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Product Development Scientific Support Department

Overview of comments on 'Total Kidney Volume (TKV) as a prognostic biomarker for use in clinical trials evaluating patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)' (EMA/CHMP/SAWP/473433/2015)

Comments from:

Name of organisation or individual
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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
n/a		

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
63		**Comment:** *"Context of use statement (as proposed by the applicant in the 20 March 2014 briefing book)"* A greater level of detail would be appreciated, especially regarding patient characteristics.	The scope of the qualification opinion document is to provide a high level information on the data presented, methods, assessment and qualification claims. More details on patient characteristics in the datasets submitted are provided in section 4.2 Data Statistics and Plots of the final briefing document. **Outcome: No changes**
91		**Comment:** Missing values in the figure on 'trial and inclusion criteria' (page 4). This guidance would only be helpful for the design of a clinical trial with prior knowledge of the boundaries and thresholds. It is recommended that the final qualification include these values.	The figure was provided by the consortium as a vision statement for the use of baseline TKV, eGFR and age for clinical trial enrichment in PKD. This is not as such endorsed by CHMP. Neither specific threshold values for age, TKV, eGFR, nor different endpoints in clinical trials, depending on regulatory claims are recommended/endorsed by CHMP in this qualification opinion. The CHMP opinion is summarised in the respective section of the document.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Outcome: **It will be highlighted in the document that the figure is the vision statement of the consortium.**
246		**Comment:** *"Cross-validation techniques have been used to ameliorate this aspect, but these cannot formally replace an independent verification step".* From the draft qualification opinion is not clear whether a separate dataset was used in which the cut-off of TKV was validated	No specific TKV cut-off is validated. The cross validation methods for the models are described in the final briefing document: 4.7 TKV-Disease Model and Validation. The independent verification step mentioned by CHMP refers to a new dataset preferably from a prospective study to verify the models. **Outcome: No change**
158-161		**Comment:** "*Moreover it is not clear whether drug induced changes of this size predict ESRD or death. Its application should therefore be restricted to those situations (e.g. phase II dose-finding), where independent replication in a phase III clinical trial with more robust endpoints is foreseen and rare disease may not be the most appropriate place to provide further evidence for surrogacy*." Some compounds do not have an acute effect on eGFR. Additionally, for orphan indications, study duration and sample size are not feasible to complete clinical trials using standard registration endpoints. Considering	It is not the objective of this qualification opinion to qualify surrogate endpoints for kidney disease outcomes in clinical trials. The wording reflects the current CHMP position on the topic. CHMP welcome further debate on the adequacy of the 30% worsening of eGFR as a surrogate marker for kidney disease outcomes in clinical trials in the context of scientific advice and qualification of novel methodologies.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		these circumstances, further clarification is requested on the use of other surrogate endpoints.	**Outcome: No change**