Questions for the committee: preclinical and clinical issues in allogeneic islet therapy

1. *Immunosuppression*

Immunosuppression is important for survival of allogeneic islets, but the immunosuppressive therapy is associated with risks to the patients, such as infection, renal injury, possible malignancy and possible islet injury. Most of the published reports of allogeneic islet therapy and most clinical investigations are in patients on existing immunosuppression because of prior organ (usually kidney) transplantation. However, the immunosuppressive regimen used in kidney transplantation may not be optimal for islet products, and it may be difficult to standardize the immunosuppression regimens when patients enter the islet cell study.

- Are current data from preclinical models of islet only therapy and / or clinical studies of kidney / islet transplantation sufficient to support islet only therapy?
- If no, please discuss the kinds of animal and human data needed to justify the added toxicity of immunosuppression in islet-only therapy.
- What is / are the most appropriate immunosuppressive regimen(s) to use for islet -only studies? What additional animal studies should be done to explore / optimize the regimen(s)?
- Which patients (demographics and disease-related aspects) are most appropriate to include in studies of islet -only therapy?

2. *Donor-recipient matching*

Historical data in the ITR on HLA mismatch, sex compatibility and ABO identity for 123 single donor islet recipients from 1990-1997 reveal no clear pattern with regard to survival of islet allografts.

- Are other pre-clinical or clinical data available which address the immunogenicity of islet preparations?
- If no, then, given the absence of clear data on the immunogenicity of islet preparations, please comment on the minimum criteria (degree of HLA disparity etc.) to be used for donor-recipient matching.
- Does the committee agree that data on donor-recipient matching should continue to be collected?

3. *Organ quality*

- Which factors related to quality of the donor organ (e.g., cold ischemia, warm ischemia, islet preparation methods), can best be assessed in preclinical studies?
- What endpoints in pre-clinical models would be useful in decisions regarding improved islet product quality?

4. *Route/site of islet cell product administration*

Most allogeneic islet preparations are administered via the portal vein, although other routes have occasionally been used; e.g., subcutaneous implants, peritoneal implants. The latter are more common with encapsulated devices and have the advantage of being accessible to surgical removal.

- Is it desirable for islet preparations to be in direct contact with the portal circulation?
- Please discuss the safety considerations of intraportal injection of islets. Are there procedural steps that may facilitate safe injection of the islets, such as portal pressure monitoring, portography or other procedures? Please discuss methods to identify those patients at high risk for complications related to intraportal injections of islets.
- Please discuss options for other routes of administration and the implications with respect to immunogenicity (e.g., advantages of "immunoprivileged" sites).
- Please discuss the utility of the various animal models to evaluate route / site of administration of islet preparations.

5. *Glucose control*

High levels of glucose during the peri-implant period may injure islets. Some protocols require "tight" control during this period.

- What should the level of glucose control be during this period? How long should this level be maintained? What types / schedules of insulin would be best to achieve this level control?
- Can / should pre-clinical studies be performed to assess the impact of tight glucose control during the peri-implant period?

6. *Islet dose*

- How should the "dose" of islets be defined; e.g., based on islet equivalent number, volume, or secretory function?

- Should varying doses of islet preparations be evaluated in animal models, and if so, how is this best done?
- How might the evaluation of dose in animal models improve our approach to dosing in clinical investigations
- Should clinical studies designed to explore different islet dosages be conducted?

7. *Second and subsequent islet therapy*

- Provided an organ is available, what criteria, e.g., biochemical evidence of graft failure, length of function of first graft, etc.) are appropriate for a second islet transplant?
- Are data available to indicate whether sensitization is likely to occur with graft rejection, decreasing the success of subsequent engraftment?
- How should second and subsequent islet product transplants be evaluated in animal models?

8. *Outcome measures*

a. Activity measures in early clinical studies include C-peptide, hemoglobin A_{1c}, glucose tolerance, insulin usage, hypoglycemic episodes, and patient diaries.

- Please comment on the appropriateness of these values. Should other measures such as somatostatin and glucagon also be evaluated?
- Should these and other potential endpoints be assessed in animal models, and if so, which ones?
- What criteria should be used to determine loss of graft function and the appropriate time to withdraw immunosuppression?

b. Efficacy endpoints in phase 3 trials should be clinically relevant measures, or surrogates that reflect clinical benefit. In cases of serious or life threatening conditions where the new product represents an advance over existing therapies, the agency may grant "accelerated approval" based on studies showing an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. In such cases, studies are required post licensure to confirm the clinical benefit.

- Please discuss potential efficacy endpoints for phase 3 trials of allogeneic islet products.
- Could improved glucose control, as measured by glycosolated hemoglobin, if durable, be an acceptable endpoint for accelerated approval? If so, how durable does the effect need to be and in what population (e.g., "brittle diabetics") would the effect most easily be demonstrated? What types of studies would be optimal for confirming clinical benefit?