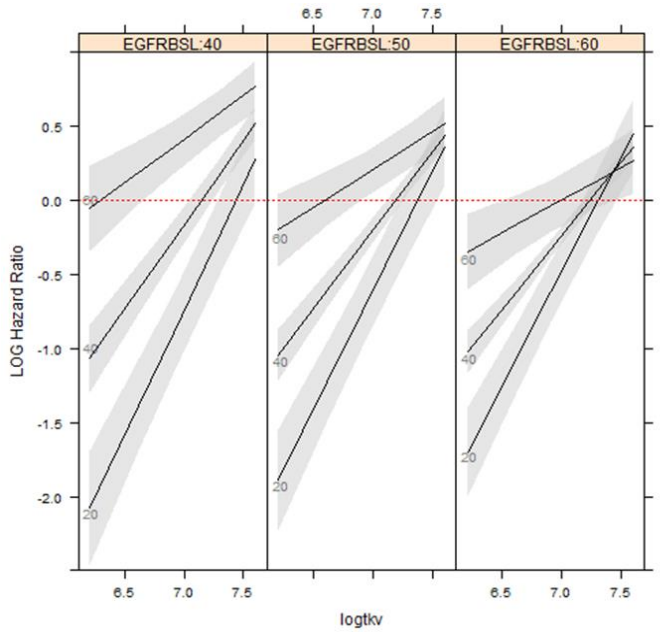
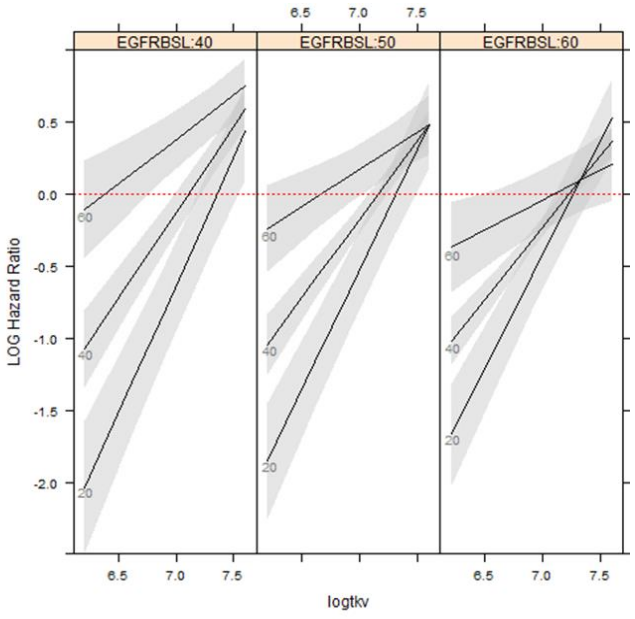


Figure 3: 30% Decline in eGFR (Hazard Ratios)



Left side = Less Restrictive Definition:
N =1185 ROC1= 0.743 ROC5= 0.705



Right side = More Restrictive Definition
N =1140 ROC1= 0.748 ROC5= 0.7001

Figure 4: 57% Decline in eGFR (Kaplan–Meier Curves)

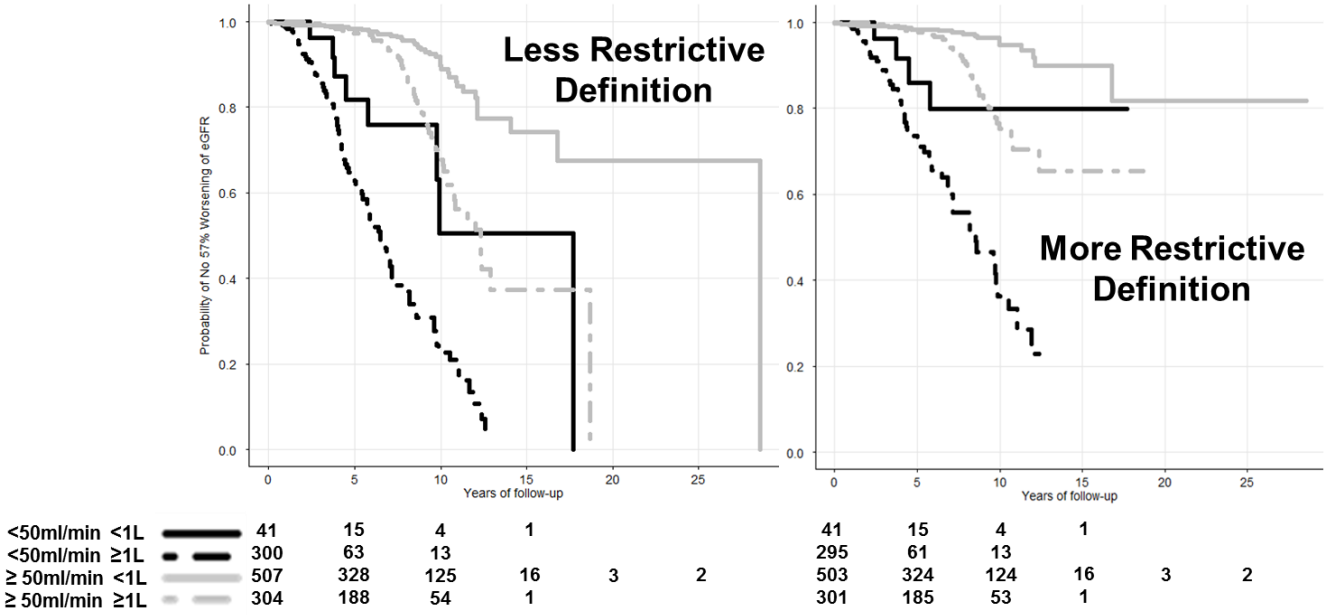
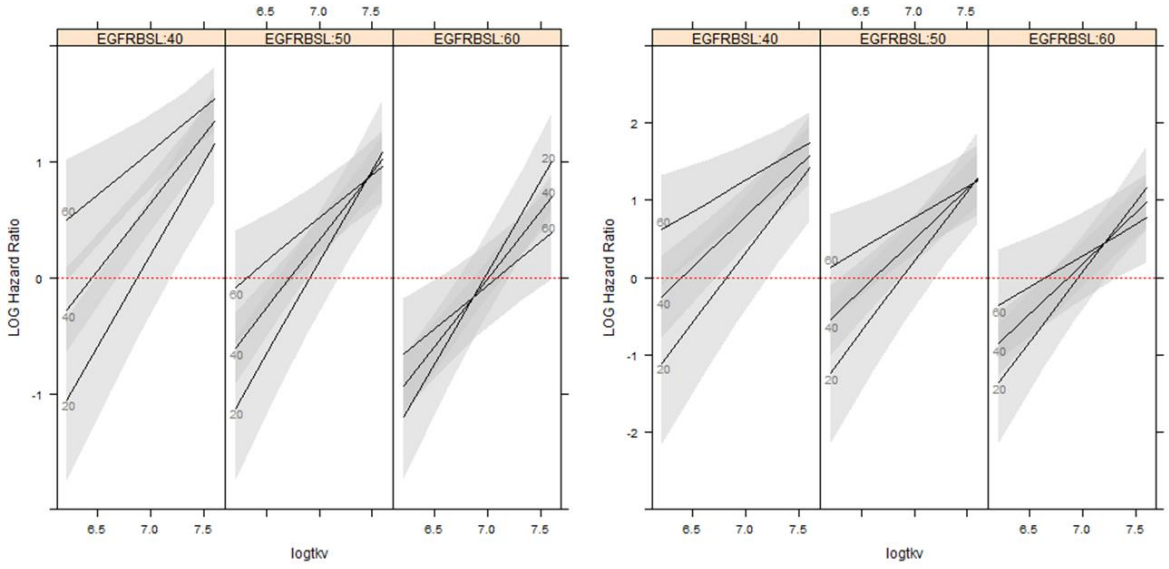


Figure 5: 57% Decline in eGFR (Hazard Ratios)



Left side = Less Restrictive Definition:
N =1152 ROC1= 0.870 ROC5= 0.815

Right side = More Restrictive Definition
N =1140 ROC1= 0.871 ROC5= 0.832

The number of patients excluded because they did not have a baseline eGFR measurement is a result of how the patients were seen in the clinics. Since most of these data are from patient registries and not from structured clinical trials, not all measurements were made at every visit, and the visits were not made at regular intervals. In order for a baseline data point to be valid it

must have both a TKV measurement and a corresponding eGFR measurement within a one year period. In many instances this was not the case.

Issue 3 – Modeling Approach for Analyzing Variables

There is some doubt about your modelling approach: Did you add further variables only after TKV (or a transformation) has been already part of the model (explanation of residual variance)? What would be the outcome, if TKV, age and eGFR were modelled jointly with a backwards selection algorithm to arrive at a parsimonious model?

PKDOC Response:

Baseline TKV was treated as an exploratory variable in the analysis and the inclusion of any covariate in the model was based on relative p-values and ROC at 1 and 5 years. For example baseline TKV was the first covariate to enter the model for the probability of a 30% worsening of eGFR, whereas baseline eGFR was the first covariate to enter the model for the probability of ESRD. Note that a backward selection was performed to remove potential redundant covariates. Additional details on the model selection and inclusion/exclusion of covariates in the various models that were developed are provided below.

- **Univariate Cox Model:** Individual covariates were tested (1-by-1) to determine whether they were significant in predicting the outcomes in question. The univariate Cox analysis was performed for exploratory purposes on TKV, eGFR, age, sex, genotype, and height.

- **Multivariate Cox Model:** The primary analysis included a stepwise testing of significant individual covariates from the univariate cox model as part of a multivariate Cox analysis. Baseline TKV, baseline eGFR, and age remained as the only significant covariates in the multivariate model (based on p-values and ROC results at 1 and 5 years). Importantly, statistically significant interactions were observed between baseline TKV, baseline eGFR, and baseline age that suggested that all three components could not be examined independently. Backward elimination testing of these three covariates was performed and indicated that all three covariates should remain in the model. Additional details are given in response #5 and confirm that TKV and eGFR are the best predictors (better than age) of disease progression. In addition, further testing was performed by including all other covariates in the parsimonious model (i.e., baseline TKV, baseline eGFR, and baseline age and interactions) and none of them were statistically significant.

- **Joint Model:** After discussions with the FDA, a joint modeling approach was agreed upon to address the potential clinical trial environment where both TKV and the probability of the clinical endpoints are simultaneously changing over time. As part of the joint model analysis, the statistically significant covariates from the above parsimonious

model (i.e., baseline TKV, baseline eGFR, and baseline age) were included in the joint model. As indicated in the multivariable Cox analyses, relative contributions of individual variables to the predictive model changed depending on the stage of disease. However, TKV *ALWAYS* added value to the predictive model regardless of when the patient entered the cohort. In early stage disease TKV has greater predictive value, but in later stage disease eGFR is better. Importantly, the analysis indicates that TKV in combination with eGFR is the best predictor of progression of renal disease, better than either alone, and that even at the latest stages of chronic kidney disease, TKV adds value to eGFR as a prognostic biomarker.

On request of EMA, a linear regression analysis was performed using a backward selection process. The details are given in response #5 and confirm that TKV and eGFR are the best predictors of disease progression.

The following information was prepared to provide a more detailed description of the PKDOC Modeling / Analysis Workflow. The documentation below starts with the details of the ESRD modeling and then provides the same references for the other endpoints (30% and 57% worsening of eGFR):

Modeling for ESRD (Briefing Section 5.3, pages 140 – 152)

Phase 1: Covariate Selection (See general information in section 4.7.1 on page 110)

Step 1: Select potential covariate candidates based on clinical relevance and available data

Step 2: Perform Kaplan-Meier analysis to provide a visual impact of TKV and eGFR on the probability of reaching ESRD

Step 3: Perform a univariate Cox analysis on each individual potential covariate to determine which ones have possible significant impact

Step 4: Proceed with stepwise testing of covariates based on p-values and ROC values at 1 and 5 years. Continue this step until no covariates can be added.

Step 5: Continue with the multivariate Cox analysis to eliminate confounding or redundant factors

Step 6: Determine the independent contribution of the interaction between covariates by including all identified significant interaction terms and evaluating them with backward elimination.

Step 7: Perform an exploratory analysis to assess whether the prognostic value of ln-transformed baseline TKV was preserved after adding other covariates in the multivariate Cox model.

Phase 2: Modality Equivalence Analysis (See general information in section 4.3 pages 95 – 100; Data Rules #12 on page 105)

Step 1: Perform Kaplan-Meier analysis of TKV and eGFR on the probability of reaching ESRD for each imaging modality

Step 2: Run the final multivariate Cox model on subsets defined by the imaging modality used (MRI/CT and US data subsets)

Step 3: Compare the results of the imaging modality subsets to determine which dataset will be used in the Joint Modeling step (Phase 3).

Phase 3: Joint Modeling (See general information in section 4.7.2 on page 111)

Step 1: Select all subjects that had two or more TKV measurements

Step 2: Develop a TKV progression linear mixed-effect model with a random intercept

Step 3: Develop a time-to-ESRD event baseline Hazard Parametric Model testing a Weibull and piecewise-linear functions. This model was chosen based on the ability to match the Kaplan-Meier curve

Step 4: Test all covariates and interaction terms that remained from the final multivariate Cox model within the joint model

Step 5: Simplify the model without reducing the predictive performance. (Some interactions are not needed when we take into account the time-varying nature of TKV)

Phase 4: Model Validation (See general information in Cross Validation Methodology on page 111)

Step 1: Randomly divide the patient population into 5 subsets (but stratified to maintain a similar proportion of patients from the CRISP and registry datasets)

Step 2: Remove one subset of data for use as a test dataset

Step 3: Fit the joint model with the remaining datasets (training)

Step 4: Predict the outcomes for the test dataset based on the prognostic values in the dataset

Step 5: Calculate the Mean Predictive Error (MPE) and the Root Mean Square Errors (RMSE) between the predicted outcome and the actual results in the data

Step 6: Repeat with the other 4 subsets

The same steps are run for 30% and 57% decline in eGFR and are shown in the following pages of the briefing book:

Modeling for 30% decline in eGFR (Section 5.1, pages 113 – 124)

Modeling for 57% decline in eGFR (Section 5.2, pages 126 – 138)

Issue 4 – Diagnostic Comparison of TKV and eGFR

It may well be that TKV may add diagnostic certainty in early phases, whereas eGFR is a good predictor in later stages of disease. Please comment and investigate your data.

PKDOC Response:

Our primary hypothesis is that TKV is an important prognostic indicator in the early stages of the disease, where it has been well established that eGFR remains stable for many years (pages 13-20, Briefing Book). It is also well established that once eGFR decline is evident, that there is inexorable progressive loss of eGFR. The results of our submitted analyses document that TKV is the *most important* prognostic indicator of early disease progression (defined as likelihood of 30% decline in eGFR) in the early stages of disease (age less than 40, TKV less than 1 liter, eGFR greater than 50) (Figures 37, 38, and 39, Briefing Book). Such characteristics represent subjects most likely to be recruited for early stage clinical trials. Only in subjects with more advanced disease (age greater than 40, TKV greater than 1 liter, eGFR less than 50) (Figures 37, 38, and 39, Briefing Book), does eGFR significantly contribute to increased likelihood of a 30% decline in eGFR. However, in these analyses, TKV remained a significant predictor as well. We agree with EMA that reduced eGFR will predict ESRD; nonetheless, larger TKV predicts more rapid progression even when eGFR is reduced. Our use of TKV as a prognostic factor focuses on early stage disease when eGFR is preserved and likely to remain stable for many years.

While not discounting the importance of baseline eGFR, the purpose of this submission is to provide useful predictive biomarkers and address the weaknesses of eGFR in the early stages of disease progression, by providing a more sensitive biomarker like TKV. The endpoints have been accepted as clinically meaningful outcomes by nephrologists and the FDA (Coresh 2014), and will provide an early signal of disease progression when patients may be more likely to respond to therapies.

Issue 5 – Logistic Regression Model and ROC Analyses

Please consider repeating the analysis with a logistic regression model. In addition ROC-analyses could be used to identify optimal cut-points for influential variables to discern between high and low risk.

PKDOC Response:

At the request of EMA, a logistic regression analysis was performed on the probability of a 30% worsening of eGFR within 5 years after the first baseline TKV. It is to be noted that the logistic regression analyses have serious limitations in analyzing time-to-event endpoints because these methods ignore censoring and drop-out as discussed in the recent conference call (held on May 22, 2014) with PKDOC and EMA.

Nevertheless, a logistic regression analysis was performed with the following assumptions: 1) patients who had events occurring 5 years after the first baseline TKV were considered to have no events, 2) patients who were lost to follow-up (drop-out) within 5 years after the first baseline TKV were considered to have no events.

A logistic regression analysis was also performed on the probability of a 30% worsening of eGFR within 3 years after the first baseline TKV. The details of the coding and results are included in the attached file (entitled *"e30_logistic.html"*).

For the logistic regression analysis to determine the probability of 30% worsening of eGFR over 3 and 5 years, a multivariate approach was used by including all baseline covariates (i.e., age, eGFR, lnTKV, race, and sex) as well as interaction terms in the model. The Akaike criteria (lower result is better) were used for the backward elimination. All covariates and interaction terms were removed from the model with the exception of baseline eGFR and baseline lnTKV for the logistic regression performed over the 3 and 5 years duration. These results suggest that baseline eGFR and baseline lnTKV were the best predictors of 30% worsening of eGFR over 3 and 5 years.

The joint model was developed as a tool to perform trial simulations and allow the assessment of a worsening of eGFR according to any baseline characteristics and study duration and more important, the potential inclusion of a drug effect. The joint model was deemed more flexible than a single cut-off to explore various scenarios and sub-populations of patients that may be enrolled in a clinical trial in order to power trials as a function of baseline characteristics, number of patients, follow-up time, and expected probabilities of a worsening of eGFR.

Issue 6 – Clinical Relevance of 30% Worsening of eGFR

Please discuss the clinical relevance of 30% worsening of eGFR (or of 57% worsening of eGFR). Is it possible to assess whether this is predictive of clinical outcomes (ESRD, transplantation, death, and composite endpoints) by analyzing your datasets.

PKDOC Response:

Doubling of serum creatinine (57% worsening of eGFR) is well established as a regulatory endpoint for clinical trials in chronic kidney disease (Levey, 2009 and from Briefing Book page 17). The clinical relevance of a 30% decline in eGFR was extensively addressed at a joint National Kidney Foundation (NKF)/US Food and Drug Administration conference held in December, 2012. These results were very recently presented at a late-breaking presentation session of the 2014 European Dialysis and Transplant Association Meeting in Amsterdam and simultaneously published in the Journal of the American Medical Association (JAMA). Coresh et al performed individual meta-analysis of 1.7 million participants with 12,344 ESRD events and 223,944 deaths from 35 cohorts in the Chronic Kidney Disease (CKD) Prognosis

Consortium with a repeated measure of serum creatinine concentration over 1 to 3 years and outcome data. Their findings demonstrated that eGFR declines smaller than 57% were strongly and consistently associated with the development of ESRD and mortality. The authors suggested that these findings supported consideration of lesser declines in eGFR (30% reduction over two years) as an alternative end point for CKD progression (Coresh 2014, article and supplement also attached).

We have consulted with Dr. Matsushita of the CKD Prognosis Consortium and one of the statisticians involved with this work. Unfortunately, our data were not collected in a manner that provided a defined baseline period with a predictable follow up time frame because the registry visits were irregular, in contrast to a clinical trial or cohort study.

Issue 7 – Assessing Confounding Factors

Please discuss thoroughly the comprehensiveness in assessing all relevant confounding factors for disease progression that are not included into the model, such as use of ACEI, ARB, hypertension control, cyst suppuration and its control.

PKDOC Response:

In order to utilize baseline data as a prognostic biomarker, it would be most useful to have pre-baseline data to assess subject characteristics more fully. We examined whether our registry data was sufficiently detailed to investigate type and level of antihypertensive agents and found that the medication data were inadequate for evaluation of dosage and exposure. Details regarding cyst suppuration and treatment similarly were not recorded in a fashion that allowed consistent analysis. The vast majority of subjects were hypertensive from the beginning of observation and thus this did not discriminate between subjects.

Issue 8 – Learning/Confirming Paradigm – External Datasets

Please discuss the feasibility of learning – confirming paradigm for the TKV qualification. Do you foresee confirming/updating your model using external datasets (e.g. European Registries)?

PKDOC Response:

PKDOC would be very interested in confirming the model when and if external datasets become available. At present, there are no datasets that could be used to externally validate the model.

Efforts were made to incorporate data from additional global sources but longitudinal data containing TKV measurements were not available (early contacts included A. Serra, Switzerland; R. Sanford, UK.; Y. Pei, Canada; A. Remuzzi, Italy; B. Knebelmann, France).

Future considerations would include using the control arms of ongoing or completed clinical trials. See below for list of potential additions, with reason for non-inclusion.

- HALT-PKD (NCT00283686): not available until completion and publication, anticipated 1/2015.
- TEMPO ¾ (NCT00428948): not available at this time per sponsor (Otsuka) as the drug is still under review by regulatory agencies.
- CERTICAN (EVEROLIMUS) (NCT00414440): not available per sponsor (Novartis).
- OVERTURE (NCT01430494): ongoing: data not yet available
- SUISSE (NCT00346918): 50 placebo subjects; potentially available pending resolution of data sharing agreement.
- LOCKCYST (NCT00565097): 16 placebo subjects; potentially available pending resolution of data sharing agreement.
- Eurocyst: under development.
- UK PKD Registry: under development

References

Levey, Andrew S, Daniel Cattran, Aaron Friedman, W Greg Miller, John Sedor, Katherine Tuttle, Bertram Kasiske, and Thomas Hostetter. 2009. "Proteinuria as a Surrogate Outcome in CKD: Report of a Scientific Workshop Sponsored by the National Kidney Foundation and the US Food and Drug Administration." *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation* 54 (2) (August): 205–226. doi:10.1053/j.ajkd.2009.04.029.

Coresh, Josef, Tanvir Chowdhury Turin, Kunihiro Matsushita, Yingying Sang, Shoshana H. Ballew, Lawrence J. Appel, Hisatomi Arima, et al. 2014. "Decline in Estimated Glomerular Filtration Rate and Subsequent Risk of End-Stage Renal Disease and Mortality." JAMA: The Journal of the American Medical Association, June. doi:10.1001/jama.2014.6634.