NOTICE OF OPPORTUNITY FOR CLINICAL TRIAL COLLABORATION

UTILIZATION OF ORAL DEXAMETHASONE IN THE FOCAL SEGMENTAL GLOMERULOSCLEROSIS CLINICAL TRIAL

The National Institute of Diabestes and Digestive and Kidney Diseases seeks oral dexamethasone to be used in one arm of an open label multicenter clinical trial designed to compare the efficacy of two immunotherapeutic regimens for Focal Segmental Glomerulosclerosis: Cyclosporine A (CSA) and Mycophenolate Mofetil (MMF) with oral pulse corticosteroids.

INTRODUCTION: The NIDDK is developing a prospective, multicenter, randomized, open label clinical trial to compare the effectiveness of a treatment regimen including cyclosporine A and ACEI therapy to a regimen including mycophenolate mofetil (MMF), oral dexamethasone, and ACEI therapy in inducing remission of proteinuria in patients with steroid resistant FSGS. Patients included in the study will cover an age range of 2 – 35 years. Additional objectives are to compare the persistence of remissions following termination of the primary therapy, rates of extrarenal complications, and change in the level of renal function between the two treatment regimens. Five hundred study participants, recruited by approximately December 2005 local participating sites in the United States and Canada associated with five Core Coordinating Centers, will be randomized for the trial. Each Core Coordinating Center is expected to randomize 100 study participants during a 26-month accrual period. Patients will then be followed for at least 18 months after randomization. Central data collection and analysis will occur at the NIDDK funded Data Coordinating Center at the Cleveland Clinic.

STUDY GOAL: The overall goal of this study is to determine whether either of the two immunosuppressive regimens has a better effect on any of the following: induction of a remission, sustaining of remission, fewer or better tolerated side effects, maintenance of glomerular filtration rate. The ACEI medication will be used as a background, standard of care part of both arms of this open label trial. For patients who are unable to tolerate treatment with ACEi, an ARB will be substituted.

SUPPLEMENTAL INFORMATION: Therapeutic interventions for the treatment of FSGS have been widely reported. However, evidence based treatment guidelines have not been developed because of the lack of controlled studies and the small number of patients included in most reports. While most studies are purportedly undertaken for the purpose of safety, the effect of therapeutic agents on proteinuria is reported and conclusions concerning efficacy are drawn despite insufficient numbers of patients enrolled in these studies to provide statistically valid outcomes. Over the past decade, a number of studies have reported therapeutic efficacy for treatment with Cyclosporine-A (CSA) in patients with nephrotic syndrome including patients with steroid resistant FSGS. There have been two controlled trials of treatment with CSA in steroid resistant FSGS, one in children and one in adult patients. Consequently, CSA is the only medication that has been documented to be efficacious in a controlled trial in both children and adults with steroid resistant FSGS. The use of aggressive high dose

intravenous steroids in the treatment of patients with steroid resistant FSGS has been strongly advocated but is controversial. Therapeutic regimens, which have included pulse corticosteroid therapy, cyclophosphamide and alternate day steroids, have been impressive in uncontrolled series with small numbers of patients. However, high dose intravenous corticosteroid therapy has been associated (although not in FSGS patients) with complications including infection, decreased bone density and demineralization, induction of diabetes mellitus and poor statural growth in children, in addition to the cost and inconvenience of intravenous therapy. Nonetheless, there is a clear consensus among the Participating Sites and the Steering Committee of the FSGS Clinical Trial that the efficacy of pulse corticosteroid therapy should be evaluated in patients with steroid resistant FSGS. Preliminary data suggests that high dose oral dexamethasone may be efficacious in patients with steroid resistant FSGS. The dose of dexamethasone that was chosen for this study is extrapolated from the dose used in a preliminary study and provides approximately 33% of the total steroid dose in the most intense intravenous therapeutic intervention. The dosage of dexamethasone will be 0.9 mg/kg per dose, with a maximum dose of 40 mg, given as a single dose on two consecutive days at the start of weeks 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 30, 34, 38, 42, 46 and 50 for a total of 46 doses. It was felt that this dose could be therapeutic, especially in combination with another agent. The experience with mycophenolate mofetil (MMF) in the treatment of patients with steroid resistant FSGS has been limited to uncontrolled trials in adult patients and children. Although these studies are uncontrolled and consist of small numbers of patients, the combination of MMF with oral pulses of corticosteroids resulted in a significant decline in proteinuria in patients with FSGS. This will be the first controlled trial comparing these two agents. The duration of the trial will be five years. The Collaborator providing the dexamethasone will be expected to provide free active drug for the duration of the study for approximately 250 enrolled participants. The Collaborator may have access to unblinded data at the completion of the trial at the same time as the participating investigators. The NIDDK Project Scientist will obtain any IND's required for the trial. The Collaborator will provide NIDDK staff with information and data necessary to meet the FDA IND requirements.

CAPABILITY STATEMENTS: A Selection Committee will utilize the information provided in the "Collaborator Capability Statements" to help in their deliberations. It is the intention of the NIDDK that qualified applicants will have the opportunity to provide information to the Selection Committee through their Capability Statements. The Capability Statement may not exceed 10 pages and should address the following criteria: Details on FDA drug approval status; Time line for ability to provide drug after selection of Collaborator is determined; Approved daily dose of drug; Known side-effects of drug; Known interactions with other drugs; Ability to provide a liquid preparation with proven bioavailability equivalent to the tablet formulation, and a shelf life of at least one month.

SUBMISSION DATES: A written statement of interest must be submitted by **1 August 2003** and all Collaborator Capability Statements must be submitted by **1 September 2003**

CONTACT INFORMATION: Submit statements of interest and Capability Statements to: Rochelle S. Blaustein, J.D., Office of Technology Transfer and Development

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