Delayed Graft Function in Kidney Transplantation: Developing Drugs for Prevention

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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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 This draft guidance is intended to serve as a focus for continued discussions among the Division of Transplant and Ophthalmology Products, pharmaceutical sponsors, the academic community, and the public.[3] 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* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[4]

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

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of drugs for DGF.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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 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. DGF generally is defined as the need for dialysis within 7 days of transplantation, although other definitions have also been published in the literature (Mallon, Summers, et al. 2013; Yarlagadda, Coca, et al. 2008), including:

- The need for one or more hemodialysis treatments following transplantation (not limited to 7 days) before the onset of graft function (Singh, Farney, 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-transplantation. The duration of DGF was defined as the time taken for the kidney to attain the threshold of 10 mL per min (Giral-Classe, Hourmant, et al. 1998).

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

DGF (and other manifestations of early graft dysfunction after transplantation) is caused by the 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 kidney 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 compared to 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, Farney, 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 a transplant. The diagnosis of PNF generally does not become established before 2 to 3 months (90 days) after transplantation (Stevens, Skorupa, et al. 2009; Woo, Jardine, et al. 1999).

SGF or fDGF describes kidney allograft dysfunction occurring early after transplantation but 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:

- 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, Shabir, 2010)

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

- Patients with 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 met the definition of mild DGF (Govani, Kwon, 2002; Rodrigo, Ruiz, et al. 2004)

- Patients with 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 met the definition of severe DGF (Govani, Kwon, 2002; Rodrigo, Ruiz, 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 is further reported that there is a long-term detrimental association between DGF and important graft outcomes like graft survival, acute rejection, and renal function (Yarlagadda, Coca, 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, Ilsely, 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 it is also possible that

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 should be superiority trials in which an active treatment is compared to placebo because there is no approved drug for the prevention of DGF and there is no standard of care that has been demonstrated to be effective.

If the drug is a new drug (i.e., not approved by the FDA for any use), two adequate and well-controlled trials generally are recommended to provide evidence of effectiveness. A single adequate and well-controlled trial supported by other independent evidence, 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 may be appropriate if the results of efficacy are highly robust. Sponsors should discuss with the FDA other independent confirmation that would be used to support the highly significant findings from a single adequate and well-controlled trial in prevention of DGF.

2. Safety Considerations

In general, we recommend a preapproval safety database of 300 patients or more on the investigational drug. 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 FDA during clinical development.

B. Specific Efficacy Trial Considerations

1. Study Design, Randomization, Stratification, and Blinding

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

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 enrollment, for example, based on study center and/or the type of induction treatment (if there is more than one). If recipients of the DCD donor kidneys or donor kidneys preserved by machine perfusion are planned to be enrolled, stratification based on the type of donor (DCD versus DBD) and organ preservation method is highly recommended.

The studies should be randomized and blinded.

2. Study Population and Specific Populations

Enrichment strategies can be used to select the study population at a higher risk for developing DGF compared to the overall kidney transplant recipient population for these clinical studies, as discussed in the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*.[6]

3. Entry Criteria

The protocol should specify the inclusion and exclusion criteria that will be used to select patients to participate in the clinical study, 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 agent(s) and the maintenance therapy. In clinical trials of DGF, it is highly recommended 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] http://optn.transplant.hrsa.gov/learn/professional-education/kidney-allocation-system/

[6] When final, this guidance will represent the FDA's current thinking on this topic.

206 *5. Dose Selection*
207
208 Dose-ranging studies should be conducted during phase 1 or phase 2 testing. Generally, studies
209 to prevent DGF (and other forms of early graft dysfunction) would be expected to have a short
210 duration of treatment, so different dosage regimens could be evaluated in the first week after
211 transplantation.
212
213 *6. Choice of Comparators*
214
215 We recommend placebo-controlled studies, because at present there are no approved therapies
216 and no standard of care for the prevention of DGF.
217
218 *7. Efficacy Endpoints*
219
220 a. Primary efficacy endpoint
221
222 Sponsors should consider the following when choosing a primary efficacy endpoint:
223
224 • **Short-term assessment or composite endpoint**
225
226 – *Short-term assessment of the graft function for efficacy* — In the short-term
227 assessment of the graft function, the common definition of DGF (i.e., the requirement
228 for hemodialysis treatment within the first 7 days following transplantation) can be
229 used as the primary endpoint. Other definitions of DGF supported by literature also
230 can be proposed.
231
232 As an alternative to the assessment of the occurrence of DGF as a binary endpoint,
233 DGF severity scoring systems can be proposed. These can include the number of
234 hemodialysis sessions required until recovery of renal function or time to recovery of
235 renal function after the diagnosis of DGF. If the DGF severity scoring endpoint is
236 chosen as the primary endpoint, a justification for the clinical significance and
237 relevance of the proposed score difference should be provided.
238
239 In addition to recording any hemodialysis sessions during the first 7 days post-
240 transplant, information on hemodialysis sessions after Day 7 until post-transplant Day
241 30, regardless of the reason for dialysis, should be collected on the CRFs to evaluate
242 the durability of treatment, and submitted in the final study report.
243
244 – *Short-term composite endpoint using SGF and fDGF* — Another option is to select a
245 short-term primary endpoint that includes DGF as well as some component of SGF or
246 fDGF. The protocol should include the specific definition of SGF and fDGF. As
247 noted above, the use of severity scoring systems for these outcomes should be
248 specified, and the prospectively defined difference in scores should be justified as
249 clinically meaningful.
250

- **Long-term efficacy and improved renal function** — If the goal of the clinical study 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.

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 following transplantation) 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 following transplantation should be among the secondary endpoints

8. Safety Considerations

Because dosing is expected to occur during the first week post-transplantation, routine laboratory testing and collection of adverse event data attributable to the drug likely can be evaluated with 30 days of follow-up. Depending on the pharmacokinetic/pharmacodynamic (PK/PD) properties of the drug, longer clinical and laboratory follow-up for drug-associated adverse events may 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 some 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 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 after transplantation should be collected

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

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

9. Study Procedures and Timing of Assessments

The primary endpoint can be assessed at Day 7 after 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.

Likewise, 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. Long-term safety evaluation should be collected at a minimum at Month 3, Month 6, and Month 12.

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 after transplantation 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 of transplant, should be included as treatment failures in the analysis. Patients who experience graft loss, or death or 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 after 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 composite 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 after 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 session per week should be considered when actual data are not available).

For the 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 study drug or control drug (e.g., placebo) and were evaluated for acute rejection, graft loss, hospitalization for serious adverse reactions, and patient death at least at Month 3, Month 6, and Month 12.

12. Accelerated Approval (Subpart H) Considerations

To be considered for accelerated approval, the new drug application (NDA) or biologics license application (BLA) should be submitted with efficacy data and at least 3 months (90 days) of safety data for all patients.[7] In this original submission, some patients should already have been followed for longer than 90 days. Safety data collected on acute rejections, graft loss, hospitalizations for serious adverse reactions, and death between Month 3 and Month 6 should be submitted in the 120-day safety update along with an integrated presentation of the Month 6 safety data (patient data in the original NDA or BLA and patient data in the 120-day safety update).

For full approval, information on acute rejections, graft loss, hospitalizations for serious adverse reactions, and death for a minimum of 12 months post-transplant should be submitted as part of the original NDA or BLA submission, or as a postmarketing requirement under accelerated approval. Additional details of the clinical trial design can be discussed during drug development.

[7] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

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 reactions requiring hospitalization, and patient death for a minimum of 12 months after transplantation. The benefit of preventing DGF should outweigh the risks of treatment.

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