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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on clinical trials in recipients of kidney transplantation

Agreed by Working Party of Immune and Inflammatory Diseases (IIWP)	June 2026
Adopted by CHMP for release for consultation	05 October 2026
Start of public consultation	16 October 2026
End of consultation (deadline for comments)	31 January 2027

The proposed guidance will pertain to specific topics relevant for kidney transplantation and will serve as an addition to the current “overarching” [Guideline on Clinical Investigation of Immunosuppressants for Solid Organ Transplantation](#) (CHMP/EWP/263148/06).

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Keywords	Immunosuppressants/immunosuppressive therapy, solid organ transplantation, kidney, graft survival, calcineurin inhibitor nephrotoxicity, sensitized transplant recipients, delayed graft function, tolerance induction, ischemia-reperfusion injury, donor-specific antibody, panel reactive antibodies
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1. Introduction

Kidney transplantation in the European Union (EU) is widely practiced but varies widely between countries in transplant rates and donor sources. Outcomes for end-stage kidney disease (ESKD) treated with transplantation are significantly better than those achieved with dialysis, as transplant patients demonstrate improved survival and quality of life. However, the functional lifespan of transplanted kidneys remains considerably shorter than that of native kidneys (Rebollo-Mesa et al. 2023¹, Liem et al., 2022²).



Major clinical challenges in kidney transplantation include managing graft rejection, infection risks, immunosuppressive therapy complications, graft failure, and complex patient management. Graft rejection remains a critical challenge despite advances in immunosuppressive therapy. It can be hyperacute, acute, or chronic, with acute rejection occurring usually within months post-transplant and chronic rejection developing over years. Acute rejection rates have decreased to 10-20% because of advances in immunotherapy. In contrast, the rate of chronic rejection has not declined, remaining a significant challenge in long-term graft survival and patient outcomes. Non-adherence to immunosuppressive regimens, especially in adolescents, is a major cause of rejection episodes (Khan et al. 2025³).

Immunosuppressants, particularly calcineurin inhibitors (CNIs), can cause nephrotoxicity, increase susceptibility to infections and malignancies, and require careful balancing to avoid under- or over-suppression. Long-term exposure contributes to graft damage and systemic complications, complicating long-term care.

Graft failure leading to return to dialysis presents clinical challenges including increased morbidity and mortality, heightened risks of cardiovascular events and infections, and difficulties in managing immunosuppression to prevent allo-sensitisation before re-transplantation (Khan et al. 2025³, Hickey et al. 2023⁴).

These challenges reflect the complex nature of kidney transplantation requiring careful coordination to optimize graft survival and patient quality of life according to consensus and guidelines in the field. Advances in understanding the pathophysiology of kidney rejection — particularly the roles of antibodies and complement — reflect a significant evolution in scientific knowledge and pave the way for progress in medical therapy (Brouard et al. 2026⁵, Niu et al. 2025⁶, Gatault et al. 2022⁷, Kervella et al. 2022⁸).

Earlier interactions of the European Society for Organ Transplantation (ESOT) working group with regulatory authorities on the development of innovative therapies in transplantation led to the development of several key recommendations, which were published in 2022. However, these updates are not currently reflected in the existing regulatory guidelines on clinical investigation of immunosuppressants for solid organ transplantation (Naesens et al. 2022⁹).

2. Problem statement

The existing Guideline on Clinical Investigation of Immunosuppressants for Solid Organ Transplantation (CHMP/EWP/263148/06) is overarching and includes guidance on the most prevalent solid organ transplants, i.e. heart, lung, liver and kidney. Given the role of kidney transplantation in driving innovation, new developments in solid organ transplantation are likely to emerge first in the kidney transplant setting.

The EMA is now considering a revision and/or adding an addendum on kidney transplantation to its 2008 guidance on solid organ transplantation. Indeed, significant advancements have been made in the field since the initial publication of the guideline. Several critical topics may warrant more in-depth discussion than what is currently provided in the published guidance.

The purpose of this concept paper is to update the guidance with pertinent issues for addition to the overarching guideline. The update concerns adult recipients of kidney transplants. Transplantation in the paediatric population will be discussed under “Special population” section, under each topic. Transplantation of other solid organs is not within the scope of this update.

3. Discussion (on the problem statement)

The revised guideline would address the design of clinical trials, criteria for patient selection, the definition of short and long-term efficacy endpoints, and the use of biomarkers and surrogate endpoints. Additionally, it would incorporate transplantation specific estimand considerations in line with the 2020 ICH E9 (R1) addendum on estimand and sensitivity analysis in clinical trials. Specific clinical scenarios to be addressed would include:

CNI-free regimen to improve long-term survival

Calcineurin inhibitor (CNI) nephrotoxicity has been recognized as a significant barrier to long-term kidney graft survival. Alternatives to CNIs have already been approved and may offer improved preservation of renal function over time. However, the risk of early rejection associated with these alternatives necessitates careful patient selection, focusing particularly on individuals with low immunologic risk.

The proposed guideline update/addendum would aim to elaborate on trial design for implementing CNI-free regimens both at the initial stages and through delayed CNI withdrawal (after one year). Furthermore, monitoring strategies, e.g. regular assessment of estimated glomerular filtration rate and the use of biopsies or alternatives are planned to be addressed.

Highly sensitized patients

Several approaches stratify rejection risk in highly sensitized kidney transplant recipients by focusing on humoral immunity. These methods evaluate donor-specific antibodies, human leukocyte antigen (HLA) mismatches, and the patient’s sensitization history to determine the likelihood of rejection.

There are limited options within the European Union for the highly sensitized kidney transplant patients with positive crossmatch against available donors. Innovative therapy could include immunomodulation and/or desensitization therapies for highly sensitized transplant recipients.

The proposed guideline update/addendum would aim to elaborate on definition and stratification of highly sensitized patients, e.g. with criteria such as donor-specific antibodies, calculated Panel Reactive Antibodies, crossmatch status and prior clinical sensitizing exposure, use of biomarkers to monitor adequacy of immunosuppression/-modulation, and safety assessments in addition to early and long-term efficacy outcomes.

Delayed graft function

Delayed graft function (DGF) after kidney transplantation is a clinical condition characterised by temporary failure of transplanted kidney to function immediately after transplantation. It is primarily driven by ischemia-reperfusion injury, often resulting from prolonged cold ischemia time during organ preservation. Additional risk factors include the use of extended donor criteria - organs from donors who do not meet the standard criteria for optimal organ donation (e.g. advanced age, high Body Mass

Index, or underlying diseases) but are deemed suitable under specific circumstances - as well as recipient-related factors such as advanced age, diabetes mellitus and prolonged dialysis duration. Transplant-related factors such as HLA mismatches, also contribute to the development of DGF.

Various approaches have been implemented in clinical practice to alleviate the issue of DGF. Strategies include optimising donor organ management during procurement and facilitating paired exchange.

The proposed guideline update/addendum intends to give guidance on the development of interventions aimed at minimising ischemia-reperfusion injury, e.g. by improving the outcome of harvested organs or delivering preventive medical management to the recipient.

Tolerance induction

Tolerance induction in transplantation has the goal of reducing and ultimately eliminating the need for lifelong immunosuppressive therapy. The development of tolerance-inducing therapies poses significant challenges in designing clinical trials due to the complexity of the therapies, patient variability, and regulatory requirements. Key challenges to be addressed include:

- Patient selection: patients exhibit considerable variability in immunological risk profiles, comorbidities, and previous exposure to immunosuppressive therapies. Consequently, the clinical programme should incorporate a comprehensive strategy for identifying suitable patient populations for initial tolerance-induction trials, alongside methodologies to potentially broaden the approach to address a wider patient population.
- Long-term follow-up: tolerance-inducing therapies necessitate prolonged follow-up periods, not only to monitor safety concerns but also to evaluate the extent and durability of tolerance, as well as to determine whether adjustments to the immunosuppressive therapy regimen are required.

4. Recommendation

The Working Party of Immune and Inflammatory Diseases (IIWP) of the Committee for Human Medicinal Products (CHMP) recommends revising and/or adding an addendum to the Guideline on Clinical Investigation of Immunosuppressants for Solid Organ Transplantation (CHMP/EWP/263148/06) taking into account the issues identified above.

5. Proposed timetable

Release for consultation on 01 November 2026; deadline for comments is 31 January 2027.

6. Resource requirements for preparation

The drafting group of the guideline update/addendum will involve representatives of the IIWP, including one Rapporteur. It is anticipated that at least one plenary session discussions at the IIWP will be needed.

7. Impact assessment (anticipated)

It is anticipated that the guideline update/addendum will have an impact on the clinical development of medicinal products for the treatment of kidney recipients. It will aim to consolidate the current regulatory view on the design of the clinical development programs of these medicinal products and is expected to be helpful to achieve consensus in the evaluation of such products by regulatory authorities.

8. Interested parties

Pharmaceutical Industry, Academia, EU Competent Authorities and patients and health care professional groups. Consultation with other working parties or committees will be initiated, as appropriate.

9. References to literature, guidelines, etc.

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