Delayed Graft Function in Kidney Transplantation: Developing Drugs for Prevention

Guidance for Industry

U.S. Department of Health and Human Services
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Delayed Graft Function in Kidney Transplantation: Developing Drugs for Prevention Guidance for Industry[1]

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the prevention of delayed graft function (DGF) in kidney transplantation.[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for systemic drugs administered to the kidney transplant recipient to support an indication of *prevention* of DGF.

This guidance does not address the *treatment* of DGF in the recipient or the treatment of the donor or the graft for the purpose of preserving or improving graft quality. These issues may be addressed in separate guidances.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively.[3]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only

[1] This guidance has been prepared by the Division of Transplant and Ophthalmology Products in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For purposes of this guidance, unless otherwise specified, references to *drugs* and *drug products* include drugs submitted for approval or approved under section 505(b) or (j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and biological products licensed under section 351 of the Public Health Service Act, other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND AND DEFINITIONS

DGF, presenting as suboptimal renal function immediately following kidney transplantation, is a manifestation of ischemia-reperfusion injury (IRI) in the transplanted kidney allograft. For the purpose of this guidance, DGF is defined as the need for dialysis within 7 days of transplantation, although other definitions and methods to assess early graft dysfunction have also been published (Mallon et al. 2013; Yarlagadda et al. 2008), including the following:

- The need for one or more hemodialysis treatments following transplantation (not limited to 7 days) before the onset of graft function (Singh et al. 2011).

- Days to reach a calculated estimated glomerular filtration rate of greater than or equal to 10 milliliters (mL) per minute (min) post-transplant. The duration of DGF was defined as number of days for the kidney to attain the threshold of 10 mL per min (Giral-Classe et al. 1998).

- Creatinine reduction ratio between Day 0 and Day 7 of less than 70 percent (Johnston et al. 2006).

DGF (and other manifestations of early graft dysfunction after transplantation) is caused by kidney allograft injury sustained during donor management, organ recovery, storage, implantation, reperfusion, and recipient-related factors. Changes consequent to brain death in donors (i.e., donation after brain death (DBD)) and IRI affect organ quality. Periods of warm ischemia related to hypotension and hypoperfusion during donor management and/or prolonged cessation of perfusion in a donor after cardiac death (DCD) cause acute injury in the allograft. The injuries sustained by the kidney allograft, along with subsequent innate and adaptive immune responses, contribute to the complex pathophysiologic mechanisms resulting in DGF. DGF is observed more frequently after deceased donor (including DBD and DCD) kidney transplantation than after living donor (LD) kidney transplantation.

Although DGF episodes with different types of donors (DCD, DBD, or LD) have similar short-term manifestations following transplantation, they may represent different pathophysiological processes with different long-term allograft outcomes. As described in the published literature, despite higher rates of DGF and acute rejection reported in recipients of DCD kidneys compared to recipients of DBD or LD kidneys, subsequent survival and organ function in recipients of DCD kidneys with DGF may be better than in recipients of DBD kidneys with DGF (Singh et al. 2011). Therefore, potential treatments may have a different effect on the prevention of DGF after transplantations of kidneys from the different types of donors. Overall, the outcome is likely to depend on the relative contribution of different donor, preservation, or recipient-related factors with a consequent differential response to the investigational drug.

In addition to DGF, other grades and severities of inadequate renal function have been defined in the published literature, including primary nonfunction (PNF) and slow graft function (SGF) or functional DGF (fDGF).

PNF describes the condition in which the kidney never functions adequately after transplantation, and the patient continues to need dialysis despite the transplant. The diagnosis of PNF generally does not become established before 2 to 3 months (60–90 days) after transplantation (Stevens et al. 2009; Woo et al. 1999).

SGF or fDGF describes kidney allograft dysfunction occurring early after transplantation, but the dysfunction may not be severe enough to warrant dialysis. These other forms of dysfunction may still portend a diminished graft and/or patient survival. Various definitions of SGF and/or fDGF are used in the published literature, including the following:

- fDGF defined as failure of serum creatinine level to decrease by at least 10 percent daily on 3 consecutive days during the first postoperative week irrespective of dialysis requirement (Moore et al. 2010)

- SGF defined as serum creatinine greater than 3 milligrams (mg) per deciliter and no need for dialysis at Day 5 post-transplant (Humar et al. 1997; Humar et al. 2002)

- Mild DGF defined as a serum creatinine reduction ratio from post-transplant Day 1 to Day 2 (CRR2) less than or equal to 30 percent plus 24-hour urine creatinine excretion (UC2) on Day 2 greater than 1,000 mg (Govani et al. 2002; Rodrigo et al. 2004)

- Severe DGF defined as a serum CRR2 less than or equal to 30 percent plus 24-hour UC2 on Day 2 less than or equal to 1,000 mg (Govani et al. 2002; Rodrigo et al. 2004)

The main reason to prevent DGF is to avoid the need for dialysis. Dialysis is a choice of last resort and puts the graft at risk because of potential hypotension, risk of thrombosis, increase in hospitalization, and worse clinical outcome, as reported in various publications cited above.

It has further been reported that DGF is associated with adverse effect on important graft outcomes such as graft survival, acute rejection, and renal function (Yarlagadda et al. 2009). A web-based model for predicting DGF after renal transplantation was developed using factors such as cold ischemia time, donor creatinine, body mass index, donation after cardiac death, and donor age (Irish et al. 2010). In addition to predicting DGF, this model also predicted long-term graft failure, thus demonstrating an unfavorable effect of DGF (or the factors leading to DGF) on long-term graft survival. Although prevention of DGF may result in long-term benefits, such as improved patient and graft survival, these benefits have yet to be demonstrated.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Efficacy Considerations

Trials to demonstrate that treatments reduce the risk of DGF should be superiority trials in which an active treatment is compared to placebo because there is no approved drug that reduces the risk of DGF and there is no standard of care that has been demonstrated to be effective.

If the drug is an unapproved drug, in general, we recommend two adequate and well-controlled trials to provide evidence of effectiveness. A single adequate and well-controlled trial supported by confirmatory information, such as a trial in a closely related indication (e.g., based on mechanism of action, target receptor), could potentially provide evidence of effectiveness in the prevention of DGF. A single adequate and well-controlled trial could provide evidence of effectiveness if the results were statistically strong and the trial had other strong features (many sites, consistent results). Sponsors should discuss with the Agency the confirmatory evidence that could support a significant finding from a single adequate and well-controlled trial.

2. Safety Considerations

In general, we recommend a preapproval safety database of 300 patients or more on the investigational drug.[4] If the same or greater dose and duration of therapy for the prevention of DGF were used in clinical trials for other disease indications, the safety information from those clinical trials can be part of the overall preapproval safety database.

For new drugs that have an important clinical benefit compared to current management strategies, depending on the benefit demonstrated, a smaller preapproval safety database may be sufficient. Sponsors should discuss the appropriate size of the preapproval safety database with the Agency during clinical development.

B. Specific Efficacy Trial Considerations

1. Study Design, Randomization, Stratification, and Blinding

The clinical trial population for efficacy trials should include *de novo* kidney transplant recipients and be representative of a U.S. patient population, including race, age, sex, and other baseline characteristics.

[4] A safety database large enough to rule out a serious adverse event that occurs at the rate of 1 in 100 or higher may be suitable when there are limited therapeutic options. For example, when there are no serious and unexpected adverse events in approximately 300 patients, then the true rate of serious and unexpected adverse events is likely to be fewer than 1 in 100 or 1 percent (Hanley and Lippman-Hand 1983).

The type of donors, preferably graded by the kidney donor profile index implemented by the new Kidney Allocation System,[5] should be specified in the protocol. Consideration should be given to stratifying the study population, for example, based on study center and/or the type of induction treatment (if there is more than one). If the sponsor plans to enroll recipients of the DCD donor kidneys or donor kidneys preserved by machine perfusion, we highly recommend stratification based on the type of donor (DCD versus DBD) and organ preservation method.

The trials should be randomized and double-blinded.

2. Study Population and Specific Populations

Enrichment strategies can be used to select a study population at a higher risk for developing DGF compared to the overall kidney transplant recipient population for these clinical trials, as discussed in the guidance for industry *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products* (March 2019).

3. Entry Criteria

The protocol should specify the inclusion and exclusion criteria that will be used to select patients to participate in the clinical trial, including any enrichment strategies.

4. Organ Storage Conditions and Use of Concurrent Immunosuppressants and Other Medications

The protocol should specify the type of organ recovery, storage, and transport conditions: machine perfusion (cold or warm) or static cold storage.

Immunosuppressive (IS) therapy after transplantation should be specified, including the induction regimen(s) and the maintenance therapy. In clinical trials of DGF, the Agency highly recommends that the type of induction, including the initial intravenous corticosteroid boluses at the time of transplantation and the maintenance IS therapy, be standardized across the treatment groups to minimize the potential confounding effect of these factors on the study endpoints.

The protocol should state that data on the IS and other medications used in the study patients should be collected on the case report forms (CRFs). For drugs managed using therapeutic drug monitoring, drug trough levels should be collected on the CRF.

5. Dose Selection

Sponsors should conduct dose-ranging studies during phase 1 or phase 2 testing. Generally, trials to prevent DGF (and other forms of early graft dysfunction) would be expected to have a short duration of treatment, so different dosage regimens could be evaluated in the first week after transplantation.

[5] See the U.S. Department of Health and Human Services Kidney Allocation System web page at https://optn.transplant.hrsa.gov/learn/professional-education/kidney-allocation-system/.

6. Choice of Comparators

Trials should be placebo-controlled, as at present there are no approved therapies and no standard of care for the prevention of DGF.

7. Efficacy Endpoints

a. Primary efficacy endpoint

Sponsors should consider the following when choosing a primary efficacy endpoint:

- **Short-term assessment endpoint**

  - *Short-term assessment of the graft function for efficacy* — In the short-term assessment of the graft function, the common definition of DGF (i.e., the requirement for hemodialysis treatment within the first 7 days post-transplant) can be used as the primary endpoint. Sponsors can also propose other definitions of DGF supported by literature.

    As an alternative to the assessment of the occurrence of DGF as a binary endpoint, DGF severity scoring systems can be proposed. These could include the number of hemodialysis sessions required until recovery of renal function or time to recovery of renal function after the diagnosis of DGF. If the DGF severity scoring endpoint is chosen as the primary endpoint, the sponsor should provide a justification for the clinical significance and relevance of the proposed score difference to be demonstrated.

    In addition to recording any hemodialysis sessions during the first 7 days post-transplant, information on hemodialysis sessions after Day 7 until post-transplant Day 30, regardless of the reason for dialysis, should be collected on the CRFs to evaluate the durability of treatment and should be submitted in the final study report.

  - *Short-term endpoint using SGF and fDGF* — Another option is to select a short-term primary endpoint based on definitions of suboptimal renal allograft function, such as SGF or fDGF. The protocol should include the specific definition of SGF and/or fDGF that will be used. If the primary endpoint definition includes a particular definition of renal allograft function, the sponsor should justify the clinical benefit of such an endpoint and the sponsor should discuss the proposed endpoint definition with the FDA. Long-term clinical benefit such as an improvement in graft or patient survival may need to be demonstrated.

- **Long-term efficacy and improved renal function** — If an additional goal of the clinical trial is to demonstrate that the drug leads to an overall sustained improvement in renal function, compared to placebo, then renal function data need to be collected for all patients for a minimum of 12 months. A clinically meaningful difference in renal

function (assessed using serum creatinine levels or glomerular filtration rate) should be justified before study initiation.

b. Secondary efficacy endpoints

Sponsors should consider the following when choosing secondary efficacy endpoints:

- **DGF** — If one of the DGF severity scoring methods is chosen for the primary endpoint, the classic definition of DGF (i.e., requirement of dialysis within the first 7 days post-transplant) should be among the secondary endpoints

- **Day 30 analysis** — The purpose of this analysis is to evaluate the durability of treatment effect after the first week post-transplant

- **Renal function** — The comparison of renal function (measured or calculated) between the treatment and placebo arms at prespecified time points for 12 months post-transplant should be among the secondary endpoints

- Definitions of SGF or fDGF can be among the secondary endpoints.

8. Safety Considerations

Because dosing is expected to occur during the first week post-transplant, intensive laboratory testing and collection of adverse event data for 30 days of follow-up may be sufficient. Depending on the pharmacokinetic/pharmacodynamic (PK/PD) properties of the drug, longer clinical and laboratory follow-up for drug-associated adverse events could be needed.

As noted above, the primary efficacy endpoint can be evaluated when data are available for the first 30 days post-transplant. However, additional follow-up is needed to understand the long-term effect of a drug to prevent DGF on the kidney allograft and patient.

For this indication, the mechanism of action of the drug is related to preventing injury and inflammation. The primary mechanism of action is not as an immunosuppressant (these drugs are not primarily intended to suppress T-cells and B-cells, per se). However, one cannot assume the drug for DGF is neutral with respect to IS or other related effects (low white blood cell, cytomegalovirus pneumonia). Therefore, acute rejection, graft loss, and death are not efficacy endpoints; rather, they are safety endpoints in trials of drugs to prevent DGF. The reason for longer follow-up is to assess whether the DGF drug has an unintended effect on the kidney allograft (toxicity) and whether that toxicity affects the kidney's ability to function, making it susceptible to rejection or other injury and affecting survival (either favorably or adversely). The general duration of follow-up for safety should be a minimum of 12 months, and information should be collected on the survival and function of the graft (including episodes of rejection), the occurrence of hospitalization, and other serious adverse events, patient survival at a minimum at Month 3 (approximately Day 90), Month 6, and Month 12, as follows:

- **Patient and graft survival** — Patient and graft survival data should be among the safety endpoints, and data for at least 12 months post-transplant should be collected

- **Rejection** — Acute cellular rejection and antibody mediated rejection episodes should be recorded on the CRFs for at least 12 months post-transplant and analyzed as part of the safety endpoints

- **Hospitalizations** — Data on hospitalizations should be collected for at least 12 months post-transplant and analyzed as part of the safety endpoints

9. Study Procedures and Timing of Assessments

The primary endpoint can be assessed at Day 7 post-transplant. The need for dialysis between Day 7 and Day 30 should also be evaluated, including the number of dialysis sessions captured on the CRF, for assessment of the durability of treatment effect.

To evaluate the comparability of the study groups, dialysis sessions in the week before transplant should be captured on the CRF.

For the assessment of safety, information on all adverse events and laboratory tests should be collected for up to Day 30 for drugs with short half-lives. However, depending on the PK characteristics and duration of PD effect, longer follow-up with collection of laboratory data and adverse event assessments may be needed.

Data on the following types of serious adverse events should be collected for a minimum of 12 months: acute rejection, graft loss, hospitalizations (e.g., for infection, new onset diabetes after transplantation, neurologic adverse events, malignancies), and patient death. All attempts should be made to collect these data; missing information on hospitalizations or acute rejection should be minimized.

10. Endpoint Adjudication

There should be no endpoint adjudication, meaning that for the intent-to-treat (ITT) analysis, all dialysis sessions that occurred within the first 7 days post-transplant should be included in the analysis. However, sponsors can perform sensitivity analyses to look at subsets of patients where the specific reason for the dialysis session (e.g., hypervolemia) is taken into consideration. These analyses can be done in addition to the ITT population analysis but should not replace it.

11. Statistical Considerations

The protocol should specify how information will be collected and how it will be analyzed. All patients with DGF, defined as dialysis within 7 days post-transplant, should be included as treatment failures in the analysis. Patients who experience graft loss, or death, or who are lost to follow-up in the first 7 days should be imputed as treatment failures. However, no patient should be lost to follow-up in the first 30 days post-transplant.

The primary efficacy endpoint should be analyzed based on the ITT population, defined as all patients randomized who receive a kidney transplant.

If the protocol specifies SGF or fDGF as part of the primary endpoint, the planned analysis should be specified in the protocol and statistical analysis plan (SAP). Strategies to handle missing data should be defined; however (as noted above), there should be no missing data in the first 30 days post-transplant.

If other measures of treatment success, such as severity scores or time to graft function recovery, are used as the primary endpoint, the protocol and SAP should describe how the results will be analyzed. For patients who experience graft loss or death in the first 30 days, an appropriate analysis strategy should be defined (e.g., imputing three dialysis sessions per week should be considered when actual data are not available).

As a secondary endpoint, a Day 30 analysis should look at the percentage of patients who received dialysis within the first 30 days post-transplant, using similar analysis strategies as for the primary endpoint. This analysis is to assess durability of the treatment. The direction and magnitude of the treatment effect should be comparable to the primary endpoint.

Safety should be analyzed in those ITT patients who received at least one dose of the investigational drug or control drug (e.g., placebo) and were evaluated for acute rejection, graft loss, hospitalization for serious adverse events, and patient death at least at Month 3, Month 6, and Month 12.

12. Accelerated Approval (Subpart H) Considerations

While a primary endpoint that includes prevention of hemodialysis treatment during the first 7 days post-transplant is associated with clinical benefit and could be used to support a traditional approval, sponsors should discuss with the FDA plans to use any surrogate endpoints that are reasonably likely to predict clinical benefit to support accelerated approval.[6] An accelerated approval pathway will require confirmation of clinical benefit through postmarketing confirmatory trials to verify and describe the anticipated effect on irreversible morbidity, mortality, or other clinical benefit.[7]

13. Risk-Benefit Considerations

The early benefit of preventing DGF should be compared to the safety of the drug, evaluated directly in the first 30 days post-transplant and the effect, if any, on the subsequent rates of acute rejection, graft loss, serious adverse events requiring hospitalization, and patient death for a minimum of 12 months post-transplant. The benefit of preventing DGF should outweigh the risks of treatment.

[6] See section 506(c) of the FD&C Act; 21 CFR part 314, subpart H; and 21 CFR part 601, subpart E.

[7] See 21 CFR 314.510; 21 CFR 601.41.

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