PKD Outcomes Consortium EMA SAWP Teleconference

(3rd List of Issues)

July 7th, 2014

Agenda

	Topic	Issues	Presenter	Time
1.	Welcome, Introductions & Objectives		Steve Broadbent	10
2.	Modeling / Analysis Methodology a. Sub-group analysis and missing data b. Full Modeling Results c. Logistic Regression Modeling	2, 3, and 5	JF Marier	30
3.	a. Diagnostic Comparison of TKV and eGFR b. Clinical relevance of 30% worsening of eGFR c. Assessing Confounding Factors	4, 6, and 7	Ron Perrone	30
4.	a. External validity of the population b. Learning/Confirming Paradigm – External Datasets	1 and 8	Steve Broadbent	10
5.	Conclusion and Next Steps		All	10

PKDOC Participants

Name	Institution	Role
Ronald Perrone	Tufts University Medical Center	Consortium Co-Director
Steve Broadbent	Critical Path Institute	Consortium Director
Lorrie Rome	PKD Foundation	Executive Committee
Arlene Chapman	Emory University	Site Principal Investigator
Berenice Gitomer	University of Colorado – Denver	Site Principal Investigator
Vicente Torres	Mayo Clinic	Site Principal Investigator
JF Marier	Pharsight	Lead Scientist – Analysis / Modeling
Samer Mouksassi	Pharsight	Scientist – Analysis/Modeling
Klaus Romero	Critical Path Institute	Clinical Pharmacologist
Jon Neville	Critical Path Institute	Data Management
Bess LeRoy	Critical Path Institute	Data Management
Bob Stafford	Critical Path Institute	Data Management
Gary Lundstrom	Critical Path Institute	Project Manager
Roland Berard	Pharsight	Project Manager
Frank Czerwiec	Otsuka	Industry Consortium Member
Mary Drake	Otsuka	Industry Consortium Member
Daniel Levy	Pfizer	Industry Consortium Member
John Neylan	Genzyme	Industry Consortium Member

Meeting Objectives

1. For each of the eight Issues:

    a. Provide summary of the PKDOC response

    b. Discuss as needed to ensure alignment

    c. Issues are presented in priority order

2. Summarize conclusions and determine next steps and timeline

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Modeling / Analysis Methodology – Sub-group analysis and missing data

Issue 2: *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.*

Response Summary:

- The inclusion of subjects into analysis subgroups was determined solely by the availability of the required data points (this includes both <u>baseline</u> and <u>post-baseline</u> values)

- Details are provided on the following slides

- Additional Kaplan-Meier and Hazard Ratio plots are provided in the written response

Modeling / Analysis Methodology – Definitions and Requirements
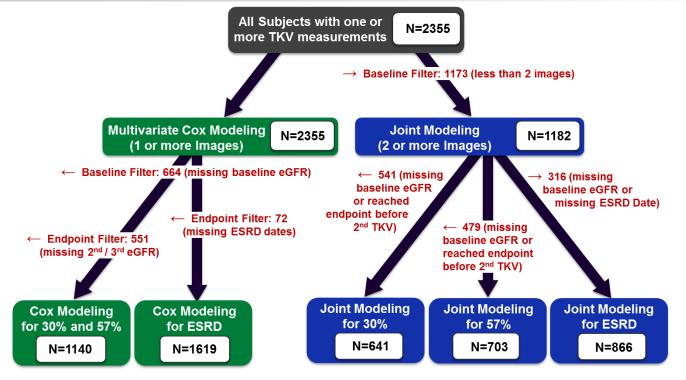
- **TKV Requirements**:
    - For Cox modeling: at least one TKV measurement
    - For Joint modeling: at lease two TKV measurements separated by a minimum of 6 months

- **Baseline Definitions:**
    - Baseline TKV – the first TKV measurement available in the dataset where a corresponding Baseline eGFR measurement within 1 year <u>after</u> the Baseline TKV is also available

- **Endpoints Requirements**:
    - A subject must have at least one post-baseline eGFR showing that the subject had reached the endpoint (30% or 57% decline in eGFR)

      AND
    - A subsequent confirming post-baseline eGFR measurement ('restrictive' definition to ensure endpoint was not transient; as requested by the FDA)

Modeling / Analysis Methodology – Filtering of Analysis Datasets

Subjects were not included in

- **any analysis** if they did not have a baseline eGFR measurement within the first year of the baseline TKV measurement.
- **the analysis for 30% and 57% decline in eGFR** if they did not have at least 2 eGFR measurements beyond the baseline.
- **the analysis for ESRD** if the date on which they reached ESRD was not available.
- **the joint modeling** if they did not have at least two TKV measurements at least six months apart.
- **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.)

Modeling / Analysis Methodology – Full Modeling Results

Issue 3: *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?*

Response Summary:

- 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 values at 1 and 5 years.

- A backwards selection was performed to remove potential redundant covariates

- Additional details are provided on the following slides

- Note: At the request of the FDA, a Modeling/Analysis Workflow was developed and is provided in the written response

Modeling / Analysis Methodology – Full Modeling Results

- **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**

  - 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. Statistically significant interactions were observed between these 3 covariates.

  - Backward elimination testing of baseline TKV, baseline eGFR, and baseline age was performed and indicated that all three covariates should remain in the model.

  - Further testing was performed by including all other covariates in the parsimonious model.

Modeling / Analysis Methodology – Full Modeling Results (cont'd)

- **Joint Modeling**

    - A joint modeling approach was used 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 were included in the joint model.

- **Conclusion**

    - TKV in combination with eGFR is the best predictor of progression of renal disease, better than either alone.

    - In early stage disease TKV has greater predictive value, but in later stage disease eGFR is better.

    - Even at the latest stages of chronic kidney disease, TKV adds value to eGFR as a prognostic biomarker.

Modeling / Analysis Methodology – Logistic Regression Modeling

Issue 5: *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.*

Response Summary:

- A logistic regression analysis was performed on the probability of a 30% worsening of eGFR within 3 years and 5 years after the first baseline TKV.

- Assumptions:
    1. Subjects who had events occurring 5 years after the first baseline TKV were considered to have no events
    2. Subjects who were lost to follow-up (drop-out) within 5 years after the first baseline TKV were considered to have no events

- A summary of the results is provided on the following slide

Modeling / Analysis Methodology – Logistic Regression Modeling

Conclusion:

- Results of the logistic regression analysis were consistent with the earlier PKDOC modeling methodology and suggest that baseline lnTKV and baseline eGFR were the best predictors of 30% worsening of eGFR over 3 and 5 years.

- Note that logistic regression analyses have serious limitations in analyzing time-to-event endpoints because these methods ignore censoring and drop-out.

- Details of the analysis are included in the written response.

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Diagnostic Comparison of TKV and eGFR

Issue 4: *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.*

Response Summary:

- TKV is the most important prognostic indicator in the early stages of the disease, where eGFR remains stable for many years
- Once eGFR decline is evident, there is inexorable progressive loss of eGFR.
- Only in subjects with more advanced disease does eGFR significantly contribute to increased likelihood of a 30% decline in eGFR. However, in these analyses, TKV remained a significant predictor as well.
- Reduced eGFR will predict ESRD; nonetheless, larger TKV predicts more rapid progression even when eGFR is reduced.

Conclusion

- While not discounting the importance of baseline eGFR, the purpose of this submission is to address the limitations of eGFR as a predictor of prognosis in the early stages of ADPKD, by establishing the value of TKV.

Clinical relevance of 30% worsening of eGFR

Issue 6: *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.*

Response Summary:

- Doubling of serum creatinine (57% worsening of eGFR) is well established as a regulatory endpoint for clinical trials in chronic kidney disease

- The clinical relevance of a 30% decline in eGFR was extensively addressed at a joint NKF/FDA conference held in December, 2012, and results were very recently presented and simultaneously published. (see written response)

Conclusion: Findings demonstrated that eGFR declines less than 57% were strongly and consistently associated with the development of ESRD and mortality

Assessing Confounding Factors

Issue 7: *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.*

Response Summary:

- PKDOC examined whether the registry data was sufficiently detailed to investigate type and level of antihypertensive agents.

Conclusion:

- The majority of subjects were hypertensive at baseline. The medication data were inadequate for evaluation of dosage and exposure, and were not recorded in a fashion that allowed for consistent analysis.

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External validity of the population

Issue 1: *Please substantiate the external validity of the population included in this exercise.*

Response Summary: the population consists of:

a. Patients who presented to the 3 nephrology clinics over almost 7 decades
- Includes all patients who entered clinics during data collection period and had a diagnosis of ADPKD
- Subjects only excluded if they were already on dialysis or had a transplant
- No other restricted entry criteria

b. 241 subjects from the NIH observational study (CRISP)
- Ages were between 15 and 46; Cockcroft-Gault creatinine clearance >70 ml/min

c. Age of ESRD: similar between PKDOC, USRDS, and European registries

Conclusion:

- The data comes from multiple, well-characterized registries by leading PKD investigators at prominent academic medical institutions and the population is representative of patients diagnosed with ADPKD

Learning/Confirming Paradigm – External Datasets

Issue 8: *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)?*

Response Summary:

- 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).

Conclusion

- Future considerations would include using the control arms of ongoing or completed clinical trials. A list of potential additions were included in the written response.

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