Overview of comments on draft Qualification opinion for GFR slope as a Validated Surrogate Endpoint for RCT in CKD

Comments from:

Name of organisation or individual
1. Renal Studies Group, Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford
2. Novo Nordisk A/S

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1. General comments

Stakeholder	General comment (if any)	EMA response
Renal Studies Group, Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford	Key comment: At the Renal Studies Group, we might consider eGFR slopes as a primary outcome in early phase trials, but we see most value in the methodology in investigating effects in subgroups in large trials. This is, in part, because we harbour a concern that trials which base sample size calculation on eGFR slope analyses may be too small to identify plausible hazard of new interventions.	The comment is acknowledged and has been reflected in the final Qualification Opinion.
Renal Studies Group, Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford	Key comment: In the context of an acute reversible eGFR dip on initiation of an intervention, trials of 2-3 year duration are challenging to interpret as they will systematically underestimate the full effect of treatment in the long-term (total slope and effects on categorical eGFR outcomes correlate but are both affected by this limitation). We welcome that the document does not give preference to analyses of total slope over chronic slope (either of which may be prespecified as the primary outcome). In patients with slowly progressive chronic kidney disease, chronic (i.e. long-term slope) is likely to be more informative for longer time horizons.	The comment is appreciated. The most appropriate analysis will depend on the context. Acute and short-term effects will have an impact on the most appropriate analysis, and it can be agreed that for slowly progressive disease for long-term analysis chronic slope will likely be more informative.
Renal Studies Group, Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford	We would encourage the intention-to-treat approach is the primary approach (i.e. a treatment policy strategy) as alternative strategies censoring data when participants stop treatment may be non-randomized (and should be limited to sensitivity analyses).	The comment is acknowledged and partly agreed. A treatment policy approach may not be the most appropriate approach in case of acute negative effects with an impact on the slope after treatment discontinuation. It is agreed that assuming data missing at random after treatment discontinuation as intercurrent event is generally not plausible, and approaches to missing data handling should likely not be based on this assumption. Handling of intercurrent events should be tailored to the setting and incorporate the knowledge

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		after characterisation of acute effects of treatment.
Renal Studies Group, Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford	We welcome EMA's draft which has not been prescriptive about the analysis model that should be used to calculate slopes. 2-slope models versus alternative simpler models may be preferable depending on the trial intervention and design (see also comments below about the limitations of current approaches to subgroup analyses).	The comment is acknowledged and agreed.
Novo Nordisk A/S	We thank the CHMP for the opportunity to review the DRAFT Qualification opinion for GFR slope as a Surrogate Endpoint in RCT for CKD. We are encouraged by the content of the draft document, we acknowledge the extensive work performed at the previously held workshops between NKF, EMA and FDA, as well as the Applicants behind the current proposal. We support CHMP´s position on using GRF slope as a validated surrogate endpoint for CKD progression in randomized controlled clinical trials as primary efficacy endpoint for standard marketing authorization and indication extension approvals. Below we provide few, minor suggestions to further strengthen the messaging of the document. Additionally, we encourage the CHMP to include additional considerations and guidance on GFR slope in the context of an active comparator.	

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder	Comment and rationale; proposed changes	EMA response
Lines 256-257	**Renal Studies Group, Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford**	Key Comment: The methodology for such subgroup analyses has not be well developed as the models developed thus far focus on absolute differences in eGFR slope between allocated interventions. The EMA recommendation to perform subgroup analyses based on eGFR, uACR and pre-baseline progression needs to acknowledge that analytical methods are currently insufficient well developed. For example, in subgroup analyses, it is critical to isolate out and compare just the effect of treatment between subgroups. Comparing absolute differences in slopes between treatment groups would conflate both any difference in baseline rate of progression with any differences in treatment effect. Assessments which focus only on differences in effects of interventions between subgroups becomes possible when slopes are converted onto a relative scale. See example from unpublished EMPA-KIDNEY analyses below (undergoing peer review). In this figure, the right- hand Forest plot presents effects on eGFR slope on a relative scale and the heterogeneity/trend test statistics assess for any difference in effects between subgroups which is accounted for by intervention. We consider this approach to be much more relevant. In contrast, the left-hand Forest plot presents the absolute differences within in subgroup which conflates baseline risk and any effect modification by a baseline characteristic. The substantial difference between the left and right hand plots illustrates the importance of this issue.	The comment is appreciated and agreed. Generally, analysis results can differ largely depending on the metric and scale used. While this is not limited to subgroups analysis, it may become apparent in context of subgroups analysis as directional differences will be important when interpreting subgroups analysis. Applicable considerations have been reflected in the final Qualification Opinion.

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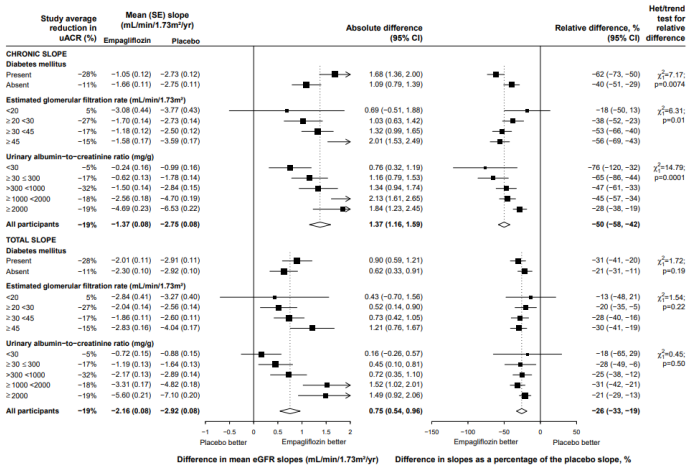
		Figure 2: Absolute and relative effects of allocation to empagliflozin on 'total slopes' and 'chronic slopes', by pre−specified diabetes subgroup, and post−hoc expanded eGFR and uACR subgroups  Proposed change (if any): Acknowledgement that subgroup analyses based on absolute differences are limited, and alternative approaches which isolate assessments of differences in effect of treatment (eg, conversion of results to a relative scale) need to be developed/considered.	
Lines 65-68	**Renal Studies Group, Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford**	Minor Comment: In slowly progressive chronic kidney disease, requiring a trial duration to be long enough to observe crossing of the eGFR slope lines may not always be feasible, and this requirement could be less definitive in the situation that the acute dip is known to be reversible.	The comment is acknowledged and has been reflected in the phrasing of the final Qualification Opinion.
Line 7	**Novo Nordisk A/S**	Comment: '…is intended to be used…' should be further strengthened	The comment is acknowledged.

Line number(s) of the relevant text	Stakeholder	Comment and rationale; proposed changes	EMA response
		Proposed change (if any): '…is to be used…'	
Line 11	**Novo Nordisk A/S**	Comment: replace ESRD with kidney failure (or ESKD) (ref Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney International (2020) 97, 1117–1129) Proposed change (if any): See above	The comment is acknowledged and agreed. The terminology in the final Qualification Opinion has been amended.
Line 7-9	**Novo Nordisk A/S**	Comment: Suggest clarifying the hierarchy/role of eGFR slope Proposed change (if any): '…validated surrogate endpoint for CKD progression in randomized controlled clinical trials **as primary efficacy endpoint** for standard marketing authorization and indication extension approvals.'	The comment is acknowledged. The qualification of GFR slope should not only cover the use a primary endpoint, as use as secondary endpoint may be more appropriate in setting where analysis of a clinical endpoint would be feasible. No change.
Line 15-16	**Novo Nordisk A/S**	Comment: When a study has been powered for a primary eGFR slope-based endpoint it will be underpowered to conclude on hard clinical endpoints including kidney failure and chance findings may occur. Thus, the word 'expectation' may be toned down or the sentence made more objective. Proposed change (if any): The classical endpoints should be assessed and will be included in the overall assessment of a kidney benefit.	The comment is acknowledged but the phrasing is maintained.
Line 14	**Novo Nordisk A/S**	Comment: Suggest specifying 'trial feasibility' Proposed change (if any): '…. when trial feasibility, e.g. trials conducted in rare or less common kidney diseases, is an	The comment is acknowledged, and the phrasing has been amended.

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		issue.'	
Line 31-32	**Novo Nordisk A/S**	Comment: The document reports the overall usability/acceptability of eGFR slope and line 31-32 suddenly questions the applicability. Proposed change (if any): Delete the last part of the sentence: ..where clinical composite endpoints are not feasible within a reasonable timeframe (e.g., 2-3 years). This would also be aligned with line 97-99.	The comment is acknowledged. The specification of application of GFR slope and its limitation are intended. No action taken.
Line 33-34	**Novo Nordisk A/S**	Comment: Align wording with the previously used (line 11-12) and adjust to Nomenclature for kidney function and disease: report of a kidney disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney International (2020) 97, 1117–1129 Proposed change (if any): See above	The comment is acknowledged and agreed. The terminology in the document has been amended.
Line 35-36	**Novo Nordisk A/S**	Comment: Same comment as to line 15-16 and a positive trend will not necessarily be observed for each individual component of a classical kidney failure composite endpoint. Proposed change (if any): -	The comment is acknowledged and the phrasing has been amended.
Line 118	**Novo Nordisk A/S**	Comment: Biology/mechanism of action of the IMP is important for the acute slope; suggest specifying Proposed change (if any): Suggest adding '… tailored to the population, and mechanism of action of the intervention.'	The comment is acknowledged and agreed. The Qualification Opinion was amended accordingly.
Line 123-134	**Novo Nordisk A/S**	Comment: We acknowledge that a final recommendation for analysis models is not done at this stage and encourage future inclusion of further considerations and	The comment is acknowledged and agreed. Further specification of intercurrent events is

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		recommendations regarding analysis models and handling of intercurrent events, including those specified in l 136+137 and KFRT or fatal events. Proposed change (if any): -	considered helpful. The Qualification Opinion was amended according to the proposal in comment just below.
Line 136	**Novo Nordisk A/S**	Comment: Suggest including KFRT and fatal events in the examples of intercurrent events as these events are expected to occur in this type of trials and will preclude the observation or interpretation of GFR. Proposed change (if any): Sponsors should use the estimand framework, justify the selected analysis model and consider how the model-based analysis in a future trial will be impacted by intercurrent events such as treatment discontinuations, KFRT, fatal events and missing data due to study drop-outs.	The comment is acknowledged and agreed. Further specification of intercurrent events is considered helpful. The Qualification Opinion was amended accordingly.
Line 181-186	**Novo Nordisk A/S**	Comment: A concluding sentence for the applicability and acceptability of chronic slope is missing and would be valuable to have included. Proposed change (if any): Like line 176-177	The comment is acknowledged and agreed. The Qualification Opinion was amended.
Line 237-238 Line 228-229	**Novo Nordisk A/S**	Comment: A clear conclusion like this is highly appreciated, however we suggest copying the wording from line 7-9 Proposed change (if any): See above	The comment is acknowledged and the phrasing of the final Qualification Opinion has been amended.