6 October 2016
EMA/CHMP/662165/2016EMA/CHMP/662165/2016
Committee for Medicinal Products for Human Use (CHMP)

# Overview of comments received on 'Draft guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency' (EMA/CHMP/355988/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

| Stakeholder no. | Name of organisation or individual |
|---|---|
| 1 | AstraZeneca |
| 2 | EFPIA |
| 3 | CBG-MEB The Netherlands |

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# 1. General comments – overview

| Stakeholder no. | General comment (if any) | Outcome (if applicable) |
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| 1 | AstraZeneca welcomes the opportunity to comment on this draft guidance. However, we have the following main concerns that could be addressed with a change in the wording.<br><br>**1. Baseline renal biopsies in patients with diabetic nephropathy:**<br><br>In most clinical settings renal biopsies are not performed on patients with diabetic nephropathy, and introducing a requirement to perform baseline renal biopsies on patients diagnosed with diabetic nephropathy (DN) may create a virtually insurmountable hurdle to the effective recruitment of patients in phase II and III studies in DN according to our internal study feasibility assessments, in particular as most patients with earlier stages of DN are only rarely managed at nephrology clinics where there is prior experience with collecting renal biopsies. However, in many forms of non-diabetic CKD biopsies can be an absolute requirement to establish the diagnosis. Hence in lines 330, we propose the following rewording.<br><br>Renal biopsies are of major importance for the proper diagnosis | 1. Baseline renal biopsies in patients with diabetic nephropathy: that is very reasonable approach for pivotal studies, whereas the mechanistic and/or PoC studies would benefit from precise diagnosis in case of mixed co-morbidity and or anamnesis (primarily, in case of primary hypertension that is not a rare event in case of type 2 diabetes).<br><br>The wording was amended to reflect this. |

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| | ***<u>of, in particular, many forms of primary or secondary CKD</u>*** e.g., ~~**of diabetic nephropathy in case of type 2 diabetes or**~~ ***<u>in glomerular diseases</u>*** or chronic allograft nephropathy. ***<u>However, renal biopsy is not required if not used in general practice to set diagnosis, e.g. diabetic nephropathy.</u>*** | |
| | **2. Measured *vs.* estimated GFR:**<br><br>Measuring clearance with the use of exogenous marker is complex, expensive, and difficult to do in routine clinical practice. Furthermore, research studies have reported a measurement error of 5 to 20 % (variation within a single clearance procedure or between clearance procedures on different days (Stevens LA et al, N Engl J Med 2006; 354: 2473-83). Thus rather than characterizing eGFR as 'less accurate' than mGFR, we suggest stating that methods for both estimated and measured GFR have limitations and study designs should take this into account.<br><br>Considering the potential size of studies, in patients with no sign of kidney disease, assessment with mGFR will be very challenging from a practical point of view. Thus mGFR should only be recommended as prioritised for selected cases. Therefore, the following revised text is proposed for consideration (line 175-184):<br><br>~~However, this method is less accurate and more variable than~~ | 2. Measured *vs.* estimated GFR: The practical difficulties in having lowest possible measurements errors are acknowledged for all modes of assessment for long time already, i.e., findings from studies more than 40 years ago (Wesson, 1969) that are cited by mentioned Stevens et al in 2006). In this situation preference is given to gold standard for GFR assessment via measured GFR.<br><br>The document highlights the need for most precise method to assess the GFR and its performance when this is essential for product development.<br><br>Further to this, GL introduce a facilitation of such studies by introducing the use of measured GFR in a pre-specified subset of patients as a confirmatory test of the eGFR.<br><br>The wording is amended to reflect this. |

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| | ~~measured GFR (mGFR)~~….<br><br>***<u>Methods for both estimated and measured GFR have limitations and study designs should take this into account, i.e. the method of measuring kidney function should be appropriate for the population and disease investigated.</u>***<br><br>Detailed comments are also provided below in section 2 - "Specific Comments on the text". | |
| 2 | EFPIA welcomes this guideline which sets out practical steps to facilitate development of compounds used to prevent development and to slow the progression of chronic renal insufficiency.<br><br>We urge to keep in mind that studies are complex and difficult to conduct. Therefore, it is of importance that the guideline strikes the **right balance** between enabling practical studies and seeking rigorous scientific data. | The comment is well taken. |
| 2 | On a general note, the draft guideline seems to miss a discussion about **biomarkers** used to predict treatment response.<br><br>Change in eGFR is too slow of an event for a clinician to use to judge that the patient is deriving benefit from the drug. **Albuminuria** reduction that occurs shortly after initiating treatment may serve that role, but possible other **novel biomarkers** may also be useful for patient selection or to demonstrate that they are deriving renal benefit | The albuminuria or any other BMs are important to assess the renal pathophysiology. The detailed positioning in product development is not discussed at this stage as no consensus could be reached for the time of GL development. |

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| 2 | For consistency with current nomenclature, suggest using the term "**Renal Impairment**" in place of "Renal Insufficiency" | Definitions are detailed and are describe the feature. |
| 2 | Various terminologies are used for synonymously terms.<br><br>It is suggested to use the appropriate respective terms and to give a short definition in the 'Definitions' section<br><br>For example:<br><br>1) The terms '*diabetic nephropathy*' and '*diabetic kidney disease*' as well as '*hypertensive nephropathy*' and '*hypertensive nephrosclerosis*' are used interchangeably throughout the text.<br><br>2) The term '***renal survival***' is mentioned several times in the document without clear definition. In the 'Definitions' section the term 'onset of renal failure' is defined. | Terminology unified for diabetic and hypertensive conditions.<br><br>Renal survival terminology is provided in the section of "Definitions" |
| 3 | A guideline for drugs developed to prevent (fast) progression of CKD and prevent ESRD is highly welcome. The guideline outlines a number of important considerations that should be addressed when developing drugs in the field.<br><br>We have some important concerns with the guideline. First of all, the conceptual approach of **primary and secondary** prevention is elegant but should be further discussed because it impacts the study designs substantially like population studied, clinical endpoints and follow-up duration. In primary prevention the aim is to protect healthy people from developing a disease or experiencing an injury in the first place whereas secondary prevention is used after an illness | 1. For the primary and secondary prevention concepts: the primary prevention is considered for the patient without any signs of renal disease but having risk factors to develop CKD, such as diabetes or hypertension. |

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| | or serious risk factors have already been diagnosed. This type of terminology is not commonly used in the setting of nephrology and classification like e.g. KDIGO is primarily based on a combination of risk factors (eGFR, albuminuria, cause of disease). Furthermore, with respect to secondary prevention, in contrast with e.g. the cardiovascular field patients 'classified' as secondary prevention have not experienced like in CVD a precise and well defined event.<br><br>Second, there is a **relationship between renal disease and cardiovascular endpoints**. This relation may be worthwhile to discuss further. In particular that any harm with respect to CV events should be excluded in certain CKD patients. Since this is a specific renal guideline, **reference** can be made to appropriate CV guidelines.<br><br>Another important issue is of the current evolving discussion on which endpoints to use in CKD (see below). | In contrast, the secondary prevention is considered for already diseased patient that have already damaged kidneys.<br><br>The concept is important for proper patient selection for drug development aimed to separate different risk levels. Thus, the routinely used clinical terminology is not entirely applicable to product development process.<br><br>The wording is amended.<br><br>2. Relationship between renal disease and cardiovascular endpoints: the control of respective disease specific factors is reiterated in the Section of "Specific effects", including cross-reference to relevant disease specific guidelines. |
| 3 | A workshop with the NKF/FDA was held in 2012 discussing the need for alternative endpoints in clinical trials for assessment of medicines for treatment of CKD. Based on this workshop several articles have been published recently (AJKD) without any formal recommendations on the use of alternative endpoints (by the FDA). However, the recommendations / conclusions from this workshop have been used to guide some recent SAWP advices on products developed to prevent deterioration of chronic kidney disease. Within Europe such a discussion has not yet taken place within the clinical nephrology society, although this may be expected very soon. Overall, the | This GL sets the scene to test medicinal product faster than scene using "classical" way of progression of kidney disease, i.e., using typical hard endpoints mentioned only. The approach taken is to use the functional marker (with an established injury marker albuminuria/proteinuria) as the main surrogate set for other endpoints.<br><br>This approach has been used in several recent EU scientific |

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| | clinical nephrology society has currently not provided formal recommendations on whether such alternative endpoints can and should be used. Therefore, recommendations may be subject to changes depending on these discussions.<br><br>It should be further discussed whether to include these recent discussions into the guideline. And it may be considered to include a statement reflecting that endpoint definitions may be subject to change.<br><br>In addition we have a number of smaller comments, which we address further below. | advises already.<br><br>Furthermore, the relevance of changes observed during the intervention might be seen reasonably favourable for medicinal product development and even additionally explored in the clinical setting, further gathering data up to full set of primary endpoints.<br><br>The statement reflecting that endpoint definitions may be subject to change is introduced. |

## 2. Specific comments on text

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| 114-117 | 1 | Comment:<br><br>It would be helpful to clarify the objectives.<br><br>"Secondary prevention" is more common to use in conditions characterised by "events" or "relapses". The most common kidney diseases are, however, continuously progressing (e.g. Diabetic Nephropathy (DN), nephrosclerosis/hypertension kidney diseases). Thus "Prevention of CKD" and "Treatment of CKD" would in our view be more adequate objectives.<br><br>Proposed change (if any):<br><br>~~Primary~~ ***Prevention of CKD***: This scenario describes the prevention of chronic kidney disease in a population with an increased risk but without demonstrable signs of chronic kidney disease<br><br>~~Secondary prevention~~ ***Treatment of CKD:*** This scenario encompasses the slowing of progression of chronic kidney disease in patients with existing signs of chronic kidney disease. | Not accepted.<br><br>The primary prevention is considered for the patient without any signs of renal disease but having risk factors to develop CKD, such as diabetes or hypertension.<br><br>In contrast, the secondary prevention is considered for already diseased patient that have already damaged kidneys. The wording is amended.<br><br>The concept is important for proper patient selection for drug development aimed to separate different risk levels. Thus, the routinely used clinical terminology is not entirely applicable to product development process. Thus, the terminology "treatment of CKD" instead of "secondary prevention" is not endorsed as the emphasis is made on "prevention" of development or progression of renal insufficiency as such and not on the "treatment" of CKD as such, where all treatment options remain outside the scope of this GL (such as treatment of CKD complications) |
| 162- 163 | 1 | Comment:<br><br>We would appreciate if the first bullet could be | Accepted and proposal elaborated further by mentioning both options (in "add-on" or "substitution" settings. |

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| | | clarified.<br><br>Proposed change (if any):<br>• To demonstrate superiority compared to standard of care (may include active comparator) or placebo ~~where justified~~ ***when added to standard of care*** | |
| 189-190 | 1 | Comment:<br><br>Albumin-to-creatinine ratio (ACR) is stated as a preferred to protein-to- creatinine ratio (PCR). Thus it would be helpful to include on what basis ACR is favoured over proteinuria and the document should consistently state ACR and not proteinuria.<br><br>However it is also important to note that some glomerular disorders causing CKD may be associated with high levels of nonselective proteinuria. In those cases measurement of albuminuria (ACR) by itself may not accurately reflect the severity of renal damage and may not provide an adequate parameter to follow for treatment response or progression. In these cases **PCR** is likely to provide a better estimate of urinary protein losses and the likelihood of subsequent protein nephrotoxic tubulointerstitial damage.<br><br>(Clin J Am Soc Nephrol 3: 1028 –1033, 2008 and | Partly accepted.<br><br>The text amended, maintaining the albuminuria as the main marker for risk stratification (as per KDIGO approach) and representing more open approach for the primary endpoints.<br><br>The tubular damage is not considered currently as the clear marker suitable for the primary endpoint. |

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| | | others) | |
| 190-192 | 1 | Comment:<br><br>**Timed urine** samples may be ideal, but they are fraught with difficulties in ensuring accurately timed and complete collections from patients, even in a well conducted trial. In addition these inaccuracies are compounded in patients who are unable to fully empty their urinary bladder due to **neuropathic** (e.g. diabetic or uremic neuropathy, post kidney allograft transplant) or other causes. Despite the comment about diurnal variation, there are several publications validating the use (extrapolation) of ACR or PCR from spot samples taken in a reproducible way; again if compared with a 24 h sample at the beginning, ACR or PCR done at set times in a set way should be valid for follow up | Partly accepted.<br><br>The text amended adding the precaution “if feasible”. |
| 196-200 | 1 | Comment:<br><br>In order to avoid confusion regarding what is intended with the current wording, in particular w/r to the difference between a composite endpoint and a co-primary endpoint we propose the following wording.<br><br>Proposed change (if any):<br><br>The composite of all-cause mortality and renal loss (CKD 5D, see definitions) should always be reported | Partly accepted<br><br>The late stage (advanced) and rapidly progressive disease is clearly differentiated from the situations when very low mortality event rates ie expected. The current wording reads as follows:<br><br>*“In case of advanced or rapidly progressive disease all-cause mortality should be considered to be included as part of the* |

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| | | and in case of advanced ***late stage nephropathy or*** rapidly progressive disease ~~**should be considered as a co-primary endpoint**~~, ***all-cause mortality is recommended to be included in the primary endpoint*** with justified acceptance criteria ***to avoid informative censoring*****.** | *co-primary endpoint.*<br><br>*The composite of all-cause mortality and renal failure (CKD 5 or 5D, see definitions) should always be reported.*<br><br>*In case of very low mortality event rate is expected, the comparative mortality might be considered as the main secondary endpoint."* |
| 385 - 386 | 1 | Comment:<br><br>Creatinine clearance is not a good marker of renal function and correlates poorly to measured GFR which is the golden standard. Estimated GFR using serum creatinine and/serum cystatin C correlates better to measured GFR. Thus we propose the following changes to (1)<br><br>Proposed change (if any):<br><br>***Progression of kidney disease*** - either a (1) decline in the level of kidney function, ~~**estimated by measuring GFR or creatinine clearance,**~~ ***observed*** in a patient who has been followed longitudinally with reliable (and comparable) assays of renal function, ***such as measured or estimated GFR.*** | The proposal to refocus the definition away from methods is endorsed. The methods are not mentioned in the definition. |
| 391 - 392 | 1 | Comment: | Partly accepted. |

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| | | We would appreciate if the sentence could be clarified e.g. does it mean that development and worsening of proteinuria would be possible to use as a surrogate marker for a drop in renal function in the future? | The value of proteinuria is discussed in the main text. This place is not a proper for such discussion. The positioning of proteinuria as stand-alone surrogate marker is not supported for the time being and not proposed in the guideline. |
| Lines 61-64 | 2 | Comment:<br><br>It is not clear what is meant by "*progression of nephropathy on the one side and certain magnitude of intrinsic renal toxicity of the compound on the other side*."<br><br>The statement seems to imply a narrow therapeutic window for drugs of this class where there may be difficulty selecting a dose that achieves a balance between sufficient efficacy and the potentially harmful effects of exaggerated pharmacology; or alternatively that preclinical studies may have demonstrated renal toxicity that must be excluded at doses tested in human studies—which would hold true in any clinical development program?<br><br>Proposed change (if any):<br><br>Please clarify or remove. | Accepted.<br><br>Further description is provided in the main text (Safety aspects). . |
| Line 92-94 | **2** | This guideline is focused on treatments that prevent or slow the progressive loss of eGFR that in turn requires a study of considerable patient size and study | Partially accepted.<br><br>The scope is specified to represent "general" nature of the |

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| | | duration.<br><br>What are not specifically addressed in this guidance are treatments directed at **types of CKD** where there is a more **limited patient population size** or that may affect other aspects of renal injury, such as treatment of **nephrotic syndrome** or treatment/prevention of renal flares in a condition such a **SLE**.<br><br>It would be helpful to specify whether such situations are included in the scope and provide **some guidance** for development programmes in kidney disease with endpoints that do not depend on loss of eGFR over time or where limited size of the patient population makes it unfeasible to power the study for hard renal endpoints. | guidance and mentioning that some specific situations that are relevant to rare or specific diseases/conditions, such as nephrotic, haemolytic uremic syndromes etc. are not discussed in this version of the document as no sufficient regulatory experience is gathered up till now.<br><br>The text introduced: “The scope of the guideline does represent current regulatory experience in the field. Other aspects may be subject to change as soon as new regulatory experience is available.” |
| Line 119 | 2 | Consistent with the comment on lines 92-94, it would be helpful to draw a distinction between a therapy associated with proteinuria reduction vs. successful treatment of nephrotic syndrome where there can be clinical benefit associated with resolution of the nephrotic syndrome independent of beneficial effects on rate of eGFR loss. | Partially accepted.<br><br>The scope is clarified. |
| Line 137 | 2 | Comment:<br><br>A comprehensive listing of all medication is not | Accepted. |

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| | | feasible. As the targeted patient population usually suffers from various co-morbidities, who are also often hospitalized and receive acute treatments. The paragraph mentions pre-defining medicinal products that could affect the results of the study. This latter is considered sufficient from a clinical trial design.<br><br>Proposed change (if any):<br><br>~~**All products taken must be documented.**~~ **Every attempt should be made to collect information on products being taken.** Medicinal products that could affect the results during the study must be predefined or excluded if feasible | |
| Line 174 | 2 | Comment:<br><br>We would like to request that remission of microalbuminuria also be considered as an endpoint. | Not accepted.<br><br>The remission of microalbuminuria is not validated as a surrogate for constant disease remission. |
| Lines 175-186 | 2 | Comment:<br><br>The implementation of **mGFR** during development is not supported. Due to a lack of evidence and the expected (practical) constraints in the conduct of clinical trials. The guideline should also acknowledge that **Cystatin C** may be used as an alternative to SCr when calculating eGFR. | Partially accepted.<br><br>The practical difficulties in having lowest possible measurements errors are acknowledged for all modes of assessment for long time already, i.e., findings from studies more than 40 years ago (Wesson, 1969) that are cited by mentioned Stevens et al in 2006). In this situation preference is given to gold standard for GFR assessment via measured |

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| | | Stevens et al 2006* state that measured GFR is complex, expensive and difficult to do in **routine clinical practice**. It has a measurement error of 5 to 20% (variation within a single clearance procedure or between procedures on different days). The variation is greater in the higher ranges of GFR on the absolute scale.<br><br>In the African-American Study of Kidney Disease and Hypertension, within patient variability over time in SCr based eGFR was slightly smaller than for mGFR using renal iothalimate clearance. This suggests that for a cystatin, one can estimate the change in renal function with SCr eGFR with similar or slightly greater precision than mGFR.<br><br>Both Urinary clearance and Plasma clearance methods are currently utilized for measured GFR (mGFR), and are only generally available in limited specialized medical facilities worldwide. All mGFR techniques are subject to **day-to-day variability**, in part secondary to **hydration status**, **protein intake, exercise**, and **diurnal variation**. The accuracy of *Urinary clearance* methods for mGFR may be affected by bladder emptying, especially in older subjects, and require additional procedures such as | GFR. Thus, the GL notes the need for most precise method to assess the GFR and its performance when this is essential for product development.<br><br>The current wording is as follows:<br><br>Whenever precise determination of GFR is considered essential, such as when the expected decline in GFR is very slow, leading to studies over prolonged periods of time (years) or when it is not reliable to estimate GFR due to great variability of non-GFR determinants of biomarkers employed for estimation it is recommended that mGFR is prioritised over eGFR. |

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| | | catheterization/ultrasound/radiation probes.<br><br>The major disadvantage of Plasma clearance mGFR is the length of time (generally > 5 h) needed to determine the disappearance curve, while even longer times may be needed in people with very low GFR (8 to 10 h). In addition, it may be difficult to obtain **repeated blood samples** in people with poor vascular access. Coefficients of variation for individual urinary and plasma mGFR methods vary from 5-18%, and differences between various methods generally average 10%. Further there appears to be no universal agreement on the **formula** to use when adjusting mGFR for body surface area.<br><br>There are also significant issues regarding the availability and selection of **exogenous markers** for mGFR. For example, **commercial sources** of inulin are very limited. 51Cr-labeled EDTA although available **in Europe**, is not available in the United States. Though clearance of various radionuclide markers, including 99mTc-labeled diethylenetriaminepentaacetic acid (DTPA), and 125I-labeled iothalamate have been used for mGFR, such markers involve special specimen handling, require radiation exposure, and are now subject to decreasing subject acceptance. A history of | |

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| | | iodine or contrast allergy precludes the use of iohexol and iothalamate mGFR.<br><br>* Ref:<br><br>*Lesley A. Stevens, M.D., Josef Coresh, M.D., Ph.D., Tom Greene, Ph.D., and Andrew S. Levey, M.D. Assessing Kidney Function — Measured and Estimated Glomerular Filtration Rate; N Engl J Med 2006;354:2473-83.* | |
| Lines 190 - 192 | 2 | Comment:<br><br>The use of timed urine samples may not be feasible. These are considered cumbersome for the patient and don't demonstrate scientific advantage in comparison to alternatives.<br><br>Heerspink et al 2010* showed in post hoc analysis of RENAAL data lower intra-individual variability with 1st morning ACR than 24 hr UPE or UAE and they conclude it is the best option to monitor albuminuria over time. This parameter also was superior to 24 hr UPE or UAE at predicting renal events. It is much easier for patients to collect as 24 hr collection is cumbersome and fraught with incomplete sample collection and inaccurate collection time | Partially agreed.<br><br>In case of non-feasibility, the repeat ACR/PCR is mentioned as well. |

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| | | **Hiddo J. Lambers Heerspink, Ron T. Gansevoort, Barry M. Brenner, Mark E. Cooper, Hans Henrik Parving, Shahnaz Shahinfar, and Dick de Zeeuw. Comparison of Different Measures of Urinary Protein Excretion for Prediction of Renal Events; J Am Soc Nephrol 21: 1355–1360, 2010.*<br><br>Proposed change:<br><br>A timed urine sample should be done after positive ACR/PCR results to confirm the findings. **After positive ACR/PCR results, a repeat ACR/PCR or a timed urine sample should be conducted to confirm the findings.** ~~**The timed urine sample is the method of choice to be used in assessing the efficacy of the treatment during the study.**~~ | |
| Line 196 | 2 | Comment:<br><br>We would propose to use eGFR as a primary endpoint (*as mentioned in comment line 175-186*). However, regarding the 50% reduction, we would like to propose to specify **reduction 30%** instead of the proposed 50%. The robustness of such an endpoint may be increased by considering replicate sampling at baseline and key time points to reduce variability.<br><br>Recent meta-analyses of outcome trials indicate that a | Not accepted.<br><br>Broad agreement to use lower than 50% GFR magnitudes is not reached for the entire CKD cluster. Although less controversies do exist in the area of diabetic and hypertensive nephropathis, less data are available in case e.g., primarily immunologically driven diseases and ADPKD. Unless more justification is available the preferred option is to maintain current wording. |

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| | | loss >30% is more often achieved in clinical trials and yet remains predictive of progression to ESRD (*Heerspink et al, Am J Kidney Dis. 2014 Feb;63(2):244-50; Coresh et al, JAMA. 2014 Jun 25;311(24):2518-31*).<br><br>Proposed change:<br><br>The recommended primary endpoint is time-to-predefined and justified **confirmed** loss in **e**GFR, such as **30%**. | On the other hand, the proposal reflects several regulatory decisions made and might be reasonable on case-by-case basis.<br><br>As the field will evolve, the GL is intended to be updated.<br><br>The text above the primary endpoints discussed is introduced to represent this.<br><br>Methods to assess the GFR is discussed in the separate section and do not need to be repeated. |
| Line 197-198 | 2 | Comment:<br><br>Suggest adding wording to end of sentence on line 198 to include qualification based on certain patient populations.<br><br>Proposed change:<br><br>"Other (lower) magnitudes of proportions might be used, provided this magnitude is qualified for specific primary disease **or specific patient populations (e.g.., pediatric patients)**." | Partially accepted.<br><br>The text is amended by "...disease or specific patient populations (e.g., extrapolating adult data to pediatric patients)." |
| Line 198 | 2 | Comment: | Accepted. |

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| | | 'Renal loss' is not clearly defined. The definition given in the 'Definitions' section is 'onset of renal failure'.<br><br>Proposed change:<br><br>This term should be used consistently. | |
| Line 199 | 2 | Comment:<br><br>It is not clear how '**advanced rapidly progressive disease**' is defined. Both parts of the term, 'advanced disease' and 'rapidly progressive disease', can be interpreted differently.<br><br>For some authors advanced disease might be defined by an eGFR < 60 ml/min/1.73 m² and for others it might start with an eGFR < 45 or 30 ml/min/1.73 m². And how does the degree of proteinuria relate to it? Also for the progression of eGFR decline over time 'rapidly' might be defined by a decline > 3 ml/min/1.73 m² per year or > 5 ml/min/1.73 m² per year. Furthermore, typically a study population in the field of CKD consist of a mixed patient population including 'slow', 'fast', and 'very fast' progressing individuals.<br><br>Proposed change:<br><br>It is suggested to change the wording to '**as feasible** | Partially accepted.<br><br>These are not necessary the two features of one process but might represent two different scenarios and the interpretation is left to the discretion of the developer. The text is clarified. |

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| | | **and justified by the stage of disease and anticipated progression rate**' (please also refer to next comment) | |
| Lines 198-200 | 2 | Comment:<br><br>We ***respectfully disagree*** that mortality should be a *mandatory* component of a renal outcomes study, since most studies for CKD progression will not be powered to detect statistically significant differences in death. Approved therapies for diabetic nephropathy (DN) have not shown meaningful differences in death events. Inclusion of mortality should therefore be considered on a case by case basis. We agree that mortality should be assessed as a secondary safety endpoint to make sure that the investigational treatment does not appear to be associated with an appreciably increased risk of mortality. But this use is different than including it as part of the primary outcome.<br><br>Proposed change:<br><br>**Inclusion of mortality in a composite endpoint should be considered on a case by case basis.** ~~The composite of all-cause mortality and renal loss (CKD 5D, see definitions) should always be reported and in case of advanced rapidly progressive disease should be considered as a co-primary endpoint with justified~~ | Partially agreed.<br><br>The mortality for advanced and rapidly progressive disease is important.<br><br>The issue of low mortality rate is expected (in the advanced or rapidly progressive disease), the comparative mortality is proposed to be considered as a main secondary endpoint.<br><br>The text is amended (see the wording above). |

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| | | ~~acceptance criteria.~~<br><br>*KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3:1, Al-Aly Z, et al. J Am Soc Nephrol 2010;21:1961, Shlipak MG, et al. J Am Soc Nephrol 2009;20:2625, Rifkin DE, et al. Arch Intern Med 2008;168:2212, Rosansky SJ, et al. Kidney Int 2014;85:723* | |
| Line 213 | 2 | Comment:<br><br>Most of the endpoints listed would only be expected to occur in studies of a very long duration and would not be expected to occur in most phase 3 studies.<br><br>Proposed change:<br><br>The following secondary endpoints for primary and secondary prevention should be considered **dependent on study duration**; | Accepted. |
| Line 214 | 2 | Comment:<br><br>The draft guideline suggests considering a secondary endpoint of renal function at different time points. It is generally agreed that it is crucial to measure renal function over time. | Partially accepted<br><br>The proposal is accepted by amending the text: "*The presence of acute hemodynamic effects should be considered for proper assessment of GFR decline. The study design* |

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| | | However, in case the test treatment exerts direct **hemodynamic effects** on the kidneys affecting renal function the determination of renal function at given time points might be misleading.<br><br>Good examples are angiotensin receptor blockers (ARB). For ARBs it has been shown that they might induce an early drop in eGFR. This worsening in renal function is fully reversible even after long term treatment. More relevant for renal protection under treatment with ARBs is the further decline in renal function after the early drop in GFR occurred. Furthermore, it has been shown that those patients with the strongest early drop in GFR benefit most from ARB treatment.<br><br>Proposed change:<br><br>Therefore, it is suggested to include the rate of decline of renal function, starting after an early drop as appropriate, as a secondary endpoint. Renal function at different time points e.g., 6, 12, 24 months, 3 and 5 years **and the difference between treatments in the slope of decline of renal function over time. Depending on the direct renal effects of the drug under investigation it can be advisable to start measurement of the slope of renal function** | *should be justified based on the specific pattern of the acute effect where the acute effect and more permanent effect of the study drug are delineated. The patterns to be detailed during exploratory studies should include the nature of acute effect (e.g., hemodynamic), the time to maximal and plateau of the acute effect (e.g., after 3 months), magnitude , proportionality, and reversibility of the acute effect, as well as the linearity and the time needed to observe long-term beneficial verum effect."* " |

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| | | **decline after a certain initial treatment phase e.g. 3 months.**<br><br>*Bakris GL, et al. Arch Int Med 2000;160:685, Evans M, et al. Nephrol Dial Transplant 2012;27:2255, Holtkamp FA, et al. Kidney Int 2011;80:282, Rosansky SJ, et al. Kidney Int 2014;85:723* | |
| Lines 221 - 231 | 2 | Comment:<br><br>We assume the timeframe for these endpoints is within the study, but this should be clarified / added. | Accepted. |
| Line 229 | 2 | Comment:<br><br>It is not clear how malnutrition would be defined. | Not accepted.<br><br>This is not a scope of this GL to describe the non-renal tests methodologies. |
| Lines 245 – 249 | 2 | Comment:<br><br>The draft guideline suggests to base trial planning on the **predicted decline** in renal function in the target population and the resulting step up in CKD stages.<br><br>It is not clear what is meant by this suggestion. Predicting the GFR decline before the trial start can't be done by using measurements from included patients (past and on-going). | Partially accepted.<br><br>This is not a request for innovative approach. The rate of progression is a matter of constant workout and considerations of at least both understanding the pathophysiology and risk factors for progression.. |

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| | | Also a definition of the risk factors for **faster decline** in GFR should be given as the differences between fast and slow progressors are not fully understood today. | |
| Lines 289 – 291 | 2 | Comment:<br>It is suggested to make a less forcefull statement regarding comparison versus approved treatments.<br><br>Angiotensin converting enzyme inhibitors (ACEi) and ARBs have been approved for the treatment of renal disease in diabetics. At the same time they are part of the antihypertensive regimen.<br>Although treatment with ARBs has been shown to be effective in the treatment of diabetic nephropathy in the RENAAL and IDNT trial event rates are still considerably high.<br><br>Guidelines strongly recommend their use. From both, ethical and practical considerations, it seems to be indicated not to withdraw ACEi or ARB treatments from patients suffering from diabetic nephropathy in long term phase III trials due to the detrimental consequences of chronic kidney disease and the complexity of guideline conform blood pressure control | Not accepted.<br><br>This is a typical request for the external validity in case of EU approved regimen (not a nationally alone). The text clarified. |

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| | | in this patient population.<br><br>Proposed change:<br><br>"If an approved regimen already exists, **then** comparison with that regimen is ~~strongly recommended~~ **recommended unless there are valid scientific reasons to select another comparator. desirable**" | |
| Lines 330 - 331 | 2 | Comment:<br><br>Renal biopsies are not recommended in clinical guidelines and are not common clinical practice. Additionally, in most of the cases this is also not considered required for clinical decision making.<br><br>This latter is especially the case in diabetic nephropathy. Renal biopsies are bearing the potential risk of bleeding with subsequent renal damage. Therefore, it is practically impossible to convince physicians and patients of the necessity of renal biopsies for clinical trials in diabetic nephropathy. Taking this into account it is recommended to limit this recommendation to renal diseases with clear indication for renal biopsies. | Partially accepted.<br><br>The proposal is very reasonable approach for pivotal studies, whereas the mechanistic and/or PoC studies would benefit from precise diagnosis in case of mixed co-morbidity and or anamnesis (primarily, in case of primary hypertension that is not a rare event in case of type 2 diabetes). The wording was amended to reflect this. |

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| | | To address the problem of disease misclassification in guidelines, e.g. K/DOQI*, a clear clinical definition of diabetic nephropathy is given which is also usually used to define the patient population for trials in diabetic nephropathy (e.g. eGFR 20 – 60 ml/min/1.73 m² and presence of macroalbuminuria and without history or signs to indicate an alternate diagnosis).<br><br>Even if the diagnosis rate were incorrect in a small percentage of DN study subjects, then the risk of a few non-responders because of incorrect diagnosis would not falsely favour efficacy.<br><br>Proposed change:<br><br>Renal biopsies are of major importance for the proper diagnosis ~~e.g., of diabetic nephropathy in case of type 2 diabetes or chronic allograft nephropathy~~ **of the specific type of chronic kidney disease. It is only recommended to perform renal biopsies in clinical trials where a specific treatment is dependent upon the histological diagnosis of the renal disease**.<br><br>** KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic* | |

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| | | *Kidney Disease. Am J Kidney Dis 49:S1-S180, 2007 (suppl 2)* | |
| Lines 338-344 | 2 | Comment:<br><br>Since the guideline acknowledges that the paediatric plan would have to be determined on a case-by-case basis, it should not proceed to describe in detail the situations where paediatric development is needed.<br><br>Proposed change:<br><br>Delete paragraph<br><br>~~Pharmacokinetic and dedicated efficacy/safety studies in children should be undertaken to address specific paediatric issues related to development or progression of CKD such as (a) treatment of all systemic diseases and risk factors (e.g. carbohydrate dysmetabolism/diabetes mellitus, hypertension) increasing the risk for renal disease; and (b) prevention of sodium and phosphates excesses, metabolic acidosis and anaemia (iron deficiency and erythropoietin supplementation), hyperuricemia, hyperlipidaemia, and dental plaque; Renal function should be measured employing most informative estimations, such as Schwartz revised composite eGFR~~ | Not accepted.<br><br>Specific aspects relevant to renal medicine development is important to emphasize. |

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| | | ~~estimation (2009).~~ | |
| Lines 352 - 374 / 364 – 366 | 2 | Comment:<br><br>Within section 4.6, there are two statements that nephrotoxicity adverse events should be monitored:<br><br>- Line 354: "*Safety is normally assessed based on treatment-emergent adverse events…*"<br><br>- Line 364-366*:"…should be carefully evaluated profiling the magnitude and time to specific nephrotoxicity events…*"<br><br>We would suggest the agency to consider a given Standardised MedDRA Query or set of Preferred Terms in general. As it is considered to be relevant, taking into consideration that these may change with time. | Not accepted.<br><br>The message in GL is informative. |
| Lines 358-360 | 2 | Comment:<br><br>We agree that patients with CKD are at risk for AKI and often develop AKI during a clinical trial. While it might be feasible in some cases to follow the patient with an AKI episode who withdraws from treatment, long term follow-up beyond the study is not practical.<br><br>Proposed change:<br><br>Data obtained from long term studies are ~~therefore~~ | Accepted. |

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| | | essential, ~~including treatment of renal insufficiency progression after acute kidney injury~~. **Where feasible, collect and analyze data on CKD progression following episodes of acute kidney injury.** | |
| Line 375 | 2 | Comment:<br><br>Suggest the eGFR is appropriately defined. | Not accepted.<br><br>The distinction between eGFR and mGFR is not necessary |
| Lines 375 - 383 | 2 | Comment:<br><br>We propose the following definitions, as per Kidney Disease Improving Global Outcomes (KDIGO), which includes further refinement of GFR category 3, into 3a and 3b based on substantial data that there are differences in outcomes and risk for those who have GFR values between 45 and 60 versus 30 and 45 ml/min/1.73 $m^2$.<br><br>The full CKD staging system includes 3 categories of albuminuria representing normal to mildly increased, moderately increased (formally called microalbuminuria) and severely increased (formally termed macroalbuminuria) as albuminuria is a risk factor independent of eGFR<br><br>Proposed change:<br><br>Category \| Description \| GFR | Not accepted.<br><br>The clinical guidelines are beneficial complement to the regulatory ones that focus more on product development from a public health perspective.<br><br>On the other hand, the rapidly changing lists of various factors and markers to be proposed for patient care are not necessary be applicable for medicines development purpose.<br><br>The GL is already designed to represent these aspects in general with cross reference to updates. Similarly, the albuminuria is already included into the definition.<br><br>No change is necessary. |

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| | | <table><tr><td></td><td></td><td>(ml/min $m^2$)</td></tr><tr><td>1</td><td>Normal or high</td><td>≥ 90</td></tr><tr><td>2</td><td>Mildly decreased*</td><td>60 – 89</td></tr><tr><td>3a</td><td>Mildly to moderately decreased</td><td>45 – 59</td></tr><tr><td>3b</td><td>Moderately to severely decreased</td><td>30 - 44</td></tr><tr><td>4</td><td>Severely decreased</td><td>15 – 29</td></tr><tr><td>5</td><td>Kidney failure</td><td><15</td></tr><tr><td colspan="3">*Relative to young adult level</td></tr></table><br>Source: “KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease,” *Kidney Disease Improving Global Outcomes (KDIGO)*, January 2013. | |
| Lines 387 – 388 | **2** | Comment:<br><br>In the draft guideline the “onset of renal failure” is defined as the initiation of renal replacement therapy. This definition is deemed to be insufficient. There is considerable geographic variation in the decision making process for initiation of renal replacement therapy.<br><br>This results in a high variability of the GFR threshold | Not accepted.<br><br>This issue is discussed in the main text (in the Section 4.3.2) |

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| | | for start of dialysis which might be in a range from 3 to more than 20 ml/min/1.73 m². It might be subject to further future changes depending on new trial results and guidelines.<br><br>In order to reduce potential bias resulting from differences in dialysis initiation policies it is recommended to include an eGFR threshold of 15 ml/min/1.73 m² into the definition of onset of renal failure. This threshold is identical to the general recommendation for start of dialysis in many guidelines.<br><br>Proposed change:<br><br>(2) onset of renal failure, defined by **reaching an eGFR of 15 ml/min/1.73 m² or, whatever comes first**, initiation of renal replacement therapy, either for symptoms or complications of decreased renal function.<br><br>*KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for 2006 Updates: Hemodialysis Adequacy, Peritoneal Dialysis Adequacy and Vascular Access. Am J Kidney Dis 48:S1-S322, 2006 (suppl 1), Rosansky SJ, et al. Kidney Int 2009;76:257* | |

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| 61-64 | 3 | Comment:<br><br>The sentence ''It is expected that an effective preventive regimen might be hampered by diverging intrinsic properties of the compound thus challenging the goal to achieve an optimal balance between clinically relevant effects in reducing the development or progression of nephropathy on the one side and certain magnitude of intrinsic renal toxicity of the compound on the other side.'' may be more suitable to mention in the Scope section (83-94). | Not accepted.<br><br>Any introductory notes might be moved if rewarded but the preferred option is to maintain both introductory part and the core text (the scope part in this case) as complementing each other and as short and clear as possible. |
| 70-73 | 3 | Comment:<br><br>reference is made to **biomarkers** for functional status, however the examples mentioned do not represent biomarkers rather **disease states**<br><br>Proposed change (if any):<br><br>biomarkers for renal function should be mentioned, of which glomerular filtration rate is the only real important and validated biomarker in this respect. As the sentence 73-75 is also referring to this the whole paragraph should be rephrased. | Not accepted.<br><br>The proposal is not clear enough and no specific change in the text is proposed. Text remains essentially not changed. |
| 87-89 | 3 | Comment:<br><br>the following sentence ''The main therapeutic goal is expected to be achieved by a preventive regimen that | Two sections (introduction and the core text) complement each other (see comment above) |

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| | | should pose an optimal balance between clinically relevant effects in development or progression of nephropathy versus toxicity, e.g. potential deleterious effects on the kidney and other adverse events.'' has already been mentioned in line 61-64. Therefore, it should be further discussed whether to delete this sentence. | |
| 114-117 | 3 | Comment:<br><br>The guideline makes a distinction between primary prevention and secondary prevention.<br><br>The conceptual approach of primary and secondary prevention should be further discussed, as it has a substantial impact on the study design; i.e. population studied, clinical endpoints and follow-up. In primary prevention the aim is to protect healthy people from developing a disease or experiencing an injury in the first place whereas secondary prevention is used after an illness or serious risk factors have already been diagnosed. This type of terminology is not commonly used in the field of nephrology and classifications like KDIGO are primarily based on a combination of risk factors (eGFR, albuminuria, cause of disease). Furthermore, the problem with secondary prevention is that in contrast with e.g. the cardiovascular field patients 'classified' as secondary prevention have not experienced a renal event if in CKD class 3 or 4. | Partially accepted.<br><br>The primary prevention is considered for the patient without any signs of renal disease but having risk factors to develop CKD, such as diabetes or hypertension.<br><br>In contrast, the secondary prevention is considered for already diseased patient that have already damaged kidneys. The wording is amended.<br><br>The concept is important for proper patient selection for drug development aimed to separate different risk levels. Thus, the routinely used clinical terminology is not entirely applicable to product development process. |

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| | | | The risk factors for concomitant diseases, such as cardiovascular, diabetic, transplantation, or immunological disturbances are not a subject of this GL.<br><br>The control of respective disease specific factors is reiterated in the Section of "Specific effects", including cross-reference to relevant disease specific guidelines. |
| 118-119 | 3 | The statements on claims represented by change in albuminuria or small changes in eGFR should be replaced to the endpoint discussion, section 4.3.2. | Not accepted.<br><br>The endpoints are perceived as the means to reach objectives. These two different topics are positioned separately. No changes are foreseen. |
| 126-132 | 3 | Comment:<br><br>The guideline distinguishes between **susceptible, initiation and progression factors**, which largely overlap. In line with the KDIGO guideline it is prosed to mention it by means of a more general description of the risk factors associated with CKD progression. Most important are cause of CKD, level of GFR, level of albuminuria, age, sex, race/ethnicity, elevated BP, hyperglycemia, dyslipidemia, smoking, obesity, history of cardiovascular disease, and ongoing exposure to nephrotoxic agents. | Partially accepted.<br><br>The primary purpose of GL is the facilitation of clinical development of medicinal product that is, although, overlapping, balancing the practicalities of routine patient care practice with the need for scientifically robust data, including distinguishing the risk factors before or during involvement of patient into the particular clinical trial that are useful for planning of the study.<br><br>As the susceptibility and initiation factors are more relevant |

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| | | | during the development for primary prevention indication, all three categories are relevant to secondary prevention indication. The text is amended accordingly. |
| 133-134 | 3 | Comment:<br><br>In general, patient inclusion in clinical studies should reflect the intended broad target population, but may be restricted, at least in initial studies, e.g., based on high risk profiling if properly justified.'' This comment is roughly repeated in the next sentence 135<br><br>Proposed change (if any):<br><br>This should be combined with the description given from line 135 on forward | Not accepted.<br><br>The omission of different approaches in initial vs final studies are not shared as they represent rather reasonable and usual way of product development. No change is introduced. |
| 137 | 3 | Comment:<br><br>"We suggest amending the following sentence: '' All products taken must be documented.''<br><br>Proposed change (if any):<br><br>''All ~~products taken must be~~ co-medication possible interfering with CKD progression should be appropriately documented.'' | Not accepted.<br><br>The proposal is risky. It is perceived important to consider not only medicinal products abut also other products (primarily, dietary supplements) and to consider not only those that are known interfering with CKD progression but also all other.<br><br>The text states that medicinal products that could affect the results during the study must be predefined or excluded if feasible. |

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| | | | This is reasonable approach not too omit the power to interpret the study results in case of various primary disease settings as well. No change is foreseen. |
| 143 | 3 | Comment:<br><br>The following sentence should be amended: ''Renal damage could be either pathological morphological abnormalities of the kidney, such as the presence of polycystic kidney disease or the presence of markers of renal damage''<br><br>Proposed change (if any):<br><br>''Renal damage could be ~~either~~ identified based on pathological morphological abnormalities of the kidney, such as the presence of polycystic kidney disease and/or the presence of markers of renal damage'' | Accepted. |
| 146-150 | 3 | Comment:<br><br>Reference is made to a 5 stage classification of chronic kidney disease. However, the recent KDIGO guideline (KI suppl., 2012) has amended this to use more than 5 stage criteria (1, 2, 3a, 3b, 4 and 5) as well as an albuminuria classification, acknowledging that both GFR level and albuminuria are both independent risk factor for kidney disease. In addition, attention has | Not accepted.<br><br>The clinical guidelines are beneficial complement to the regulatory ones that focus more on product development from a public health perspective. |

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| | | been given to the cause of the disease including personal and family history, social and environmental factors, medications, physical examination, laboratory measures, imaging, and pathologic diagnosis. However, a commentary workgroup of K/DIQO has published commentary on this guideline (Inker, AJKD, 2012). They consider it premature to add the cause of CKD to the classification scheme as there are currently no accurate methods to quantify risk based on cause of disease, although they acknowledge that some specific causes have been related to faster rate of CKD progression.<br><br>Therefore, the classification description has to be amended according to this updated information. | On the other hand, the rapidly changing lists of various factors and markers to be proposed for patient care are not necessary be applicable for medicines development purpose<br><br>The GL is already designed to represent these aspects in general with cross reference to updates. Similarly, the albuminuria is already included into the definition.<br><br>No change is necessary. |
| 170-174 | 3 | Comment:<br><br>As already mentioned, the conceptual approach of primary and secondary prevention should be further discussed, as it impacts the further discussion on the clinical endpoints. When primary prevention and secondary prevention is considered, this can impact the time for reaching the proposed endpoints. Generally, for patients with higher levels of GFR a longer follow-up time is foreseen. (See e.g. Greene AJKD 2014).<br><br>The use of the primary endpoints in primary | Partially accepted.<br><br>For the primary and secondary prevention concepts - the primary prevention is considered for the patient without any signs of renal disease but having risk factors to develop CKD, such as diabetes or hypertension.<br><br>In contrast, the secondary prevention is considered for already diseased patient that have already damaged kidneys. The concept is important for proper patient selection for drug development aimed to separate different risk levels. Thus, the routinely used clinical terminology is not entirely applicable to |

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| | | prevention or patients with high levels of GFR should be further discussed.<br><br>First of all, **slope analysis** is considered of major interest. Therefore, we would propose the following order of endpoints<br><br>- Difference in meaningful GFR loss rate, which should be clinically substantiated.<br><br>- Prevention of proteinuria/albuminuria (if applicable)<br><br>- CKD staging<br><br>However, combination of endpoints and further validation of individual endpoints should be discussed within the guideline. Choices for suitable endpoint(s) in a particular program should be thoroughly justified, as there is currently no academic consensus on what is the single most appropriate endpoint.<br><br>Endpoints focussing on CKD staging should however be used as supportive. They represent absolute changes (time to CKD3), which include a very broad interval of disease staging and thus is not considered a very precise defined endpoint. | product development process.<br><br>The wording is amended.<br><br>The order of endpoints is changed as far as the putting priority to the “GFR loss rate”:<br><br>For primary prevention:<br><br>*“The primary efficacy endpoint should be the prevention or slowing of decline in the level of renal function, defined as*<br>*- Clinically meaningful and stable GFR loss rate (measured either via slope or time to event analyses)*<br><br>*with or without one of co-primary endpoints, either*<br><br>*(a) Prevention of proteinuria/albuminuria or*<br>*(b) Time to occurrence of CKD 3 or*<br>*(c) Incidence rate of CKD 3 or higher*<br><br>*Alternatively these (a) to (c) endpoints should be considered* |

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| | | | *as key secondary."*<br><br>For the seceondary prevention:<br><br>"*The recommended primary endpoint is time to a predefined and justified loss in GFR, such as 50%.*<br><br>*...*<br><br>*In case of advanced or rapidly progressive disease all-cause mortality should be considered to be included as part of the co-primary endpoint*"<br><br>The proposals to mixing primary with secondary preventions concepts that are not endorsed (see comments above)<br><br>No further specific reasoning and proposals are provided. |
| 175-186 | 3 | Comment:<br><br>It is agreed that in case precise determination of GFR is considered essential, measured GFR (mGFR) is prioritised over estimated GFR (eGFR). However, this method is patient unfriendly and not routinely available because of the complexity of measurement protocols. EGFR is a more easy method and integrated | Partially accepted.<br><br>The comment is taken into consideration as well as the proposal to use measured GFR in a pre-specified subset of patients as a confirmatory test of the eGFR. |

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| | | in common clinical practice making **multiple measurements** more feasible. In particular, for multiple measurements during large trials eGFR is the method of choice as mGFR seems unfeasible to measure on such a large scale. eGFR equations provide more accurate estimates from serum markers than serum markers alone and can be used in some specific trials, but have serious limitations in some clinical circumstances. It is propagated to use measured GFR in a pre-specified subset of patients as a confirmatory test of the eGFR. Furthermore, the strengths and limitations of the used equation in the trial should be taking into account against the patient population studied. | |
| 182-183 | 3 | Comment:<br><br>The following sentence is not understood: ''due to great variability of non-GFR determinants of biomarkers employed for estimation '' | Not accepted.<br><br>Non-GFR determinants are generic term for the other than renal functioning related factors influencing the values of BM (such as changes in protein intake, immobilisation for creatinine or inflammation for Cystatin C) |
| 184-186 | 3 | Comment:<br><br>The following is described: ''eGFR using validated equations e.g. the Modification of Diet in Renal Disease Study Groups' (MDRD) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) may also be | Partially accepted.<br><br>The comment is taken into consideration as well as the proposal to use measured GFR in a pre-specified subset of patients as a confirmatory test of the eGFR. |

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| | | used to complement mGFR.''<br><br>See also the discussion on line 175-186. Which equitation to use should be justified by the company. | |
| 194-195 | 3 | Comment:<br><br>The following is described: ''The goals of secondary prevention in CKD are (1) to slow GFR decline, and (2) to reduce proteinuria/albuminuria. ''<br><br>These goals may be disputed, as we consider the main goal to slow the progression of kidney disease to delay or prevent the need for dialysis or renal replacement therapy and death. To reduce proteinuria and albuminuria may be one of the goals but not considered a primary goal in terms of clinical outcome. | Not accepted.<br><br>This GL sets the scene to test medicinal product faster than scene using “classical” way of progression of kidney disease, i.e., using typical hard endpoints mentioned only.<br><br>The approach taken is to use the functional marker (with an established injury marker albuminuria/proteinuria) as the main surrogate set for other hard endpoints. This approach has been used in several recent EU scientific advises already.<br><br>Furthermore, the relevance of changes observed during the intervention might be seen reasonably favourable for medicinal product development and even additionally explored in the clinical setting, further gathering data up to full set of hard endpoints. |
| 196-197 | 3 | Comment:<br><br>For secondary prevention the following is described on clinical endpoints to be used: ''The recommended | Not accepted. |

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| | | primary endpoint is time to a predefined and justified loss in GFR, such as 50%. Other (lower) magnitudes of proportions might be used, provided this magnitude is qualified for specific primary disease. The composite of all-cause mortality and renal loss (CKD 5D, see definitions) should always be reported and in case of advanced rapidly progressive disease should be considered as a co-primary endpoint with justified acceptance criteria.''<br><br>Recent discussion (FDA workshop 2012) and publications have suggested that lower levels than the 50% decline in GFR (roughly a doubling of serum creatinine) may be used in certain settings. These studies suggest that a 40% decline in GFR may be considered in certain circumstances in combination with ESRD provided that the robustness of this endpoint can be properly justified for the disease and treatment under investigation. A 30% decline in GFR may be more problematic to use, in particular when initial pharmacodynamic acute treatment effects may be present. A detailed understanding of the expected performance with regard to the trajectory of the GFR with the drug under investigation is deemed necessary for a good justification of the endpoint and design of the confirmatory phase 3 studies (e.g. initial drop in eGFR, proportionality of treatment effect). | See comment above.<br><br>Broad agreement to use lower than 50% GFR magnitudes is not reached for the entire CKD cluster. Although less controversies do exist in the area of DN and Hypertensive nephropathy, less data are available in case e.g., primarily immunologically driven diseases and ADPKD. Unless more justification is available the preferred option is to maintain current wording.<br><br>On the other hand, the proposal reflects several regulatory decisions made and might be reasonable on case-by-case basis.<br><br>As the field will evolve, the GL is intended to be updated.. |

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| | | It should be further discussed whether to include these recent discussions into the guideline. A formal position has not been taken on this either by the NKF/FDA or the clinical nephrology society in general. The clinical nephrology society is currently initiating efforts in investigating and reaching consensus on which endpoints are considered appropriate. A statement reflecting that endpoint definitions may be subject to change should be considered to be included. | |
| 198 | 3 | Comment:<br><br>We suggest to amend the following: ''… renal loss''<br><br>Proposed change (if any):<br><br>''… ~~renal loss~~ end stage renal disease'' | Partially accepted.<br><br>The term "renal loss" is replaced with "renal failure" |
| 200 | 3 | Comment:<br><br>The following is described: ''endpoint with justified acceptance criteria.''<br><br>It is not clear what is meant by justified acceptance criteria. Probably this refers to the appropriate use of statistical criteria for accepting the hypothesis proposed. This should be clarified. | Partially accepted.<br><br>The acceptance criteria are devoted to the lower magnitudes of GFR decline. This is clarified in the text. |
| 201-202 | 3 | Comment:<br><br>We propose to amend the following: ''Because of | Partially accepted. |

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| | | potential effects of differences in clinical treatment decisions on primary endpoints, sensitivity analysis should be planned''.<br><br>Probably, criteria definitions for end stage renal disease and the need for dialysis are meant here. Also, it should be considered to mention this under the section 4.4.4. Methodological considerations.<br><br>Proposed change (if any):<br><br>''Because ~~of potential effects of differences in clinical treatment decisions on primary endpoints~~ differences can occur in the decision to start dialysis, this may affect defining and meeting the endpoint an endpoint of end stage renal disease within a trial. Therefore, sensitivity analysis should be planned.'' | The sentence is extended providing the example, i.e., encountering various geographical approaches in starting renal replacement therapies or the considerations mentioned in Section 4.4.4 |
| 208-211 | 3 | Comment:<br><br>The guideline mentions the following as the first paragraph under the section of secondary endpoints ''Particular interest might be seen to report the benefit in the prevention of clinically relevant development or progression of newly developed complications of CKD. These could be evaluated by assessing the start of the first treatment episode(s) or by assessing the time point at which intensifying concomitant therapy(ies) is deemed necessary.'' | Partially accepted.<br><br>The list is not designed as one ranking the priorities and the ranking is the object of the particular development program. This is clarified in the text. |

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| | | These statements are not considered the **most relevant** in terms of which secondary endpoints to apply. We would recommend to replace this to a lower position in this section. In addition, these might be very exploratory as several other factors may interfere with this such as comorbidities, CIs, interactions, adverse events (tolerability). | |
| 221 | 3 | Comment:<br><br>The following is stated on cardiovascular evaluation: ''incidence and/or time to first cardiovascular events''.<br><br>Cardiovascular evaluation has not been given the appropriate attention in the guideline. There is a relationship between renal disease and cardiovascular endpoints. Elaboration on this relation may be worthwhile to discuss. In particular that any harm with respect to CV events should be excluded in certain CKD patients. Since this is a specific renal guideline, reference can be made to appropriate CV guidelines. | Partially accepted.<br><br>It is agreed that there might be both ways relationship between renal and the primary diseases, especially in case of cardiovascular disease. This is relevant in assessing the endpoints. Any harm with respect to primary disease events should be excluded in CKD patients. The respective guideline for primary disease should be taken into consideration. The text is amended accordingly. |
| 213-232 | 3 | The number of secondary endpoints as currently proposed is far too extended and should be prioterized. In this respect, time to occurrence of CV endpoints, death, ESRD, CKD staging, and albuminuria are considered the most important. | Not accepted.<br><br>The particular condition and the product might be the reason for certain different priorities in choosing secondary endpoints. The position is not to generalise the priorities for such an “umbrella” type guideline. |

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| 224-231 | 3 | Comment:<br><br>The guideline proposes to evaluate ***background therapy*** for e.g. blood pressure, dyslipidaemia, and treatment of metabolic acidosis. However, this may be affected by many factors such as alteration of diet, physical exercise etc. and seems complicated to evaluate. In addition, these might be very exploratory as several other factors may interfere with this such as comorbidities, CIs, interactions, adverse events (tolerability). It would be more relevant to **measure (laboratory) values** of BP, lipids, electrolytes etc. to have an understanding of the patients or population alterations in the background factors for CV and CKD progression and on safety parameters (hyperkalaemia, hypotension etc.). | Partially accepted.<br><br>To reflect the request, the text now highlights that for the background therapy considerations should be given to number of essential known risk factors for progression, including the "*measures to undertake in order to optimise background therapy for the treatment complications of CKD, such as dysregulated electrolyte/phosphate/ calcium* homeostasisNo universal recipe is envisioned. |
| 232 | 3 | Comment:<br><br>Quality of Life may be a relevant outcome in CKD patients, in particular in patients with severe CKD. Currently the guideline does not pay much attention to this outcome and the way this outcome should be assessed. Quality of life is of particular interest in patients at more severe stages of CKD. Validated questionnaires can be used to assess QoL to support the primary and other secondary analyses. | Not accepted.<br><br>QoL is included into GL already. There is no specific proposal ready to propose more for the time being. |

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| 237-239 | 3 | Statements on multiplicity is typically a subject to be discussed under Methodological considerations (section 4.4.4) | Accepted.<br><br>This is a general remark and is deleted as not specific enough. |
| 243 | 3 | Comment:<br><br>We suggest to amend the following: ''and it is assumed that the normal annual decline of GFR''<br><br>Proposed change (if any):<br><br>''~~and it is assumed that~~ while the normal annual decline of GFR'' | Accepted. |
| 245 | 3 | Comment:<br><br>We suggest to amend the following: ''risk for nephropathy development or CKD progression''<br><br>Proposed change (if any):<br><br>''risk for ~~nephropathy development or CKD progression~~ development or progression of CKD'' | Accepted. |
| 250-251 | 3 | Comment: The following is described: ''The characteristics of the population as regards the predicted acute/chronic GFR decline rate should be used to justify the choice of the endpoint and the | Not accepted.<br><br>The information is relevant to both exploratory and |

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| | | planning of the duration of the trial''<br><br>This information should be combined with the previous paragraph as the sentence in 245-246 is describing approximately similar information. See also next commentary.<br><br>In addition, this information should be mentioned under section 4.4.2. Exploratory trials. | confirmatory trials and this section is applicable to both types. |
| 252-270 | 3 | Comment:<br><br>This paragraph does not pay sufficient attention to the treatment effect with respect to the course of the GFR and the GFR slope. It is of particular interest to have a good understanding of this GFR pattern to have essential information for further confirmatory phase 3 study design, including understanding of the existence of an initial hemodynamic effect and the proportionality of the GFR slope. It is proposed to include this information. | Not accepted.<br><br>See comment above. |
| 255-256 | 3 | Comment:<br><br>We suggest to amend the following: ''renal insufficiency.''<br><br>Proposed change (if any): | Not accepted.<br><br>The GL focuses on both prevent development and slow progression. The change would not cover entire spectrum of conditions. Text not changed essentially. |

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| | | '' ~~renal insufficiency~~ progressive renal disease'' | |
| 257-259 | 3 | It is mentioned that the impact on PK of CKD should be taken into account during investigation of dose finding. However, unnecessary complex restrictions should not be applied to design of such studies, in particular when rare diseases are considered. | Not accepted.<br><br>PK considerations in renally excreted products are essential for proper exposure. In case if rare diseases, the issue might be solved by other mans that is out of the scope of this GL. Text not changed. |
| 265 | 3 | Comment:<br><br>''The same principles as outlined in Section 4.4.3 for the use of mGFR or eGRF.'' is referring to section 4.4.3, however this is only discussed under section 4.3.2. | Accepted. |
| 266-268 | 3 | Comment:<br><br>We suggest to amend the following: ''Other beneficial effects in qualified biomarkers for particular purpose, including substantially reduced urine albuminuria for diabetic nephropathy are reasonable options for exploratory purposes in relatively short term studies.''<br><br>Albuminuria has been identified as a risk factor for renal disease and cardiovascular disease in CKD. We would not suggest to consider assessment of albuminuria **just exploratory** as albuminuria may be in the causal pathway of chronic kidney disease. | Partially accepted.<br><br>Despite attractiveness to use the albuminuria as stand-alone endpoint the proposal to extent the albuminuria based endpoint outside the exploratory purposes (including dose finding) is questionable as this biomarker is not a universal and not validated yet for surrogacy of renal hard endpoints.<br><br>The notion to use albuminuria or other BM as supportive endpoints are agreed and supported. The text is amended accordingly. |

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| | | Supporting evidence of reduction of albuminuria in relation to the slowing of the progression of renal disease can be of interest, in particular when one can connect the dose dependent reduction of albuminuria to an associated protection in kidney disease. In this respect, a blood pressure independent mechanism to demonstrate reduction of albuminuria is of particular interest as the former has failed to demonstrate renal protection when blood pressure is substantially reduced (e.g. dual RAS blockade). Albuminuria may be used for dose finding during phase 2 evaluation **depending on the mechanism of action** of the drug under investigation and may be considered a supportive endpoint during phase 3 evaluating when a proof-of-concept of albuminuria reduction possibly leading to renal protection can be demonstrated. | |
| 269 | 3 | Comment:<br><br>The sentence ''use of pharmacodynamic markers, such as structural, functional, or immunological markers'' is not considered correct. For instance, a structural marker probably means a marker of structural damage to the kidney, while a pharmacodynamic marker implies a pharmacodynamic change to kidney function. Probably, pharmacological markers are meant here. | Not accepted.<br><br>The TKV could be an example of possible structural PD marker (considering the concept of pharmacodynamic changes as part of pharmacological ones). No changes introduced. |
| 272 | 3 | Comment:<br><br>The sentence 'New products are developed with the | Accepted. |

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| | | hope of prevention of loss of renal function'' should be rephrased to the following. In addition, such a sentence has been repeatedly given throughout the document, so deletion of the sentence may also be considered.<br><br>Proposed change (if any):<br>'New products are developed with the ~~hope~~ aim of prevention of loss of renal function' | |
| 296 | 3 | Comment:<br>As previously mentioned, a distinction between primary prevention and secondary prevention should not further discussed. | Not accepted.<br><br>See discussion above. |
| 298 | 3 | Comment:<br>''deterioration'' should be indicated more precisely<br><br>Proposed change (if any):<br>'' ~~deterioration~~ renal function decline'' | The level of baseline injury is an important factor (see discussion above). No change introduced |
| 300-301 | 3 | Comment:<br>''The study duration could be adapted based on the expected rate of progression and stage of CKD at | Partially accepted.<br><br>Terminology "adapted" is changed to "adjusted" to avoid |

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| | | entry.'' Is not entirely supported.<br><br>The word ''adapted'' suggests that study duration can be altered during the study, however study duration should be predefined. | confusions. |
| 304-331 | 3 | Comment:<br><br>The section on Methodological considerations is currently lacking typical methodological issues. For instance, sensitivity analysis of endpoints, GFR slope assessment (how to deal with the acute effect, mixed model use, missing data), interim analyses, multiplicity for secondary endpoints, confounding factors etc. have not been discussed. | Not accepted.<br><br>As no specific proposals for renal insufficiency development/progression are given, no further detailing are considered. |
| 324 | 3 | Comment:<br><br>The sentence "or ACE inhibitors in renal arterial bilateral stenosis'' is not considered entirely accurate. Stenosis it itself is already a risk factor for less renal perfusion. ACE inhibitors can be one of the contributing risk factor in this context. Therefore, we would propose to amend as indicated below.<br><br>Proposed change (if any):<br><br>'' ~~or ACE inhibitors in renal arterial bilateral stenosis~~ renal arterial bilateral stenosis'' | Not accepted.<br><br>The preference is seen to maintain the focus on therapy related factors as compared the disease related ones. Text not changed. |

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| 330 | 3 | Comment:<br><br>The following sentence ''Renal biopsies are of major importance for the proper diagnosis, e.g., of diabetic nephropathy in case of type 2 diabetes or chronic allograft nephropathy.'' may be relevant information, however, may be of less importance when conducting a clinical trial for such an indication. For instance, risk for ESRD and death for diabetic nephropathy is based on GFR and albuminuria quantification. In addition, as also mentioned in this document, the K/DIQO comments (Inker, 2012) indicate that the cause may not be relevant to predict the risk and level of GFR decline. | Partially accepted.<br><br>The text is clarified.<br><br>Renal biopsies are of major importance for the proper diagnosis of, in particular, many forms of primary or secondary CKD, e.g., in glomerular diseases, chronic allograft nephropathy.<br><br>The mechanistic and/or PoC studies would benefit from precise diagnosis in case of mixed co-morbidity and or anamnesis (primarily, in case of primary hypertension that is not a rare event in case of type 2 diabetes). |
| 347-349 | 3 | Comment:<br><br>We suggest to amend the following: ''Confirmatory studies should reflect this and generally there should be no restriction because of old age and a sufficient number of elderly should be included (Studies in support of special populations: geriatrics – CPMP/ICH/379/99 (ICH E7)).''<br><br>Proposed change (if any):<br><br>''Confirmatory studies should ~~reflect this and generally~~ | Partially accepted.<br><br>Text is simplified. |

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| | | ~~there should be no restriction because of old age and a~~ include a sufficient number of elderly ~~should be included~~ patients without any restrictions to the upper age limit. (Studies in support of special populations: geriatrics – CPMP/ICH/379/99 (ICH E7)).'' | |
| 351 | 3 | Comment:<br><br>We suggest to amend the following: ''are both important in this group''<br><br>Proposed change (if any):<br><br>''are both important considerations in this age group.'' | Accepted. |
| 353-362 | 3 | Comment:<br><br>A statement should be considered to exclude a detrimental effect on mortality based on a sufficiently large database. It should be justified when such a large database in terns of safety seems not feasible. | Not accepted.<br><br>No specific to renal indications proposals for the detrimental effect is proposed in addition to ones mentioned in section 4.3.3 (patient survival). No change in this section. |
| 354-356 | 3 | Comment:<br><br>We suggest to amend the following: ''Safety is normally assessed based on treatment-emergent adverse events, the results of routine clinical laboratory tests and vital sign measurements at time intervals relevant for particular rate of decline of renal function and type of medicinal product under | Not accepted.<br><br>The proposal would diminish specificity in guidance document and the rationale not understood. No change in this section. |

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| | | evaluation.''<br><br>Proposed change (if any):<br><br>''Safety is normally assessed based on treatment-emergent adverse events, the results of routine clinical evaluation, laboratory tests and vital sign measurements at relevant time intervals ~~relevant for particular rate of decline of renal function and type of medicinal product under evaluation~~.'' | |
| 367-369 | 3 | Comment:<br><br>We suggest amending the following: ''In order to detect changes early the validation/qualification of new and existing candidate biomarkers, such as Kidney injury molecule 1 (KIM-1) or Neutrophil gelatinase-associated lipocalin (NGAL), is encouraged.''<br><br>Proposed change (if any):<br><br>''~~In order to detect changes early the~~ It is encouraged to ~~validation/qualification~~ validate/qualify ~~of~~ new and existing candidate biomarkers for early safety signals, such as Kidney injury molecule 1 (KIM-1) or Neutrophil gelatinase-associated lipocalin (NGAL)~~, is encouraged~~ No such biomarkers have currently been validated.'' | Partially accepted.<br><br>The linguistic proposals are acceptable.<br><br>The validation status is not intended to be mentioned as the process is rapidly changing. |

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| 367-368 | 3 | Comment:<br><br>An additional discussion in section 4.4.2 should be included on the use of novel biomarkers to apply for proof of concept in renal disease. For instance, information is lacking on biomarkers used for assessing inflammatory processes involved in the progression and development of renal disease. | Not accepted.<br><br>The intention is to include all known biomarkers and the processes. No change in this section. |
| 375 | 3 | Comment:<br><br>This should be numbered with section 5. See also line 39. | New template is introduced |
| 376-383 | 3 | Comment:<br><br>Definitions for CKD staging has been discussed under line 146-150. Amendments in this section are needed accordingly. | Not accepted.<br><br>The clinical guidelines are beneficial to the regulatory ones that focus more on product development as compared to daily patient care.<br><br>The rapidly changing lists of various factors and markers are not intended to be repeated each and every time when clinical guideline is updated.<br><br>The GL is already designed to represent these aspects in general with cross reference to updates. Similarly, the albuminuria is already included into the definition. |

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| | | | No change is necessary. |
| 391-392 | 3 | Comment:<br><br>The following is not understood: ''For consideration of therapy for diabetic kidney disease, development and worsening of proteinuria was also included in the definition of progression of renal disease.'' | Partially accepted.<br><br>The text addresses the content in the section 4.3.2 (previous template). As the text is not an essential for definition, it is deleted. |