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Guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency

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Guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency

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Executive summary

The aim of this guideline is to provide guidance on the clinical development of compounds used to prevent the development and to slow the progression of chronic renal insufficiency.

The main focus of the guideline is on the different potential claims/indications in relation to the kidney disorder (i.e., primary and secondary prevention), description of study populations including prognostic factors for the evolution of the kidney disorder and study objectives and endpoints.

Recommendations are given regarding assessment methods to be used in relation to selected endpoints, strategy and design of clinical trials, criteria for the choice of comparator, study duration, factors confounding the interpretation of study results, specific aspects to be considered for paediatric and elderly patients, and for safety assessment, focusing on overlapping safety signals and encouraging broader exploration of more sensitive tools, namely biomarkers.

This document is intended as general guidance and should be read in conjunction with other relevant EU and ICH guidelines (see Section 3 'Legal basis'). Due to ongoing developments in this field, frequent revisions and amendments are foreseen.

1. Introduction (background)

Renal insufficiency is the result of acute and/or chronic, pathophysiologic processes and has a major impact on public health.

Several medicinal compounds have been licensed or are under development with the aim to slow or prevent renal disease progression. Although renal insufficiency and ESRD could be preceded by either acute or chronic kidney damage, this document is predominantly devoted to prevention and/or slowing of progression of chronic kidney damage (Chronic Kidney Disease (CKD) see Section 5 "Definitions").

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. Due to the diversity of the underlying conditions ranging from common conditions such as hypertension and diabetes to less common diseases such as AA amyloidosis, nephrotic syndrome, primary membranoproliferative glomerulonephritis or polycystic kidney disease, this guideline is meant to serve as an adjunct to disease specific guidelines where available and will focus on renal specific topics.

In general, CKD can be associated with a number of biomarkers representing both renal damage (such as active urinary sediment, proteinuria/albuminuria, or leakage markers) and functional status (primarily failure to filtrate plasma as well as to absorb primary urine, secrete hydrogen ions, endogenous substances, contribute to endocrine function i.e., erythropoiesis and phosphorus metabolism). As the initial decline in renal function is asymptomatic, and clinical manifestations of renal insufficiency occur later in the course of the disease, definitions of kidney disease have therefore focused on measures of function (glomerular filtration rate, GFR) and measures of damage, such as proteinuria and morphological abnormalities.

The main focus of the guideline is on the claims/indications in relation to the kidney disorder, description of study populations, prognostic factors for the evolution of the kidney disorder and endpoints in relation to the objectives of treatments. Also discussed are recommended assessment methods to be used in relation to selected endpoints, factors confounding the interpretation of study

results and specific aspects to be considered in paediatric or aging developments related to renal insufficiency.

2. Scope

The aim of this document is to provide guidance on the conduct of clinical studies with medicinal products intended to prevent or slow progression of chronic renal insufficiency by defining treatment goals, study designs, outcome measures and data analyses.

The main therapeutic goal is expected to be achieved by a preventive regimen that 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. The current major regulatory experience has been gained with medicinal products developed in various chronic kidney diseases, such as diabetic nephropathy, hypertensive nephropathy and chronic renal allograft dysfunction. With respect to adaptation of the development program to other conditions such as acute kidney injury and regenerative medicine it is advisable to follow the relevant guidance available and seek European scientific advice prior to the initiation of confirmatory studies.

3. Legal basis

This document should be read in conjunction with Directive 2001/83/EC, as amended and relevant provisions of Regulation (EC) No 141/2000 on orphan medicinal products as well as Regulation (EC) No 726/2004.

In addition, relevant general and disease-specific CHMP guidelines should be taken into account. These include but are not limited to:

- Dose-Response information to Support Drug Registration – CPMP/ICH/378/95 (ICH E4);
- Studies in support of special populations: geriatrics – CPMP/ICH/379/99 (ICH E7);
- Clinical investigation of medicinal products in the paediatric population – CPMP/ICH/2711/99 ICH E11);
- Points to Consider on Multiplicity Issues in Clinical Trials - CPMP/EWP/908/99;
- Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function - CHMP/EWP/225/02.

4. Clinical investigation of medicinal products to prevent/slow progression of chronic renal insufficiency

4.1. Objectives

Prevention or slowing of the progression of renal insufficiency is a management priority in CKD. Two different objectives of therapy can be foreseen that would support a specific therapeutic claim:

- Primary prevention: This scenario describes the prevention of chronic kidney disease in a population with an increased risk but without demonstrable signs of chronic kidney disease.
- Secondary prevention: This scenario encompasses the slowing of progression of chronic kidney disease in patients with existing signs of chronic kidney disease.

It is not expected that additional claims representing only limited aspects of renal pathology tested, such as proteinuria only or small changes in GFR values only would be acceptable as an independent

indication or constitute an independent part of the indication. These clinically relevant benefits could be reflected in Section 5.1 of the SmPC.

4.2. Subject characteristics and selection of subjects

It is acknowledged that there is no consensus with regard to the importance of every individual risk factor for CKD and how to define cut-off levels for increased risk, but the following categories should be considered:

- Susceptibility factors, increasing susceptibility to renal damage, such as older age, family history, and race.
- Initiation factors, directly initiating renal damage, such as diabetes, high blood pressure, specific autoimmune disease, and others such as nephrotoxic medicines.
- Progression factors, causing worsening of renal damage and faster decline in renal function after initiation of renal damage, such as high level of proteinuria, high blood pressure, poor glycaemic control, nephrotoxic medicines or hypovolemia.

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.

The study population should be representative of the target population and be characterised at baseline with respect to risk factors for the development or progression of renal insufficiency, co-morbidities and co-medication used. All products taken must be documented. Medicinal products that could affect the results during the study must be predefined or excluded if feasible. Documentation of the diagnostic criteria is required. The impact of differences in risks for disease progression between study groups should be considered and minimised as far as possible.

For CKD, laboratory and clinical data are needed to define the presence of renal damage for at least 3 months. 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, such as proteinuria/albuminuria, or GFR less than 60 ml/min/1.73 m2 without any other evidence of renal damage.

Clinical guidelines also define a five-stage system for classification of CKD (see section 5 „Definitions“). The staging system represents the increasing azotaemia burden as GFR declines and recognizes the common manifestations of reduced renal functions including anaemia and hyperparathyroidism that can occur independently of the aetiology of the underlying kidney disease (e.g. diabetic nephropathy, glomerulonephritis, or hypertensive nephrosclerosis).

Enrolment of patients in clinical studies is expected to be governed by region specific policies and practices (such as starting renal replacement therapies earlier than at CKD 5, employing different pre-emptive transplantation policies). Consideration should therefore be given on representativeness of the population for the EU and on consequences for trial design (e.g. stratification).

4.3. Methods to assess efficacy criteria

4.3.1. General considerations

The ultimate aims of prevention or slowing progression of renal insufficiency in CKD are preserved kidney function, improved renal and overall survival. The particular aim for development of the medicinal product for early, middle, and late stage disease might be different but should be

representing the relevant clinical burdens to be managed. The goals of development of new medicinal products for prevention or for slowing progression of renal insufficiency are:

- To demonstrate superiority compared to standard of care (may include active comparator) or placebo, where justified.
- To demonstrate non-inferior efficacy compared to an authorised active comparator

These could be sought for primary or secondary prevention of progression to renal failure.

4.3.2. Primary endpoints

Primary prevention

The primary efficacy endpoint should be the prevention or slowing of decline in the level of renal function, defined as either

- Time to occurrence of CKD 3 or

- incidence rate of CKD 3 or higher or

Clinically meaningful and stable difference in of GFR loss rate (see also Section 4.4.1)

with or without

- Prevention of proteinuria/albuminuria

Serum creatinine measurement and estimated GFR (eGFR) was used in a number of trials to assess renal function and could also be accepted in future trials, However, this method is less accurate and more variable than measured GFR (mGFR) using clearance of exogenous substances (iohexol, iothalamat or other validated markers). In the event that eGFR is used for the assessment of renal function all confounders generating creatinine variability and their influence on data interpretation need to be taken into account. Whenever precise determination of GFR is considered essential, such as when the expected decline in GFR is 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 measured GFR (mGFR) is prioritised over estimated GFR (eGFR). 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 used to complement mGFR.

Proteinuria should be assessed quantitatively using a timed (e.g. 24 hours) or untimed (spot) urine collection to measure albumin-to-creatinine ratio (ACR) or protein-to-creatinine (PCR). To account for diurnal variation the untimed urine specimen should be collected on first morning samples. ACR is preferable to PCR, particularly at lower levels of proteinuria. A timed urine sample should be done after positive ACR/PCR results 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.

Secondary prevention

The goals of secondary prevention in CKD are (1) to slow GFR decline, and (2) to reduce proteinuria/albuminuria.

The recommended 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.

Because of potential effects of differences in clinical treatment decisions on primary endpoints, such as the start of dialysis, sensitivity analyses should be planned. Depending on the trial design additional evaluations of the outcome measures should be planned, e.g. independent blinded reviewers should assess the outcomes of an open trial and this should be performed following pre-defined rules. In cases where there is lack of concordance between independent reviewers a centralised blinded adjudication panel should decide on the outcome for such cases.

4.3.3. 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. The utility of these endpoints to serve as primary endpoint is currently not deemed sufficiently validated

The following secondary endpoints for primary and secondary prevention should be considered:

- Renal function at different time points e.g., 6, 12, 24 months, 3 and 5 years;
- Proteinuria, the frequency of measurement should be determined by the study aims and the agent being used (e.g. every 2 to 3 months for those with nephrotic-range proteinuria and every 6 months for those with subnephrotic proteinuria);
- Time to reach different CKD stages representing progression of renal damage;
- Renal survival at different time points, with reasons for renal loss;
- Patient survival at different time points, with reasons for death;
- Incidence and/or time to first cardiovascular event;

Other clinically relevant endpoints to be considered in CKD population:

- Incidence and/or time to second cardiovascular event;
- Incidence and/or time to first episode / intensified antihypertensive therapy;
- Incidence and/or time to first episode / intensified dyslipidaemia therapy;
- Incidence and/or time to first episode / intensified anaemia therapy;
- Incidence and/or time to first / intensified bone and mineral dysmetabolism therapy;
- Incidence and/or time to first / intensified metabolic acidosis therapy;
- Incidence and/or time to malnutrition;
- Incidence and/or time to first / intensified sodium and water restriction therapy;
- Incidence and/or time to first / intensified hyperkalaemia therapy;
- Quality of life (QoL) outcome.

All criteria to start the first episode or to intensify the concomitant therapy can be influenced by different subjective investigators' judgement. In order to facilitate the interpretation of those data and to avoid biases, predefined criteria should be specified in a protocol and the compliance with these criteria should be monitored.

In case claims related to a secondary endpoint are foreseen, care should be taken to correct for multiplicity in the statistical analysis (Points to Consider on Multiplicity Issues in Clinical Trials - CPMP/EWP/908/99).

4.4. Strategy and design of clinical trials

4.4.1. General considerations

The level of renal function tends to decline progressively over time in most patients with CKD. The GFR loss in CKD is typically 2 to 5 ml/min per year and it is assumed that the normal annual decline of GFR is about 0.5-1 ml/min per year.

The rate of GFR decline should be estimated in patients with risk for nephropathy development or CKD progression in order to predict the time for progression to the next CKD stage. Ideally, the rate of GFR decline should be predicted either by (i) computing the GFR decline from past and on-going measurement of serum creatinine or (ii) determining risk factors for faster (>5 ml/min/1.73 m^2 per year) versus slower GFR decline.

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 planning of the duration of the trial.

4.4.2. Exploratory trials

In addition to the usual dose finding studies to be performed during any medicinal product development (Dose-Response information to Support Drug Registration – CPMP/ICH/378/95 (ICH E4)), several special considerations are needed in developing a medicinal product for an indication in renal insufficiency.

The strategy for dose-finding should take into consideration the possible impact of changes in PK in different CKD stages (see also Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function - CHMP/EWP/225/02). Dose-finding studies should be preferably performed in a parallel, fixed-dose design, using a sufficient number of dose levels. The use of controls is recommended (placebo if possible); background therapy should be best standard of care regimen acceptable from a clinical perspective.

In addition to the endpoints listed in section 4.3.3, other efficacy criteria could be tested, such as clinically relevant delay of milder renal function loss (e.g., loss of 30% or 20% in eGFR). The same principles as outlined in Section 4.4.3 for the use of mGFR or eGFR apply for trials in the exploratory setting. 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.

Use of pharmacodynamic markers, such as structural, functional, or immunologic markers is encouraged.

4.4.3. Confirmatory trials

New products are developed with the hope of prevention of loss of renal function in case of renal damage of certain aetiology. Other products would be intended for renal damage of diverse aetiologies and separate confirmatory studies might be required.

Most clinical trials are designed to compare the efficacy or safety of a new regimen with a well-established standard therapy. Comparative trials should be designed as randomised, parallel group, double blind studies according to the aims of product development:

(A) To substitute one or several therapeutic components of well-established regimens preventing or slowing progression of renal insufficiency and thus improving efficacy, safety or compliance; this may include new concepts of treatment or

(B) As add-on to improve efficacy of a well-established regimen.

In case non-inferior efficacy against well-established medicinal products has been demonstrated safety data should be reassuring to exclude a disadvantage, however a different safety profile could also be regarded as advantageous. In this case, the clinically relevant safety endpoints should be prospectively defined and may be dependent on the type of established medicinal product and the underlying disease. The study duration should be sufficient to cover an adequate number of the targeted events.

Choice of comparator

The choice of comparator(s) and dosage will depend on the indication sought, type of renal disease and risk of progression of renal insufficiency. If an approved regimen already exists, comparison with that regimen is strongly recommended. In the absence of approved regimen for a given indication or where the standard clinical practice is use of a non-approved regimen, best standard of care should be employed.

With respect to the choice of non-approved comparator(s) at the European level, it is advisable to seek European scientific advice with respect to the choice of comparator(s) prior to the initiation of confirmatory studies.

Study duration

For primary prevention the study duration should normally be based on the predicted rate of deterioration and the baseline GFR of the cohort selected at entry (see also the Section 4.4.1). It is expected that studies in primary prevention might require a substantial time.

For secondary prevention, the same general principles as for primary prevention apply; the study duration could be adapted based on the expected rate of progression and stage of CKD at entry. In the case of slowly deteriorating CKD, focusing on moderately or severely impaired renal function might be necessary for the initial development.

4.4.4. Methodological considerations

Known and unknown factors besides the actual treatment might impact on study results. Risk of progression of renal insufficiency and region specific standards of care (see above) are factors often considered to be of major importance in the design of clinical studies.

In addition, for non-specific management of CKD the adequacy of treatment of the primary disease is important and should be considered in the design of the study. This can include the following:

- Glycaemic control;
- Control of blood pressure;
- ACE inhibitor/ARB therapy;
- Statin treatment;
- Avoidance of DHP calcium channel blockers unless needed for blood pressure control;

- Control of protein intake;
- Monitoring of proper fluid balance, avoidance of dehydration;
- Measures to undertake in order to optimise background therapy for the treatment complications of CKD, such as dysregulated electrolyte/phosphate/ calcium homeostasis.

CKD patients may require reassessment if renal function suddenly declines faster than predicted during follow-up; the main possible causes to be considered are dehydration (including over-diuresis or insufficient fluid intake, diarrhoea, or vomiting), nephrotoxic medicines (NSAIDs, and some specific medicines with nephrotoxicity, such as chemotherapy agents), disease relapse, disease acceleration, infection, obstruction, and compromised renal perfusion (primarily due to heart failure, myocardial infarction, tachyarrhythmias, or ACE inhibitors in renal arterial bilateral stenosis).

Certain types of kidney disease may undergo complete remission in a substantial number of patients, e.g., idiopathic membranous nephropathy and primary focal segmental glomerulosclerosis.

These factors should be reported and the most important confounding factors should be identified and taken into consideration, by proper stratification of the randomisation and / or inclusion of these factors into the analysis model.

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.

4.5. Studies in special populations

Paediatric population.

The medicines development plan in the paediatric population and the appropriate timing for conducting clinical investigation should be determined on a case-by-case basis. The specific clinical aspects should be detailed by age category in the Paediatric Investigation Plan (see also Clinical investigation of medicinal products in the paediatric population – CPMP/ICH/2711/99 ICH E11).

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 estimation (2009).

Elderly population

Older age is an important risk factor in CKD and the age of transplant recipients is increasing. 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)). The accurate measurement of renal function (using age-specific reference ranges) and optimal management of concomitant diseases (e.g. cardiovascular disease, diabetes mellitus, renal bone disease) are both important in this group.

4.6. Clinical safety evaluation

4.6.1. General considerations

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 evaluation.

Subjects who are expected to have progression of renal insufficiency are required to receive long-term observation and treatment with renoprotective medicinal products. Data obtained from long-term studies are therefore essential, including treatment of renal insufficiency progression after acute kidney injury.

Subjects included in pivotal clinical trials should reflect the target clinical population in terms of renal disease and co-morbidities.

4.6.2. Specific adverse events

Risks of nephrotoxicity, arising due to either the medicinal product under investigation or due to concomitant baseline therapy should be carefully evaluated profiling the magnitude and time to specific nephrotoxicity events thus enabling to assess the tolerance level and the impact on the indication claimed. 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.

Overlapping safety signals (such as de novo diabetes mellitus induced by medicinal product , hyperlipidaemia, nephrotoxicity, cardiovascular complications, wound healing complications or other known adverse effects of concomitant immunosuppressants developed for chronic allograft nephropathy or due to disease progression) should be specifically investigated enabling to distinguish these effects from the natural cause of the disease.

Definitions

Chronic kidney disease (CKD) - renal damage or glomerular filtration rate (GFR) below 60 ml/min per 1.73 m2 for 3 months or more, irrespective of the cause. The original CKD classification is based as per Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines that have classified CKD into five stages. Briefly, the stages 1 and 2 are defined by the presence of markers of renal damage and distinguished from each other by the absence (GFR >90 ml/min/1.73m2, or stage 1) or presence (GFR 60-89 ml/min/1.73m2, or stage 2) of mildly reduced GFR. Stages 3 to 5 are based solely on the level of GFR: 30-59 ml/min/1.73m2, or stage 3, 15-29 ml/min/1.73m2, or stage 4; and <15 ml/min/1.73m2, or stage 5. Dialysis stage is noted as Stage 5D.

Other relevant updates, such as KDIGO or NICE modifications could be considered where relevant.

Progression of kidney disease - either a (1) decline in the level of kidney function, estimated by measuring GFR or creatinine clearance, in a patient who has been followed longitudinally with reliable (and comparable) assays of renal function, or (2) onset of renal failure, defined by initiation of renal replacement therapy, either for symptoms or complications of decreased renal function. Renal replacement therapy includes haemodialysis, peritoneal dialysis or renal transplantation. Term “renal insufficiency” is applied for any deterioration of normal and age related kidney function.

For consideration of therapy for diabetic kidney disease, development and worsening of proteinuria was also included in the definition of progression of renal disease.