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Reflection paper on regulatory requirements for the development of medicinal products for Acute Kidney Injury (AKI)

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Table of contents

1. Introduction

Acute kidney injury (AKI) is a clinical syndrome, which presents itself as an acute loss of renal function and can occur based on different aetiologies and as part of different clinical settings.

AKI can have significant clinical short to long-term consequences. Furthermore, there is currently limited progress in submitting and consequently approving medicinal products in this field. Therefore, any medicinal product that can efficiently and safely prevent and/or treat AKI would potentially address an unmet medical need.

Currently, there is no specific regulatory guidance in the development strategies for the prevention and/or treatment of AKI. However, there could be an overlap with the recommendations in the clinical guideline on sepsis, based on the clinical setting and patient population(s) selected.

2. Scope

This reflection paper aims to provide high level guidance about developing medicinal products for the prevention and treatment of AKI, based on current regulatory experience in conjunction with currently available scientific research and knowledge in this area. Due to the limited regulatory experience in the development of medicinal products for prevention and treatment or AKI so far, detailed recommendations are limited, or not yet possible, depending on the specific aetiology of AKI.

3. Relevant guidelines

This document should be read in conjunction with the introduction and general principles of the Annex I to Directive 2001/83/EC as amended, and with the following guidelines:

- Guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency (EMA/CHMP/500825/2016)
- Guideline on the clinical investigation of medicinal products for the treatment of sepsis (CHMP/EWP/4713/03)
- Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis (EMA/CHMP/51230/2013 corr. 1)
- Guideline on clinical investigation of immunosuppressants for solid organ transplantation (CHMP/EWP/263148/06)
- Guideline on clinical investigation of medicinal products in the treatment of patients with acute respiratory distress syndrome (EMEA/CPMP/EWP/504/97 Rev 1)
- Guideline on Points to consider on application with 1. Meta-Analyses; 2. One Pivotal Study (CPMP/EWP/2330/99)
- Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design (CHMP/EWP/2459/02)
- Reflection Paper on establishing efficacy based on Single Arm Trials submitted as pivotal evidence in a marketing authorisation (CHMP/564424/2021)
- Note for Guidance on General Considerations for Clinical Trials (CHMP/ICH/291/95, ICH E8 (R1))
- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95, ICH E6)

- Note for Guidance on Dose Response Information to support Drug Registration (CPMP/ICH/378/95, ICH E4)
- Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96, ICH E9)
- Note for Guidance on Choice of Control Group for Clinical Trials (CPMP/ICH/364/96, ICH E10)
- EC 2008 "Ethical considerations for clinical trials on medicinal products conducted with the paediatric population"
- ICH Guideline E11A on paediatric extrapolation
- Structured guidance on the use of extrapolation (EMA/CHMP/13622/2022)
- EMA/CHMP/458101/2016 Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling 5 and simulation
- ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017)

4. Discussion

4.1. General considerations

Differentiation between the prevention of AKI and the treatment of AKI is of relevance. The proposed target indication for the medicinal product being developed should be clear with respect to prevention or treatment of AKI, as this can have important implications for the clinical development strategy of the medicinal product.

The cause of AKI can be divided into pre-renal, renal, and post-renal. The categories of AKI mostly relevant for development of medicinal products include cardiovascular surgery associated AKI (CSA-AKI) and sepsis associated AKI (SA-AKI).

The Kidney Disease Improving Global Outcomes (KDIGO) definition is leading and globally accepted in diagnosing and staging of AKI. However, this general definition can have limitations in a specific development programme for a particular AKI setting, and alternatives to this definition may be used if appropriately scientifically justified. Furthermore, patients with AKI have an increased risk of chronic kidney disease (CKD) or worsening of underlying CKD, and this may reflect the continuum of a pathophysiological process.

4.2. Selection of patient population(s)

Selection of patients for studies in the prevention and/or treatment of AKI should be appropriately justified with respect to AKI category, including those mentioned in section 4.1.

Strategies can include selection of patients based either on established risk factors for AKI (e.g., older age, CKD, diabetes etc.) or validated and justified risk scores for AKI. The patients included in the trials should generally be representative of the target population. Stratification according to important risk factors and/or the pathophysiological concept may be needed and should be justified. In order to ensure applicability of results to the European population, the standard of care should be sufficiently representative of European practice, independent of dominating region(s) involved in study conduct.

There is a fast-growing knowledge and scientific evidence on the use of newly developed biomarkers to identify patients at increased risk of AKI, or to identify patients based on a shared pathway of development of AKI, regardless of the aetiology of the syndrome. Any strategies using biomarker(s)

(profiles) could be applied, both in a prevention setting and treatment setting. However, in the absence of a formally qualified biomarker (or set of biomarkers) for the context of use of interest, the use of a particular biomarker to identify the appropriate patient population should be appropriately justified. Understanding of the pathophysiology and the mechanism of action of the medicinal product are important factors in justifying a particular strategy.

If, based on a biomarker set, a specific patient phenotyping is selected as needed for optimal effect of the medicinal product, this should be appropriately reflected in the indication. Any extrapolation to a broader population should be duly justified. Furthermore, specific requirements for the biomarker need to be demonstrated and justified, such as the clinical relevance of the use of the biomarker to select the appropriate patient phenotype for treatment with the medicinal product (e.g., as a companion diagnostic).

4.3. Study design and endpoints

4.3.1. Phase 2 studies

Any phase 2 studies should be designed to retrieve information on efficacy and safety effectively, in order to be able to subsequently optimally design the confirmatory phase. Critical elements are e.g., the population to be included, posology, selection of endpoint(s) (measurements), timing of intervention and follow-up time.

The primary endpoint should be sensitive enough to distinguish the potential difference in treatment effect between the evaluated doses and to determine the appropriate therapeutic dose range. It is not necessarily required that the primary endpoint at this stage will also be the primary endpoint in the phase 3 studies; however, any link to clinically relevant endpoints is preferred. Furthermore, if the primary endpoint differs between phase 2 and phase 3 studies, it is highly recommended to include the planned phase 3 endpoint in phase 2 trial as an additional endpoint.

4.4. Confirmatory phase 3 studies

4.4.1.1. General study design

Apart from standard clinical management including e.g., hemodynamic control, there are currently no medicinal products specifically licensed for treatment or prevention of AKI across different categories of AKI. Therefore, a randomised double-blind placebo-controlled clinical study is likely to be the most preferrable study design. Nevertheless, patients should receive adequate background therapy in accordance with guideline recommendations and the use of such therapy should be carefully documented in the study protocol. If decisions to change background medication are allowed to be made and implemented after randomisation, these changes should be regarded as intercurrent events and appropriately addressed in line with the scientific question of interest.

Since experience and positive clinical programmes are very limited and any (recently) licensed products are not available, evidence based on a single pivotal confirmatory trial is not likely to be accepted unless further justified.

4.4.1.2. Study endpoints

Endpoints should be carefully selected based on the mechanism of action, expected clinical effect and possible consequences in relation to the indication being sought.

As a general rule, any treatment effect on the chosen primary endpoint should be supported by an adequate understanding of the treatment effect over time. Selection of a co-primary endpoint or a key secondary endpoint at a different time point could be part of such support. Furthermore, clinically relevant other endpoints are important to accommodate for further understanding of the treatment effect. However, such endpoints should be carefully selected in relation to the clinical relevance for the proposed target population, underlying pathophysiology and believed mechanism of action of the medicinal product. Patient reported outcomes can be important and of clinical relevance but are not considered suitable as primary endpoint(s).

The endogenous filtration marker creatinine is most widely used and currently the best available follow-up marker for renal function. The most accurate method of renal function estimation available should be used. In this context, any potential pitfalls using this endogenous filtration marker in relation to the method being used to estimate renal function should be appropriately addressed, e.g., stability of the marker over time, possible muscle mass alterations or volume status, etc. The use of any alternative proposed marker to evaluate renal function should be appropriately justified.

Evaluation of novel biomarkers is encouraged but is currently not considered appropriate for key efficacy or safety evaluation. Also, risk scores are generally not acceptable to evaluate the key treatment effect in the confirmatory phase in absence of demonstrated robust correlations to clinically relevant treatment outcomes (see below). However, these can be helpful in the evaluation of treatment effect in a phase 2 exploratory setting, or, possibly, as a supportive endpoint during phase 3 trials.

Major Adverse Kidney Events (MAKE) can be considered suitable as an endpoint for the evaluation of several different AKI categories (see section 4.3.3). Such composite endpoint can include the components of a certain level of eGFR decline, receipt of new renal replacement therapy (RRT) and all-cause mortality. However, no strong consensus exists on the exact (percentage) level of eGFR decline recommended to be included as part of this composite endpoint. In general, minimal changes are considered of less clinical relevance while likely to drive increasingly the composite event rate. The chosen level of change in eGFR should be justified, and other complementary analyses using greater percent changes should be planned. At least a 90-day follow-up period is recommended for efficacy evaluation as this is in the continuum of the renal pathophysiological process generally recognised as the time of translation from an acute to a more chronic phase. However, any earlier time point for the primary endpoint may need to be justified. In any case, 3-months and preferably 6-months data should support the primary endpoint(s). Furthermore, components of the MAKE endpoints should demonstrate directional concordance and preferably comparable contribution to any possible beneficial treatment effect demonstrated by the composite, in order to avoid challenges in interpretation of the efficacy results. The totality of data (including the outcome of secondary and exploratory endpoints) is important to demonstrate the robustness of the treatment effect and to understand the treatment effect over time.

When a definition of "renal recovery'' is being proposed, similar considerations will apply. Furthermore, a proper retrieval of an accurate baseline eGFR level is of importance. There is no strong consensus on the method being used to set this baseline level.

4.5. Aetiology

4.5.1.1. Sepsis associated AKI (SA-AKI)

The current effective guideline on sepsis (Guideline on the clinical investigation of medicinal products for the treatment of sepsis (CHMP/EWP/4713/03)) reflects the basic principles in design and endpoints relevant for evaluation of the treatment effect in this clinical setting. In contrast to the sepsis

guideline, in the current setting, other outcome measures than that of mortality might be acceptable as primary endpoints. In such case, the use of a primary endpoint of MAKE could be reasonable. The considerations with respect to follow-up and interpretation of the MAKE endpoint are described under the section *"Endpoints"*. Mortality is considered an important component of the primary endpoint and should be included as a secondary endpoint. In this context, a detrimental effect needs to be excluded at an adequate level of precision.

Regulatory experience on development programmes of medicinal products for the prevention of AKI in patients with sepsis are currently not available. In this circumstance, it is recommended to seek scientific and regulatory advice.

4.5.1.2. Cardiovascular surgery associated AKI (CSA-AKI)

In a prevention of AKI setting, the occurrence of sustained GFR decline is the most clinically relevant endpoint to be evaluated. A reasonable balance should be applied between the use of clinically relevant endpoints and study feasibility in terms of the likelihood of demonstrating an interpretable treatment effect (based on study duration, background event rate, anticipated treatment effect, etc.). For the prevention of AKI in cardiovascular surgery, a composite of MAKE as a primary endpoint is considered reasonable. The considerations with respect to follow-up and interpretation of the MAKE endpoint are described under the section *"Endpoints"*.

Any regulatory experience on development programmes of medicinal products for the treatment of AKI in patients with a history of cardiovascular surgery are not available. In such circumstances, it is recommended to seek scientific and regulatory advice.

4.6. Methodological considerations

The scientific question(s) of interest, i.e., what the trial seeks to address and to quantify what is to be estimated (estimand), should be specified in all its attributes. The trial planning, design, conduct, analysis and interpretation should be aligned with the estimand framecontrast work (ICH E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials (EMA/CHMP/ICH/436221/2017)).

For investigating AKI treatments, a randomised controlled trial is the preferred trial design. All potential intercurrent events regarding the clinical trials objectives, such as treatment discontinuation, change in background medication, use of additional medication and/or procedures potentially affecting outcome, should be considered. However, the outcome, regardless of the occurrence of intercurrent events (treatment policy strategy), is generally the primary efficacy assessment of interest. Secondary estimand(s) of a hypothetical strategy could be proposed when considered of clinical or regulatory relevance.

The applicant is recommended to submit the clinical development plan to the competent authority within the framework of a scientific advice, to discuss and agree about the estimand and analysis plan.

4.7. Safety evaluation

Requirements regarding the overall exposure and extent of the safety database will depend on the type of drug and the context of use.

In the setting of a single, or a very short-term administration, the effects of the drug itself become difficult to differentiate from other causes of adverse effects over time, particularly those related to co-morbidities. At least safety data over six months period are expected, although one-year exposure data is generally preferred. Any shorter follow-up would need an appropriate justification. For sepsis

associated AKI, any demonstration of superiority on mortality as primary endpoint would alleviate such general safety requirements.

All adverse events (AE) should be collected and analysed using a pre-planned methodology. Special emphasis should be put on AEs predicted by the pharmacodynamic properties of the investigational product.

Consideration should also be given to the potential interference/contribution of concomitant therapy. It is expected that the database is of adequate size and quality to evaluate this sufficiently. Careful considerations should be given to any possible concomitant drugs with potential nephrotoxicity.

4.8. Considerations for the paediatric population

Due to the limited regulatory experience in the development of medicinal products for prevention and/or treatment or AKI in the paediatric population, the recommendations that can be made are narrow. AKI can present itself in the full age range of the paediatric population. AKI in paediatric (hospitalised) patients is associated with increased morbidity and mortality. Several AKI definitions, including KDIGO, Paediatric Risk, Injury, Failure, Loss, End Stage Renal Disease (pRIFLE) and Acute Kidney Injury (AKIN), have been adapted to the paediatric population. The KDIGO definition and staging system is the most recent and the preferred one. However, depending on the clinical setting, other AKI definitions may be justified.

Depending on the clinical setting, the risk for and cause of AKI may be different from that of adults and may also vary within the different paediatric age categories. Moreover, the vulnerability of some subgroups, such as neonates, provides additional challenges in designing clinical trials addressing AKI in the paediatric population compared to the adult population. Additionally, due to the wide range of normal creatinine levels in children of different sizes and age categories, the use of serum creatinine as a marker to diagnose and stage AKI and to determine treatment evidence may be more challenging than in adults. Still, many of the considerations outlined in this document concerning the adult study population, study design and endpoints also apply to the evaluation of AKI in paediatrics.

If any extrapolation from the adult population is foreseen, the Structured guidance on the use of extrapolation (EMA/CHMP/13622/2022) outlines the basic requirements. A sound extrapolation concept is needed to provide sufficient confidence for any extrapolation exercise. However, since experience and positive clinical programmes in adults are limited, it is likely that substantial evidence generation in a significant part of the paediatric target population is required.

5. Conclusion

Acute kidney injury (AKI) is a syndrome which clinically presents itself as an acute loss of renal function and can occur based on different aetiologies and as part of different clinical settings and can have intermediate and long-term consequences. Due to very limited applications for/approvals of medicinal products in this field, any new product could address a high unmet medical need. This lack of applications/approvals may be partly due to the limited understanding of AKI pathophysiology in different clinical settings and challenges in design of effective studies including selection of the appropriate patient population, clinical endpoints, timing of intervention, amongst others. Nevertheless, this reflection paper is aimed to provide high level guidance about the development of medicinal products for the prevention and/or treatment of AKI, based on current limited regulatory experience in conjunction with currently available scientific research and knowledge in this area.

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