STUDY PROTOCOL

NOVEL THERAPIES FOR RESISTANT FSGS
PHASE II CLINICAL TRIAL
PHASED INNOVATION AWARD (DK70341)

A MULTICENTER TRIAL IN CHILDREN AND ADULTS
NCT0081425

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1: INTRODUCTION – BACKGROUND AND SIGNIFICANCE

1.1: Background

1. Clinical trials in FSGS
FSGS is a clinical entity with a distinctive histopathological appearance, which may be either primary or secondary to other etiologies. This lesion may account for 10-20% of cases of primary nephrotic syndrome in children and 35% of cases in adults. In the majority of patients, the primary lesion is refractory to therapeutic interventions using traditional immunosuppressive agents. The final common pathway for advancing disease in primary FSGS is progressive fibrosis leading to ESRD in 50 to 75% of patients over a 10-year period (1, 2, 3, 4, 5). Consequently, the morbidity and mortality of patients with FSGS is compounded by that of superimposed ESRD. The life expectancy for a 10-year old child who is dialysis-dependent is approximately 29 years. Moreover, even if renal transplantation is performed, life expectancy is approximately 55 years compared to 84 years in the general US population. Following renal transplantation for FSGS, a high recurrence rate results in a 20-25% allograft loss and further diminishes the likelihood of long-term survival. Thus, the opportunity for patient survival is dependent upon success in achieving renal survival (6, 7, 8).

The lack of adequate randomized clinical trials has hindered clinical research in the treatment of FSGS. The majority of studies that have evaluated potential therapies for FSGS have either been uncontrolled, have not articulated well-defined end-points, or have been unable to incorporate sufficiently long treatment periods (1, 9). This has engendered a great deal of controversy about optimal treatment of FSGS and variability in practice from the onset of the disease and throughout its course. For example, there is uncertainty about the advisability of administering corticosteroid therapy and how long this therapy should be maintained before categorizing patients as steroid resistant (9,10). Although there are some investigators that consider cyclosporine the best option for patients with steroid-resistant disease (11) this is not a universal opinion. The lack of effective agents after cyclosporine failure is underscored by the observation that only 1 out of 14 invited articles dealing with FSGS described alternative treatments, most of which had only been studied in small uncontrolled patient cohorts (12).

The R33 portion of this project will use a Phase II study design to evaluate the potential efficacy of two novel therapies, and to generate data upon which to more accurately estimate effect sizes. This staged approach to clinical research helps avoid large expenditures for serious diseases with unworthy and untested therapeutic agents.

2. Importance of reductions in proteinuria
The goal of therapy in proteinuric diseases such as primary FSGS is complete remission of proteinuria defined as a urinary protein:creatinine ratio <0.2. However, this is rarely achieved in patients with resistant FSGS (1, 4). Instead, it is more likely that a reduction in proteinuria, albeit still in the abnormal range, can be accomplished. Long-term follow-up from the MDRD cohort and the REIN studies indicates that this is a worthwhile therapeutic objective because long-term renal outcome in patients with chronic glomerulopathies is directly related to the degree of reduction in proteinuria achieved in response to therapy (13, 14). This finding has also been documented in cohorts of adults and children with FSGS (15, 16). Thus, absent a therapy that is

targeted at the putative cause of FSGS, it is still valuable to achieve a significant decline in proteinuria.

3. Progress in anti-fibrosis therapy for renal diseases

Great strides have been made in understanding renal fibrosis. Both TNF-α antagonists and PPARγ agonists can reduce renal fibrosis in experimental models of renal disease that have features in common with FSGS. Inhibition of the scarring process should be equally applicable in sporadic and genetic forms of FSGS (17, 18, 19, 20). Moreover, fibrosis is an inviting target in patients who are resistant to immunosuppressive medications. Because concern that antifibrotic therapy may be ineffective in patients with FSGS whose disease has crossed a specific fibrosis threshold, only patients with an estimated GFR $\geq$ 40mL/min/1.73m^2 will be investigated. Response to antifibrotic treatment is not likely to be affected by age; however, racial background may be a confounding factor in evaluating efficacy of novel therapies because of differences in the incidence of FSGS (21, 22, 23) and enhanced expression of profibrotic cytokines in African Americans (24).

4. Role of conservative medical therapy

When specific therapy is unable to induce remission in patients with primary FSGS, a number of agents have been promoted as renoprotective with a potential to delay progression of CKD to ESRD. ACEi and ARB are two such drugs that reduce proteinuria when used alone and have been shown to have an additive effect on proteinuria reduction when prescribed in combination (25-34). Prescription of HMG-CoA reductase inhibitors in doses that lower hyperlipidemia is associated with stabilization of GFR and improved kidney function in chronic non-diabetic nephropathies (35). Combined use of all of these agents – an ACEi, an ARB, and a lipid lowering drug is likely to represent optimal conservative medical therapy in patients with resistant FSGS and has been advocated as renoprotective treatment (36, 37, 38, 39).

5. Tumor necrosis factor-α (TNF-α)

TNF-α is an inflammatory cytokine that is produced by circulating or infiltrating mononuclear cells, macrophages, and kidney mesangial cells (40, 41, 42). Postulated mechanisms for TNF-α induced proteinuria in FSGS include recruitment of leukocytes to the site of glomerular injury, induction of cytokines and growth factors, generation of oxygen radicals including superoxide resulting in increased glomerular endothelial cell permeability to albumin, direct cytotoxicity to glomerular mesangial and epithelial cells, and induction of apoptosis (43, 44, 45, 46).

In immune-mediated nephritis, there are elevated levels of TNF-α mRNA, high serum levels of TNF-α and subsequent renal injury (47). However, tubulointerstitial infiltration of macrophages and lymphocytes is also a prominent feature in non-immune renal diseases (48). For example, in the double-transgenic rat harboring human renin and angiotensinogen genes, early onset of hypertension, albuminuria, renal fibrosis and mortality are associated with increased entry of mononuclear cells into the renal interstitium. TNF-α antagonism with the soluble TNF-α receptor, etanercept, decreased albuminuria, nuclear factor-kB activation, and infiltration by immunocompetent cells (49). In the 5/6 nephrectomy model of CKD, progressive macrophage recruitment is paralleled by increased renal steady state levels of TNF-α mRNA (50). Upregulation of TNF-α is linked to higher levels of the profibrotic cytokine transforming growth factor-β

(TGF-β) (51). Exposure of mesangial cells in vitro to the combination of TNF-α and TGF-β has a synergistic effect on fibronectin accumulation compared to incubation with each cytokine separately, suggesting that TNF-α is a key mediator of glomerulosclerosis (52).

TNF-α gene expression is increased in glomeruli and medullary tissue during the nephrotic and sclerotic phases of puromycin aminonucleoside nephropathy in rats, a model of FSGS (51). Enhanced production of TNF-α occurs in experimental diabetic nephropathy, a disease that like FSGS is characterized by minimal inflammation. Urinary excretion of TNF-α is increased 3 days after induction of streptozocin-diabetes and injection of a soluble TNF-α receptor fusion protein reduced sodium retention and renal hypertrophy in this model (53). Enhanced urinary excretion of TNF-α is paralleled by a rise in renal interstitial concentrations of the cytokine (54). TNF-α mRNA levels rise more than 4-fold in glomeruli and medullary tissue obtained from rats with streptozocin-diabetes for 24 weeks (56).

In patients with primary nephrotic syndrome including FSGS, elevated serum and urinary TNF-α levels at disease onset decline during remission (56,57,58). Circulating concentrations of TNF-α are higher in nephrotic patients compared with healthy controls with nearly a 20-fold increase in FSGS versus MCNS. Leukocyte cell surface expression of TNF receptors 1 and 2 is increased in steroid-resistant patients (59). Serum TNF-α levels rise just prior to the onset of a relapse, implicating TNF-α in the increased glomerular permeability (57). The increased urinary TNF-α excretion in patients with FSGS does not decline with cyclosporine therapy (58,59).

TNF-α release by cultured peripheral blood mononuclear cells is increased in patients with active nephrotic syndrome and normalizes during remission. Cytokine release correlates with the degree of proteinuria, mesangial hypercellularity, and glomerulosclerosis and a cut-off value of 50 pg/mL for TNF-α production is highly predictive of steroid resistance (58). Supernatants of cultured peripheral blood mononuclear cells obtained from patients with active FSGS syndrome have high TNF-α level. Infusion of this material into rats results in reduced density of anionic sites in the lamina rara externa and provokes albuminuria. (60). This indicates that peripheral blood mononuclear cell-derived TNF-α plays a role in the development of proteinuria in patients with FSGS.

In summary, the potential for TNF-α antagonism to reduce proteinuria in resistant FSGS is based on its role in promoting renal fibrosis, the finding of elevated TNF-α levels in experimental models of the disease and patients with FSGS, reduction in proteinuria with a TNF-α antagonist in the angiotensin II- induced renal injury model, and induction of proteinuria in animals by TNF-α produced by mononuclear cells taken from patients with FSGS.

6. Galactose

Published reports indicate that nearly 50% of patients with primary steroid resistant FSGS have elevated serum levels of a circulating factor that increases the permeability of glomeruli to albumin, P_{alb}, *in vitro* (61). P_{alb} testing provides a sensitive measure of the integrity of the permeability barrier. Experimental values vary from 0, normal, to 1.0, representing maximal loss of barrier function (62). The FSGS permeability factor is

present in a fraction of plasmapheresis effluent obtained from patients with recurrent FSGS after renal transplantation (63, 64). This fraction contains anionic sialoproteins with molecular weights in the range of 30 kDa (65) and a candidate molecule, cardiotrophin-like cytokine-1 has been identified (66). In plasma samples from healthy control patients, cardiotrophin-like cytokine-1 levels are below 10 pg/ml; in contrast, plasmapheresis effluents or plasma from patients with recurrent FSGS have levels exceeding 100 pg/ml. The active fraction of FSGS plasma is obtained by affinity chromatography using galactose coated agarose beads. The active substance(s) bind to the beads and can be eluted using a galactose solution; activity is evident only after removal of galactose by extensive dialysis.

A potential role for galactose in the treatment of resistant FSGS is suggested by the following observations. Addition of 10^{-12} M galactose inhibits the permeability effect *in vitro* and removal of galactose by dialysis restores activity. In contrast, extensive dialysis of sera obtained after prolonged oral galactose does NOT restore activity, suggesting that galactose supplementation may foster removal of active protein(s) from the circulation by enhancing clearance by hepatic galactose binding proteins. In one patient with recurrent FSGS in a second renal transplant, galactose was given intravenously and P_{alb} activity decreased immediately and remained low for several days. Oral administration of galactose at a later date resulted in a delayed decrease in P_{alb} that was evident within 2 weeks and persisted for 4 weeks after the final dose of galactose (67). In a recent case report, oral galactose treatment for over 1 year resulted in normalization of P_{alb}, a decline in proteinuria from 4.2 to 0.6 gm per 24 hr, without a decline in GFRe (68). Two other patients treated at the same center also had improvement in proteinuria (personal communication). Mild gastrointestinal bloating was the only side effect in the treated subjects.

Exposure of glomerular mesangial cells *in vitro* to serum containing the FSGS permeability factor results in inhibition of gene and protein expression of inducible nitric oxide synthase (69). Because nitric oxide inhibits net accumulation of extracellular matrix proteins in the glomerulus by reducing mesangial cell synthesis and enhancing degradation of these molecules (70, 71), this provides another mechanism, in addition to a direct effect on glomerular permeability, by which a reduction in the circulating level of the FSGS permeability factor by galactose would diminish glomerulosclerosis and tubulointerstitial scarring. Taken together, these findings support the premise that galactose may be a safe and effective treatment to remove the FSGS permeability factor, lower proteinuria, and prevent renal fibrosis in patents with resistant FSGS.

In an open-label pilot study, galactose was administered to 23 patients with primary FSGS. Administration of the sugar was authorized by the FDA under IND #77,091. D-galactose, low endotoxin, purchased from Ferro Pfanstiehl (Ferro Corp., Waukegan, IL), was administered orally, 0.2 g/kg body weight per dose, twice a day for 28 days. The 4-week course of oral galactose was tolerated without any clinical adverse events. No patient developed hyperglycemia or any other abnormal laboratory test result. The pilot project was not intended to determine whether galactose treatment can effect a change in urinary protein excretion because the 28-day Treatment Period was too short to achieve this goal in the cohort of patients with resistant FSGS.

In summary, based on the safety and tolerability and anecdotal evidence that galactose can lower high Palb levels in patients with primary FSGS, we conclude that there is

ample justification to proceed to a Phase II clinical trial evaluation of the efficacy of galactose as an antifibrotic renoprotective agent. A longer course of galactose treatment may reveal anti-proteinuric and renoprotective effects in resistant FSGS.

1.2: Preliminary Data: Summary of R21

Preliminary safety, patient tolerance, and PK data for the two novel therapies, rosiglitazone and adalimumab, that will be used in the Phase II trial were generated through the successful performance of a Phase I study.

In the Phase I study, a total of 21 patients were enrolled. 11 were assigned to receive rosiglitazone, and 10 were assigned to receive adalimumab. The patients were evenly divided by gender and pubertal stage. All patients had a GFR >50 mL/min/1.73 m^2.

There were no serious adverse events necessitating the withdrawal of study drug. Rosiglitazone was stopped in one child due to a questionable allergy. The patients tolerated the experimental medications adequately based on the results of the Treatment Satisfaction Questionnaire for Medication (TSQM) which was administered at week 16.

The PK analyses indicated that the rosiglitazone dose needs to be increased to account for increased clearance and reduced area under the curve in patients with resistant FSGS and nephrotic range proteinuria. For adalimumab, clearance was also enhanced especially after receiving multiple doses. However, despite these results of the adalimumab PK analyses, no dose adjustment has been implemented to avoid the long-term side effects associated this antibody, i.e. malignancy and reactivation of TB.

The PK and safety data for each drug were presented in abstract form at the annual meeting of the American Society of Nephrology and published in Clin J Am Soc Nephrol 2009;4:379-47 (rosiglitazone) and Am J Kid Dis 2010;55:50-60 (adalimumab). A manuscript detailing the findings of follow-up observation for approximately 15 months after completion of the Treatment Period has been published in BMC Nephrology 2010 Jan 29;11:2.

Despite the safety and tolerability of rosiglitazone noted in the Phase I testing of the drug in patients with resistant FSGS, recent safety concerns have been raised about this glucose-lowering agent. In several meta-analyses of clinical trials that evaluated the efficacy of the rosiglitazone in adults with type 2 diabetes, there has been an increased risk of myocardial infarction. This hazard may be unique to the drug and not generalizable to the thiazolidinedione class because pioglitazone may not share the same cardiovascular risk profile. Nonetheless, because of the persistent safety issues surrounding rosiglitazone and the strict black box warning and restrictions on its use and fear that including it as an experimental treatment may hinder patient enrollment, this arm is being deleted from the FONT Phase II clinical trial.

The FONT Phase II will again rely on the considerable investment of time and resources on the part of the study investigators and the NIH/NIDDK gained through the FSGS-CT (UO1-DK-63455) and the Phase I portion of the FONT study (DK70341). Steven and Alexandra Cohen Children's Medical Center of New York (CCMC) and University of Michigan resources including the GCRC and CTSA that were utilized in the R21 phase of the study will be available for the R33 portion of the FONT project.

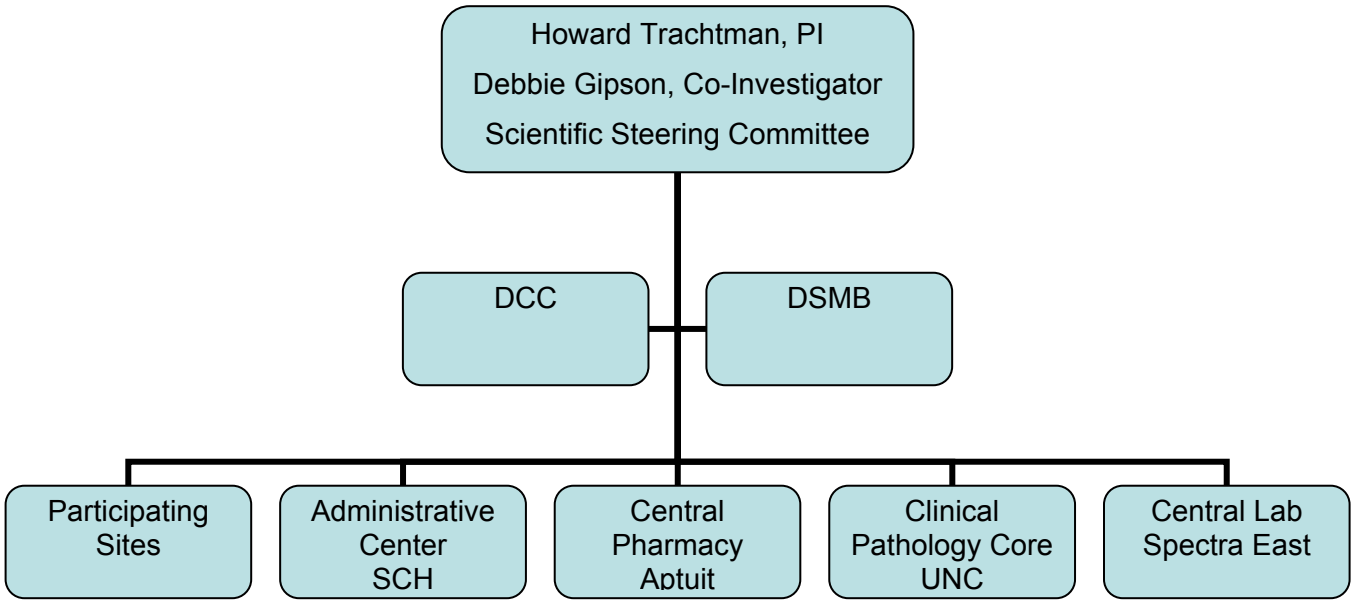
1.3: Specific Aims

A significant percentage of patients with primary FSGS are resistant to corticosteroids and other immunosuppressive medications. In view of the rising incidence of this disease and the grim prognosis for patients with resistant disease, it is imperative that new therapeutic approaches be evaluated in an efficient and systematic manner. This will enable accurate assessment of the risk-benefit ratio of novel therapies and guide the design of future Phase III randomized clinical trials.

Specific Aim #1: To evaluate two novel therapies for resistant FSGS -- anti-TNF-α antibody, and galactose -- against standard therapy

Specific Aim #2: To identify one or more novel agents as candidates for future study in a Phase III randomized clinical trial

1.4: Organizational Structure of the Project



Role of the PI and Co-Investigator: The PI and Co-Investigator will share all responsibilities for study design, construction of the database, creation of clinical report forms, identification of participating sites, training of medical personnel and study coordinators in the proper performance of the protocols, and analysis and reporting of the study outcomes.

Howard Trachtman MD, PI of the project, working at the Steven and Alexandra Cohen Children's Medical Center of New York (CCMC) Clinical Coordinating Center, will oversee subject recruitment, monitor compliance with the protocol, and insure timely collection of experimental specimens and completion of clinical report forms. In addition, he will be responsible for reimbursement to participating sites for effort devoted to this project. Dr Sethna will oversee subject recruitment at Steven and Alexandra Cohen Children's Medical Center of New York (CCMC).

Debbie Gipson MD, Co-Investigator, working at the University of Michigan (Ann Arbor, MI) Clinical Coordinating Center will oversee the Central Pharmacy to make sure that drug supply is adequate and the participating centers are receiving medications on

schedule. In addition, Dr. Gipson will oversee the activities of the Pathology Core to insure that there is prompt confirmation of the diagnosis of FSGS (within 2 weeks). This will enable efficient recruitment of subjects. She will assist with oversight of subject recruitment, compliance monitoring of with the protocol, collection of experimental specimens, and completion of clinical report forms and required regulatory procedures of all participating sites.

Scientific Steering Committee: This group will assist in the oversight of the trial. Their roles include the following:

1. Assessment of the efficacy of the experimental treatments
2. Guidance on adverse event monitoring and discontinuation of the trial
3. Issues pertaining to subject recruitment and site selection
4. Modifications to the protocol
5. Recommendations of future novel agents to be tested in the FONT network

Non-voting representatives of Glaxo Smith Kline, Philadelphia, PA and Abbott Laboratories, Chicago, IL will provide liaison between the Steering Committee and private industry.

DCC (Data Coordinating Center): This unit will be directed by Jennifer Gassman PhD. She has supervised the DCC that is involved in the FSGS-CT and this expertise has facilitated rapid establishment of a database for the R33 phase of this project. They will assist in the identification of treatment and screen failures throughout the trial and will interact with the PI, Co-Investigator and study coordinators to collect data, analyze the results, and provide reports to the DSMB in a timely manner.

Data and Safety Monitoring Board (DSMB): The DSMB is an independent Board comprised of physicians with expertise in nephrology, rheumatology, endocrinology, infectious diseases, clinical pharmacology and biostatistics. The DSMB is responsible for monitoring the project and for subject safety and adequacy of data quality. Details of DSMB activities can be found in the Charter Statement for the Safety and Monitoring Committee.

Independent External Monitor: The Office of Research Compliance at NS-LIJ Health System and the Feinstein Institute for Medical Research will perform an independent external review of all activities related to research compliance to ensure that the FONT Clinical Trial is preformed in accord with all federal and institutional regulations. This monitoring is mandated because Howard Trachtman is Principal Investigator and sponsor of the study and also holds the IND for the use of the experimental drugs.

Pathology Laboratory: The FONT II study pathologist will review existing renal biopsy material to confirm the diagnosis of primary FSGS for all subjects who enroll in the R33 study. This will not be necessary in subjects who have already had a review of the renal histopathology by an FSGS-CT Core Pathologist. This assessment will be done during the screening period for the Phase II trial.

PROMIS Assessment team: Darren DeWalt MD MPH, David Thissen, and Nan Rothrock will interact with the FONT Principal Investigators to integrate the Patient Reported Outcomes Measurement Information Systems (PROMIS) Survey into the

Phase II clinical trial. They will assist in the implementation of this aspect of the project, collection of data, and analysis of the findings.

2: TIMELINES AND DOCUMENTATION

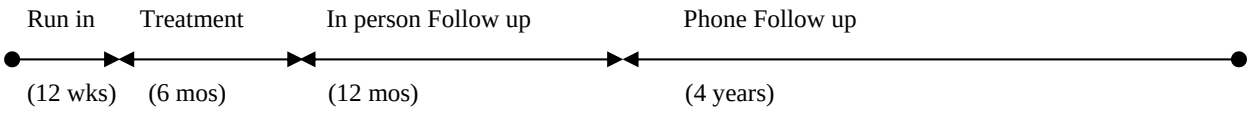
2.1: Project Timeline

03/2010	to	06/2010	Participating Site Training and IRB Approval
08/2010	to	03/2012	Subject Enrollment*
04/2012	to	07/2014	Data collection for efficacy
07/2014	to	10/2014	Data analysis for efficacy
07/2014	to	10/2018	Data Collection for late effects
After		11/201	Final Study Closeout and Data analysis

* During the Subject Enrollment Period, there will be a mandatory 6 month pause in enrollment after the first 17 subjects are assigned into each treatment arm. This will be done in order to permit assessment of the therapeutic response in these subjects and to determine whether there is sufficient preliminary evidence of efficacy to justify proceeding to the target of 42 subjects.

2.2: Patient Timeline

Patient Timeline	Duration
Run In period to stabilize other treatments	2 -12 weeks
Treatment period	6 months
Follow up after Treatment Period	5 years
In person follow up	12 months
Phone follow up	4 years



2.3: Documentation: Protocol, Manual and Forms

2.3.1: Purpose of the Protocol

The protocol describes the study, explains which procedures will be done, why they will be done and how the results will be utilized and interpreted.

2.3.2: Manual of Operations

The Manual of Operations includes the detailed instructions for performing the procedures required by the protocol. Sections of the Manual of Operations will be aimed

toward the Core Coordinating Center Study Coordinator, the Core Coordinating Center Data Entry Specialist, and the Participating Site Study Coordinator.

2.3.3: Forms and Reports

All CRFs and instructions for completion can be found on the Cleveland Clinic Website: https://clinapps.bio.ri.ccf.org

3: OBJECTIVES AND DESIGN

3.1: Co-Primary Endpoints

A subject will be classified as a "responder" if both of the following criteria are achieved:

- A reduction in proteinuria at 6 months by ≥ 50% of the value at the time of screening, AND
- An estimated GFR (eGFR) at 6 months ≥ 75% of the value at the time of randomization in those with an initial eGFR <75 mL/min/1.73 m^2 OR eGFR persistently ≥75 mL/min/1.73 m^2 in those who renal function was ≥75 mL/min/1.73 m^2 at the time of randomization

Rationale: The proteinuria endpoint is a quantifiable variable that is represents an accepted intermediate outcome measure for studies of FSGS that can be achieved in a short-term study (72). In addition, ≥50% reduction in proteinuria is a large enough difference to justify further evaluation of a novel therapy. However, because of concerns that proteinuria alone may be an insensitive measure of efficacy in subjects with advanced resistant FSGS, stabilization of eGFR is included as a second component of a composite primary endpoint. Thus, the combined endpoint defined by the occurrence of either a ≥50% reduction in proteinuria or a stable eGFR value as defined above will define responders for the primary Analysis. The proteinuria at the time of screening will be used to determine eligibility and efficacy to enable determination of whether addition of the antifibrotic agents consolidates the benefits of conservative medical therapy. While a GFR ≥40 mL/min/1.73m^2 at screening will be used to determine eligibility, the GFR at the time of randomization will be used to determine efficacy to account for the hemodynamic impact of intensified combination therapy with ACEi and ARB agents.

3.2: Secondary Endpoints

- Adverse effect profile
- Patient satisfaction score using the TSQM questionnaire (73)
- Quality of Life and PROMIS scores
- Percent change in proteinuria (evaluated as a continuous variable)
- Change in or time to doubling of eGFR
- Response to the experimental treatments and long-term outcome in relationship to podocyte mutations

3.3: Statistical Considerations

Addition of galactose arm: When originally designed, the FONT Phase II trial included three treatment arms. A fourth experimental treatment arm, oral administration of

galactose, was incorporated into the initial randomization. Removal of the rosiglitazone arm will restore the project to a 3-arm study design. This will restore the statistical methods to the original set up. In order to accomplish balanced randomization into the three arm protocol the site investigators will initiate the process of obtaining IRB approval for the revised study, which will enable subjects to be assigned to any of the three arms in the revised Phase II trial as quickly as possible. When the three treatment groups have each reached 17 total subjects, this will initiate the mandatory 6-month pause that has been built into the design of the FONT II trial. At this time, each treatment arm will be independently assessed for the pre-defined retention criteria of at least 2 of 17 subjects demonstrate evidence of efficacy with Up/c reduction by at least 50% and preservation of GFRe.

Primary Analysis and Design Characteristics: FONT II is conceived as a Phase II clinical trial to choose which treatment or treatments are worthy of further study in a future randomized Phase III clinical trial. A hybrid Phase II design as described by Liu et al (74) will be used which incorporates a ranking/selection comparison (75,76) between the treatment groups as well as a minimum activity requirement within each treatment group. The ranking/selection component of the design compares the response rates between the treatment groups, and selects the treatment regimen with the best response rate, irrespective of how large or small the advantage over the others may be. The sample size in such a selection design is selected to assure that if one of the treatments has an underlying response rate which is clearly superior to that of the other treatments; it will be selected with high probability. FONT II includes a sample size of 42 subjects in each of the 2 treatment groups (standard therapy, adalimumab) for a total sample size of 84. With the addition of N=53 in the Galactose arm, the total sample size for FONT III will be 137. This sample size will insure that the treatment with the best response rate will be correctly selected with a probability of 85% if one of the treatments has a response rate $\geq$40% and all the remaining treatments have response rates no higher than 25%.

This first stage of the study's conduct checks for a minimum activity threshold of each drug and provides a separate assessment of activity for each treatment group. This component of the design is based on the parameters p0, the estimated response rate to an "ineffective novel therapy", and p1, the projected response rate to an "effective novel therapy" that we would like to evaluate in a randomized clinical trial (RCT). Based on experience gathered from the Collaborative Glomerular Disease Network, we anticipate that optimal conservative medical therapy will result in response rate ($\geq$50% reduction in proteinuria) of approximately 10%. Taking p0 = 10% and p1 = 30% (designating a 20% improved response for a successful novel therapy), the following two-stage procedure has Type I and Type II error rates of 2% and 10%, respectively.

The two-stage procedure will be conducted within each novel experimental treatment group as follows: Subjects will be enrolled until each of the three treatment groups has approximately 17 randomized subjects. At this point, randomization will be temporarily halted, and there will be a 6 month pause during which the first set of subjects assigned to each of the three arms will be allowed to complete the treatment period and have their response to the therapy evaluated. This is the Stage 1 period for each experimental treatment group.

After the subjects in each of the treatment groups (standard therapy, adalimumab, and galactose) complete the Treatment Period their response to the therapy will be evaluated. If, in any of the adalimumab, and Galactose groups, there are no responders or there is only one responder, that group will be dropped from further consideration. After the 6-month pause, the study will continue to its second stage. Since we anticipate 6 months prior to the pause followed by a 6-month pause, it is anticipated that 8 months of the 20-month recruitment period will remain.

During the remaining 8 months of enrollment, randomization will continue until we meet the sample size goal of 42 subjects (for standard therapy and adalimumab,) and 53 subjects (for galactose) since it is anticipated that a total of 53 subjects will need to be randomized to the galactose arm to insure that at least 42 have a $P_{alb}>0.5$.

At the end of the second stage of the study, there will be a total of 53 subjects in the Galactose arm (to provide a projected total of at least 42 with $P_{alb}>0.5$) and a total of 42 subjects in each of the other two treatment groups. For the primary analysis, only those Galactose subjects with $P_{alb}>0.5$ will be considered. Any treatment with a total of at least 9 responses (out of 42 subjects) will be identified as having a response rate sufficiently greater than 10% and be considered to be “active” and worthy of further study. (The threshold for the number of responses to be classified as “active” in the Galactose arm will be modified if necessary if the actual Galactose arm sample size exceeds 42.)

The requirement of 2 or more responses for the two experimental treatments in the first stage reduces the risk of continuing to enroll subjects into a treatment group for which the early results indicate a low response rate. On the other hand, the 2-stage design has at least a 98% probability of proceeding to the second stage if the true response rate of either of the two initial experimental treatments is 30% or greater. The overall type I and II error rates of 2 and 10% indicate that for each treatment group, the proposed design has a probability of 2% of incorrectly designating a regimen with a 10% response rate as “active”, and a probability of 90% of correctly designating a regimen with a 30% response rate as “active”.

This hybrid Phase II design provides two types of information: The minimum activity assessment for each treatment group indicates whether that regimen is sufficiently promising for further study. The ranking/selection comparison provides a further indication of the single regimen with the best observed response rate, which has a high probability of being the regimen with the optimum response rate should one of the regimens be substantially superior to the two others. If no regimen attains the minimum threshold of required responses in the minimum activity component of the design, the ranking/selection component of the design will not be conducted and none of the regimens will be recommended for further study.

The three groups will each have a different percentage of Subjects with $P_{alb}>0.5$ but sufficient subjects will be assigned to the galactose arm to insure that there are at least 42 with $P_{alb}>0.5$, and the primary analysis of the galactose arm will be done on those with $P_{alb}>0.5$; secondary analyses will include all 53 Galactose arm subjects. This Phase II trial design is not intended to provide a definitive comparison of the novel treatment regimens with each other or with standard medical therapy, but rather is

designed to identify one or more promising agents for further study in a Phase III randomized clinical trial with a larger number of subjects.

In particular, if the underlying population response rates of the top two regimens differ by less than 15%, there may be a substantial probability that the ranking/selection procedure will miss the optimum treatment (76). Thus, if two or more treatment groups meet the minimum activity threshold, and resources are available, consideration should be given to testing each of these treatment regimens in Phase III trials. On the other hand, if resources are sufficient to test only a single regimen, the ranking/selection component of the design provides some guidance as to which regimen should be evaluated in a subsequent Phase 3 trial.

Other Statistical Analyses: In addition to the primary analysis described above, several secondary analyses will also be considered in the decision as to which agent(s) should be pursued in subsequent trials. These analyses will be carried out in treatment arms that proceed to Stage 2 and enroll 42 (or 53 galactose-treated) subjects. Race (black vs. non-black), baseline GFRe <70 vs >70 mL/min/1.73m^2, P_{alb} ≤0.5 versus >0.5, and presence or absence of podocyte gene mutations (analysis to be done at the NIDDK by George Nelson MD, a statistical geneticist) will be included as covariates in secondary analyses. Changes in log transformed proteinuria and estimated GFR (expressed as continuous variables) from baseline to the respective follow-up assessments will be evaluated using mixed effects models incorporating subject specific intercepts and slopes (and higher order terms if necessary) (77). In some but not all scenarios, analyses of these outcomes as continuous variables may have higher statistical power than analyses of the binary primary composite endpoint (78). Mixed effects models will also be used in the analysis of other biochemistry parameters and the subject satisfaction score. Transformations will be considered to make the continuous outcomes approach a normal distribution. Repeated binary outcomes, such as occurrence of adverse events (e.g., yes/no variables defined by occurrences of specific adverse events, decline in proteinuria by 50% at specific visits, or a >33.3% decline in estimated GFR to an estimated GFR < 75 mL/min/1.73m^2 at specific visits) will be analyzed using random effects logistic regression, with random effects for each subject. The effects of treatment assignment on ordered categorical variables (such as the ordered CTC severity categories) will be addressed with longitudinal models adapted for ordered categorical response variables (79,80). Changes in means or proportions (with 95% confidence intervals computed according to methods appropriate for Phase II trials) (81,82) will be estimated separately within each treatment group, and then compared between treatment groups using 2-sided statistical tests with a significance level of 5%. Analyses of secondary endpoints will be regarded as exploratory, and will be interpreted with the context of limitations in statistical power and the possibility of Type I errors due to multiple comparisons between treatment groups.

The frequency of adverse events and differences in subject satisfaction, two of the secondary end points, will be analyzed using the same criteria of drug feasibility that were used in the R21 Phase I studies. The other two secondary endpoints, percent change in proteinuria (evaluated as a continuous variable) and change in or time to doubling of GFRe, will be analyzed using standard methods.

Randomization schedules for the R33 Phase II trial will be prepared by the DCC prior to initiation of enrollment. Randomization will be performed online by an interactive tool

programmed in the study database. After verifying that all baseline case report forms have been entered and enrollment criteria are met, the randomization assignment will be displayed on the screen and e-mailed to the participating site and the central pharmacy to arrange shipment of the assigned drug.

The treatments included in this Phase II clinical trial are at therapeutic equipoise and have a comparable *a priori* likelihood of achieving the primary outcome, namely a 20% increase in the proportion of subjects who experience ≥50% reduction in proteinuria and/or preservation of GFRe in response to the specific novel therapy compared to conservative medical therapy. The rationale for including a control comparison group is because there are few reliable data about the rate of remission (≥50% reduction in proteinuria) following rigorously applied conservative management as a consequence of the prevailing practice to continue aggressive immunosuppressive therapy in steroid resistant subjects with FSGS.

Secondary Endpoints

- Adverse effect profile
- Patient satisfaction score using the TSQM questionnaire (73)
- Quality of Life and PROMIS scores (83)
- Percent change in proteinuria (evaluated as a continuous variable)
- Change in or time to doubling of GFRe
- Response to the experimental treatments and long-term outcome in relationship to podocyte mutations

Data Management: All clinical and laboratory data collected at each visit will be recorded on the case report form and entered into the Oracle Clinical database maintained by the DCC at the Cleveland Clinic Foundation. The only exception will be the Patient Reported Outcome Management Information System (PROMIS) survey which will be completed by the study subject on a secure PROMIS internet based site managed through the NIH sponsored PROMIS Assessment Center, Northwestern University, under the direction of Nan Rothrock, Northwestern University. The survey will be administered under a PROMIS specific subject identifier. This PROMIS identifier will be linked to the FONT II study ID number at the FONT II DCC. Data in the PROMIS Assessment Center data management system will be batch transferred to the FONT II DCC using a secure data file.

4: STUDY POPULATION

4.1: Inclusion Criteria

1. Primary FSGS confirmed by renal biopsy OR documentation of a genetic mutation in a podocyte protein associated with the disease
2. Failure to respond to prior therapy at least one of the following immunosuppressive medications -- cyclosporine, tacrolimus, mycophenolate mofetil, sirolimus – or other agents prescribed to lower proteinuria
3. Age 1-65 years at onset of proteinuria
4. Age 1-65 years at time of randomization
5. Estimated GFR ≥40 mL/min/1.73 m^2 using Schwartz (age <18 yr) or Cockcroft-Gault (age ≥ 18 yr) formula at screening and ≥30 mL/min/1.73 m^2 at the end of the Run-In Period and prior to randomization
6. Up/c > 1.0 g/g creatinine on first morning void
7. Steroid resistance defined as failure to achieve sustained Up/c < 1.0 following a standard course of prednisone/prednisolone/methylprednisolone prescribed for FSGS therapy, OR contraindication/anticipated intolerance to steroid therapy defined as severe obesity, documented decreased bone density, family history of diabetes, or a psychiatric disorder.
8. Willingness to follow the protocol, including medications, baseline and follow-up visits, and procedures.

Rationale: The eligibility criteria for this project are modified from those used in the FSGS-CT based upon the collective clinical experience in that study and to overcome obstacles to enrollment of potential subjects FSGS can occur as a consequence of genetic mutations in structural proteins in the podocyte (84,85,86,87) The more widespread use of genetic testing provides an alternative method of establishing a diagnosis of primary FSGS and is a suitable criterion for enrollment, independent of the kidney biopsy findings. The wider age range will allow more subjects to be considered without compromising the homogeneity of the disease cohort. The steroid resistance criterion has been revised to acknowledge the justifiable resistance of internal medicine nephrologists to administer a prescribed course of steroids in all subjects because of potential life-threatening consequences that might result from this medication.

Although genetic screening for podocyte gene mutations will serve as a revised inclusion criterion, this testing is not mandatory because of a lack of data on expected response rates in the presence or absence of podocyte mutations. In addition, progressive renal fibrosis is similar in primary FSGS, regardless of whether or not there is a defined genetic mutation.

There is also no exclusion criterion based on obesity because antifibrotic agents should also be beneficial in subjects with obesity-related FSGS. Therefore, all subjects with resistant FSGS may benefit from the novel therapies being tested.

4.2: Exclusion Criteria

1. Lactation, pregnancy, or refusal of birth control in women of child-bearing potential
2. Participation in another therapeutic trial involving protocol mandated administration of a immunosuppressive medication concurrently or 30 days prior to randomization
3. Active/serious infection (including, but not limited to Hepatitis B or C, HIV)
4. History of malignancy
5. Abnormality in age appropriate cancer screening in accord with ACS 2003 guidelines (see appendix located in MOP-Manual of Operations) (88)
6. Patients with uncontrolled blood pressure >140/90 or >95th percentile for age/height at the end of the run in period
7. Diabetes mellitus Type I or II
8. Organ or bone marrow transplantation
9. Congestive heart failure
10. History of prior myocardial infarction
11. SLE or multiple sclerosis
12. Hepatic disease, defined as serum ALT/AST levels more than 2.5x the upper limit of normal
13. Hematocrit <27%
14. Immunosuppressive therapy with cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, rapamycin, or cyclophosphamide in the 30 days prior to randomization or Rituximab in the 90 days prior to randomization
15. Use of corticosteroids in the 30 days (prior to randomization) except for minimal dosage required for stabilization of edema. The site PI must consult with the PI or Co-PI to provide justification for this minimum dosage and reassurance that it will remain fixed for the duration of the treatment period.
16. Prior treatment with the study medications, adalimumab or galactose
17. Allergy to one of the study medications, i.e., adalimumab, galactose, lisinopril, losartan or atorvastatin
18. Abnormal Pap smear (more than CIN1) unless treated and follow-up indicates a normal Pap smear.

Rationale: The cardiovascular exclusion is expanded to insure patient safety in those who are assigned to either experimental treatment. Any prior history of malignancy is also an exclusion criterion to insure safety in those who are assigned to the adalimumab treatment arm.

5: IRB AND INFORMED CONSENT

5.1: General Principles of Consent

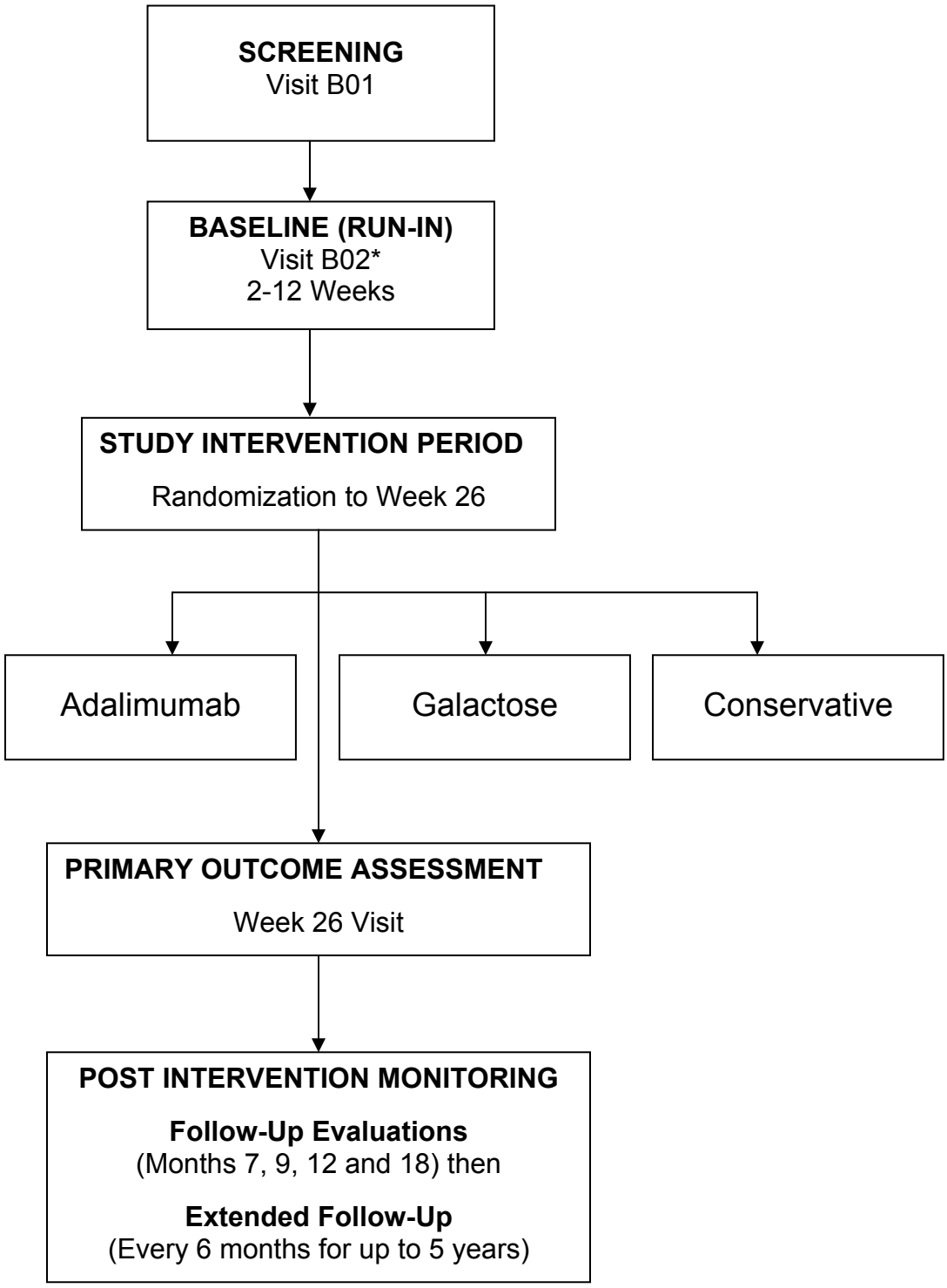
1. To be eligible for the study, each subject must meet preliminary eligibility criteria and the subject or guardian must be willing to sign a statement of informed consent (see Template “Consent For Participation in a Research Study” located in the Manual of Operations). This will document the agreement of the subject to take part in the study activities.
2. The time frame of a subject signing an informed consent to actually being randomized must be ≤ 6 months. If this time frame is greater than 6 months, it will be necessary to reconsent the subject before being randomized into the FONT II study.
3. Separate informed consent will be obtained for participation in the clinical trial and for obtaining and storing of biological samples (see Template "Material Consent for Provision of Biorepository Samples” located in the Manual of Operations). Although subjects will be permitted to join in the therapeutic trial without granting permission for collection and storage of biological samples, they will not be invited to provide biological specimens without being part of the clinical trial. (Note: NIH approval is required for *Repository Consents* before specimens can be taken out of the Repository.)
4. For each subject in the FONT II Study a de-identified copy of his/her informed consent signature page, specifying the assigned identification number, will be faxed to the DCC.
5. Subjects will be asked by study personnel not to participate in any other therapeutic research studies during the subject’s follow-up period from baseline to the 18-month visit. A template informed consent form is provided in the Manual of Operations (MOP).

Privacy

1. At the beginning of the study, each subject is assigned an identification number and a study code.
2. In any individual tabulation, subjects will be identified only by number.
3. The medical records of subjects in the FONT II study will be confidential. Subject documentation and files will be stored in numerical order and stored in a secure and accessible place and manner.
4. Specific study related information may be made available to the Food and Drug Administration (FDA) and the National Institutes of Health (NIH).
5. All procedures will be in compliance with HIPAA (Health Information Portability and Accountability Act) regulations.

6: SUBJECT MANAGEMENT AND STUDY VISITS

The following figure outlines the course of the Phase II trial.



*The baseline (B02) assessments will not be done, if the subject meets the criteria for the abbreviated screening period.

Frequency of visits: After the screening period, subjects will be evaluated after 0, 2, 8, 16, and 26 weeks of treatment with the novel therapy or conservative medical therapy alone. This timing will coincide with the adalimumab dosing schedule and allow reinforcement of education about the technique of drug administration for subjects assigned to this medication. Thus, there will be a total of 7 visits including the screening/run-in period and the treatment period.

Visits will be performed within ±7 days of the target visit date. All visits should be scheduled as close as possible to the day defined by the protocol. If a visit must be rescheduled, make every effort to schedule the visit within 2 days before or after the designated date.

A follow-up evaluation will be performed at 1 month, 3 months, and 6 months after discontinuation of the novel therapy, and then every 6 months until the end of the funding period.

6.1: Procedures During Screening/Run-In (B01 and B02)

Screening/Run-In: There is no formal run-in period in the phase II trial because subjects with resistant FSGS who will be eligible for this study often have unstable kidney function and are prone to sudden decline in GFR. An effort will be made to achieve randomization between 2 and 12 weeks of the initial screening visit (B01).

In order to achieve a comparable baseline assessment prior to initiation of one of the novel therapies, the subjects must be off all immunosuppressive medications including corticosteroids (except for minimal dosage to control edema) for 30 days (prior to randomization). In addition, subjects will be placed on the maximal tolerated doses of an ACEi, and an ARB based upon measurements of blood pressure, serum K^+, and creatinine. Subjects will have to be on stable doses of the ACEi/ARB treatment for a minimum of 2 weeks prior to randomization into the FONT Phase II study to insure that the initiation of novel therapy does not coincide with a hemodynamically induced change in proteinuria. In order to implement this part of conservative medical therapy, a 2-12 week Screening/Run-In period will precede randomization. Blood pressure will be controlled in accord with published guidelines in pediatric and adult patients (89,90).

Those subjects who already meet the screening criteria at Visit B01 may forego Visit B02. This will be explained in greater detail later in this protocol.

Rescreening will be necessary if subjects are not randomized to one of the three treatment arms within 12 weeks of the initial screening assessment. If the rescreening is done within 3 months, the participating site will need to repeat only those tests that excluded the subject plus a serum creatinine. Otherwise if time lapse is greater than three months, all tests for screening will need to be repeated. The participating site may rescreen a subject one time only.

Screening/run-in evaluation (Visits B01):
At the B01 visit, informed consent will be obtained and preliminary eligibility will be determined.

Study ID Number
The assigned ID number will have three parts – 123-001. The first 6 digits will be composed of the 3 digit number assigned to each site by the FONT DCC followed by a consecutive number for each subject enrolled at the site beginning with 001. The last 2 digits will be a unique alpha code assigned to each subject.

Initial assessment
During the Screening Period, subjects with FSGS who are potentially eligible for the Phase II clinical trial should be evaluated to ensure that they satisfy the inclusion criteria. Special attention should be made to ensure that they have biopsy-proven primary FSGS that is resistant to steroids and a second immunosuppressant therapy, that their estimated GFR is greater than 40 mL/min/1.73 $m^{2.}$, and that their urine protein:creatinine ratio is greater than 1.0 g/g creatinine. This evaluation can be performed during a routine clinic visit.

Medications
Subjects should be queried about use of any of the immunosuppressive medication including steroids. Subjects must be off these drugs for 30 days prior to randomization in the study. If minimal doses of corticosteroids are considered necessary for subject stability, this should be discussed with Howard Trachtman, MD, Principal Investigator or Debbie Gipson, MD, Co-Investigator during the Screening/Run-in Period prior to randomization. Otherwise, they are disqualified from participating in the study. Subjects who are receiving concomitant treatment with an ACEi and ARB for control of blood pressure or to lower proteinuria will be allowed to continue these medications in doses prescribed by the protocol. The study doses of lisinopril, losartan, and atorvastatin are described in section 8. Subjects may receive vitamin E or diuretics.

Clinical Management
During the Screening/Run-in period, subjects who are not already on the medications should be started on a combination of the ACEi (lisinopril) and the ARB (losartan). By the end of the Screening/Run-in Period, subjects must be on the maximum tolerated doses of lisinopril and losartan combination. **For children weighing less than 40 kg, the maximum doses are 10 mg of lisinopril and 25 mg of losartan. For subjects weighing 40 kg or more, the maximum doses are 20 mg of lisinopril and 50 mg of losartan.** These are target doses and they can be adjusted downward for reasons of safety and/or tolerance. If a subject requires additional treatment for hypertension, the lisinopril or losartan dose may be increased at the preference of the study investigator. Additional antihypertensive agents should be used if blood pressure is not controlled on lisinopril and losartan. If a subject is intolerant of ACEi because of cough, then the losartan dose can be doubled if necessary.

There is no protocol-mandated escalation schedule for the lisinopril and losartan and this can be done at the discretion of the site investigator as long as the maximum doses are reached by the end of the Screening/ Run-in period or if escalation to full dose is prevented by signs of intolerance such as orthostasis or hyperkalemia. The doses of these medications should be left unchanged for the duration of the 6-month treatment.

PLEASE NOTE: During the course of the trial, subjects will be given a prescription for lisinopril and losartan and these medications will be provided via the subject's regular medical insurance coverage because these drugs are considered standard of care in patients with FSGS and persistent proteinuria.

Required Screening data (B01)

1. History and physical examination, including examination of lymph nodes, liver and spleen. Measurement of vital signs, height and weight.
2. Urine protein and creatinine excretion - Proteinuria (Up/c) will be expressed as the protein:creatinine ratio (mg:mg) in an early morning specimen. The value will represent the average of two samples collected during the week before this study visit.
3. B01 labs (see Schedule of Events in Section 6.5).
4. HIV, Hepatitis B and C serology, if not done in previous 12 months. In cases where there is a low clinical suspicion of HIV, serology results may be reported as negative within the previous 36 months.
5. TB skin test, if not done in the previous 12 months.
6. A urine pregnancy test will be obtained for females of childbearing potential.
7. A request will be made to collect urine, plasma, serum, and DNA samples from all subjects who are enrolled in the FONT Phase II clinical trial. These samples will be obtained from subjects who provide consent for collection and storage of repository samples. The repository samples should be obtained prior to initiation of novel therapy (at either visit B01 or B02) for storage in the NIDDK Biorepositories. See Section 6.4 for Repository Sample details.
8. Existing renal biopsy tissue will be assessed by the study pathologist for all subjects who have not had the diagnosis of FSGS confirmed by an FSGS-CT core pathologist.
9. Quality of life assessment with PedsQL (children) or SF-36 (adults) and PROMIS (age 8 years and greater) (84,91, 92,93) if B02 visit is not required

*During the B01 visit – **KEY POINTS**:*

1. Review all prescribed medications and record on Medication Form
2. Ensure that the subject is not receiving medication that would result in exclusion
3. Screen for any condition that precludes the subject from being randomized to either of the study regimens. Any medication that does not result in the exclusion of the subject may be continued if it is required during the study.
4. If the subject is not yet taking an ACEi or ARB then these drugs should be started (see Clinical Management section above).
5. The Up/c must be > 1.0 mg/mg to be eligible for inclusion in the study.
6. Ensure that the subject has a negative cancer screening 2003 guidelines according to the American Cancer Society (ACS) 2003 guidelines (88), as appropriate to subject demographics and clinical status.

Because of the potential risk of development of malignancy as a result of adalimumab treatment, eligible subjects must have current cancer screening according to the American Cancer Society (ACS) 2003 guidelines (88), as appropriate to subject demographics and clinical status. Flowcharts outlining the ACS 2003 guidelines are provided in MOP (Manual of Operations). A history of any type of cancer constitutes an exclusion criterion.

Abbreviated Screening Period
If a subject is already on medication and has reached target doses of ACEi and ARB for a minimum of 2 weeks at the time of the B01 visit, the B02 visit will not be required.

The B02 visit is held primarily for safety reasons. It is done to ensure that implementation of the combination of ACEi and ARB at the target doses does not cause a decline in GFR below 30 mL/min/1.73 m^2, the eligibility cut off. The subject will receive a screening GFR at B01 to ensure that a decline below 30 mL/min/1.73 m^2 has not occurred.

Screening/run-in evaluation (Visit B02):

If the patient starts the ACEi and ARB at the B01 visit, then the B02 visit should take place once the subject has reached the target doses of these medications. The visit must be completed within 2 to 12 weeks after the B01 assessment. The duration of the Screening/Run-in period is left to the discretion of the site investigator but must be within the 2-12 week range. If the subject meets the screening criteria at Visit B01, then Visit B02 may not be necessary.

The following procedures will be completed at the B02 visit

1. Interval History and physical examination, including examination of lymph nodes, liver and spleen. Measurement of vital signs sure, height and weight will also be done. .
2. B02 labs (blood and urine tests) (see Schedule of Events in Section 6.5). These tests should be sent to the central laboratory (Spectra). They can be obtained and sent either from the participating site or from the office of a local physician provided the laboratory tests are sent to the central laboratory. These arrangements should be made in advance to make enrollment into the study and initiation of the Treatment Period as convenient as possible for the individual subject.
3. Quality of life assessment with PedsQL (children) or SF-36 (adults) and PROMIS (age 8 years and greater) (84,91, 92,93). If the B02 visit is not necessary, these assessments will be done at B01.
4. Adverse event assessment
5. Record concomitant medications

Assessment of Eligibility and Randomization
Subjects will be considered eligible for randomization if they provide consent to participate, if all of the required screening data is collected and validated, and no additional exclusion criteria are identified during the screening/run-in period.

For safety reasons, if the estimated GFR is less than 30 mL/min/1.73 m^2, at the B02 assessment, then the subject will not be eligible for randomization and will be excluded from further study. The urine protein:creatinine ratio at the time of the screening visit (B01) is the value used for trial eligibility.

Please note that the potassium, creatinine concentrations, CBC and pregnancy test **must be repeated** at the B02 Visit even if they were measured at the Screening Visit.

(***If the subject meets the criteria for the abbreviated screening period, none of the B02 Visit labs are necessary***.)

If the subject satisfies the inclusion criteria and the studies confirm that enrollment is safe, then he/she will then be randomized to either:

(1) Conservative Medical Therapy (standard therapy),
(2) Adalimumab, or
(3) Galactose.

Subjects will be randomly assigned to one of the three treatment arms. The adalimumab vs. galactose vs. standard therapy 1:1:1allocation scheme will be used to overcome subject heterogeneity caused by eligibility criteria that enable immediate or delayed enrollment. In addition, all study arms are at therapeutic equipoise and have a comparable *a priori* likelihood of being safe and acceptable to subjects.

6.2 Study Intervention Period (Week 0 through Week 26):

Duration of novel therapy: Novel therapies will be administered for 6 months before assessing efficacy, i.e., ≥50% reduction in proteinuria. Although the novel therapies target renal fibrosis, it is anticipated that this period of treatment will be sufficient to document a beneficial effect on proteinuria.

Week 0 Visit:
Subjects will then return to the participating site at the Week 0 visit to receive their assigned study medications and will be instructed on the continuation of the Conservative arm or the appropriate method of administration of galactose (oral powder), and adalimumab (subcutaneous injection every other week). Atorvastatin will be dispensed at this visit and subjects will be given instructions on how to achieve the target dosage of the statin. For information on statin dosing see section 7.1 - Conservative medical therapy.

Week 02, 08 and 16 Visit:
Study Intervention Procedures:

1. Interval History and physical examination, including examination of lymph nodes, liver and spleen, measurement of vital signs, height and weight.
2. Labs and urine protein:creatinine (see Schedule of Events in Section 6.5). These tests should be sent to the central laboratory (Spectra).
3. Adverse event assessment
4. Record concomitant medications

Final Outcome Visit (Week 26)

1. History and physical examination, including documented examination of lymph nodes, liver and spleen, including the measurement of vital signs, height and weight.
2. Morning urine protein and creatinine excretion x 2 (The value will represent the average of two samples collected during the week before the visit.)
3. Labs (see Schedule of Events in Section 6.5)
4. Urine, serum and plasma for Biorepository

5. TSQM, age appropriate QOL and PROMIS questionnaires
6. Adverse event assessment
7. Record concomitant medications

6.3: Follow-Up Evaluations (after discontinuation of study medication)

Follow-Up Evaluations (Month 7, 9, 12, 18):
After completion of the 6-month Treatment Period, an in-person follow-up evaluation will be performed at 1 month (M07), 3 months (M09), and 6 months (M12) and 12 months (M18) after discontinuation of the novel therapy. Testing at local labs may be utilized if adverse events occur that require urgent clarification and the subject cannot travel to the participating site.

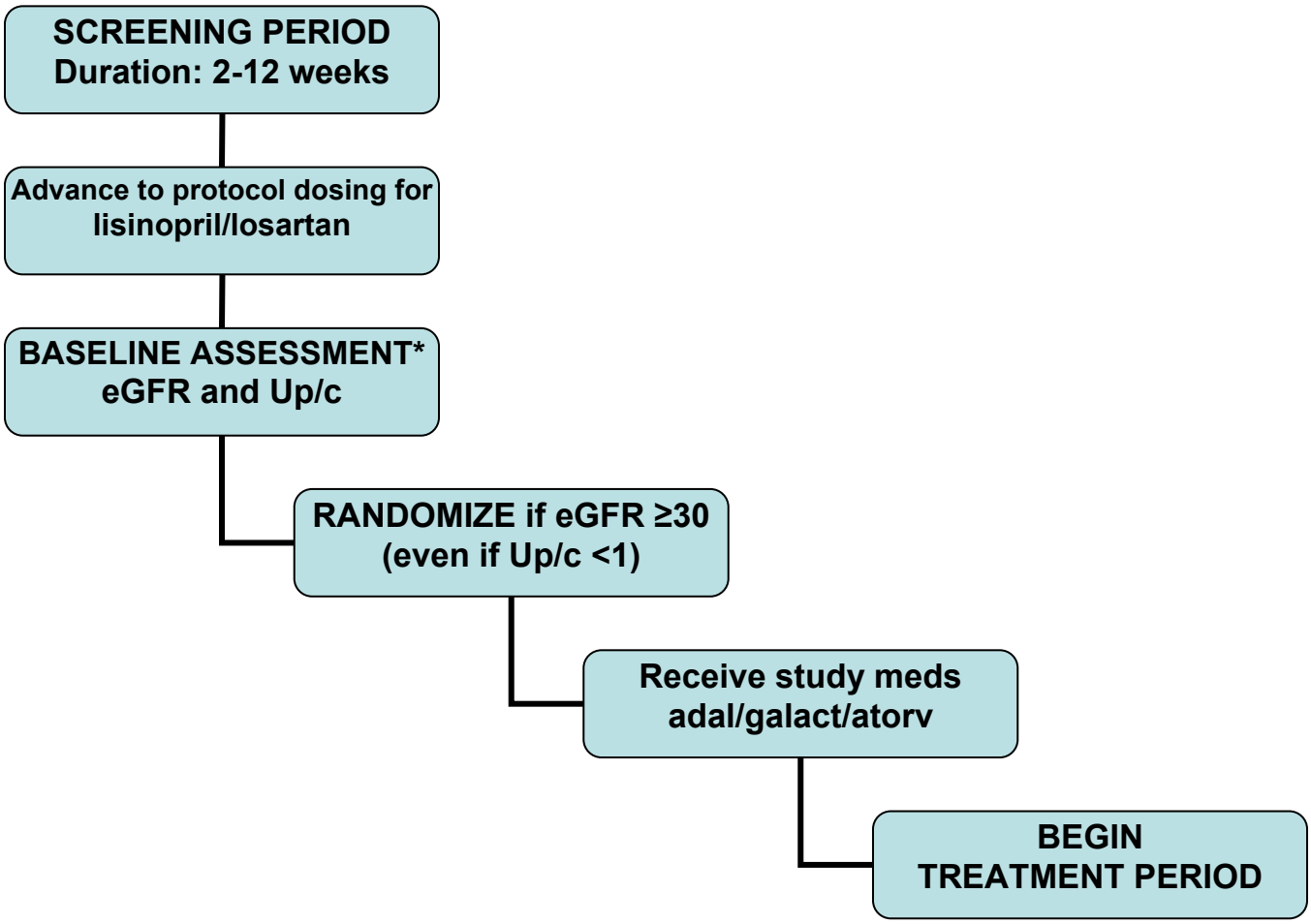
1. History and physical examination, including documented examination of lymph nodes, liver and spleen and measurement of vital signs, height and weight.
2. Labs and urine protein:creatinine (see Schedule of Events in Section 6.5)
3. Age appropriate Quality of Life (Months 12 and 24)
4. Adverse event assessment
5. Record concomitant medications

Extended Follow-up Period Evaluations (After Month 18 Visit):
After Month 18, visits can be done by telephone collecting available information. Quality of Life forms may be completed at home and submitted by mail.

After the completion of the 12 months of direct clinical follow-up (after the treatment period) information can be collected in-person or by telephone to document any new diagnoses in the past 6-12 months (i.e., lymph node enlargement, weight loss that was unanticipated, kidney failure, dialysis treatment, etc.). This information will be collected for up to 5 years from end of subject's treatment period.

SUBJECT MANAGEMENT

The relationship between the Screening/Run-in period, baseline assessment and randomization are summarized in the following figure:



*The baseline (B02) assessments will not be done, if the subject meets the criteria for the abbreviated screening period.

6.4: General Study Procedures

The following subsections describe the specific procedures for the FONT study protocol.

First Morning Urine (FMU) Samples

1. First morning urine collections for measurement of the urine protein: creatinine ratio (Up/c) should be obtained at each protocol visit. The urinary protein and creatinine concentrations should be measured as mg/dl.
2. In order to obtain the most reliable estimate of urinary protein excretion and to eliminate any orthostatic component, this determination will be done in early morning specimens rather than random spot urine samples. The early morning urine sample should be collected as soon as the subject awakes in the morning prior to engaging

in any activity. It is advisable to place a specimen cup in the bathroom in the evening prior to specimen collection.

3. A specimen should be collected on the morning prior to (urine should be less than seven days old when brought in for their visit) the screening and all follow-up visits. Subjects should bring these specimens in to the clinic. (Refrigerate specimens prior to visit for analysis)
4. The Up/c ratio at the Screening and week 26 outcome visit will be an average of 2 first morning urine samples. The intermediate follow-up visits will be calculated using a single value measured in one early morning urine sample. Subjects should be instructed to avoid drugs that interfere with creatinine excretion (e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, Tagamet (cimetidine), and NSAIDs for 48 hours prior to Up/c determination. Common NSAIDs include: Ibuprofen (Advil) and Naproxen (Aleve).
5. It is recommended that subjects be contacted prior to a scheduled visit to inquire if he/she has any of the following problems:
    a. Intercurrent illness
    b. Fever > 38º C (100.4º F)
    c. Temporary use of a medication that interferes with creatinine excretion (see list of medications above). These conditions might cause a transient increase in proteinuria or alter the Up/c. If any of these circumstances apply, then reschedule the planned visit.

Note: All visits should be scheduled as close as possible to the day defined by the protocol. If a visit must be rescheduled because of illness or other problems such as school tests or transportation difficulties, make every effort to schedule the visit within 2 days before or after the designated date. This procedure will enable repeat testing, if needed, to be performed in a timely manner. If the subject is found to have fever or an intercurrent illness at a scheduled follow-up visit, then the urine sample should be discarded and a repeat sample should be obtained.

Blood Pressure Determinations

The normal values for blood pressure in pediatric age subjects are be based on the Second Task Force on Blood Pressure in Children (89) and in adults on the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (90). The blood pressure charts can be found in the MOP.

1. Blood pressure should be measured by trained personnel at each visit.
2. A sitting blood pressure should be recorded at each visit.
3. If possible, it is advisable that the same individual should measure the blood pressure in a subject at the baseline and follow-up visits to minimize inter-observer variability.
4. An appropriate size cuff should be used. This is defined as a blood pressure cuff containing a bladder, which covers at least 2/3 of the distance from the acromion to the olecranon. If there is any doubt about cuff size, then a larger rather than an inappropriately small cuff should be used. In adolescents or overweight adults, it may be necessary to use a large adult or thigh cuff to obtain an accurate measurement. If there is any doubt, it is preferable to err to the side of using a cuff that is too large rather than using a cuff that is too small.
5. The subject should be seated with arm extended at heart level for approximately 5 minutes prior to making the measurement.

6. Blood pressure can be measured using standard auscultatory methods or using an oscillometric device such as the Dinamapp. Auscultation is preferred. Try to use the same method throughout the study.
7. The method of measuring blood pressure should be recorded with each reading.
8. Investigators are encouraged to adjust antihypertensive agents to optimize blood pressure control throughout the trial. Lisinopril and Losartan doses will be optimized prior to study entry and should remain unchanged except for toxicity reasons.

Laboratory Tests

1. Blood will be collected at any time of the day.
2. Blood and urine assays will be conducted in the Central Laboratory. Although urinalysis is recommended as standard of care, it is not mandatory at the screening visit.
3. Pregnancy test, Human Chorionic Gonadotropin (HCG), should be assessed at B01, B02 and at the specified visits in women of childbearing potential (post pubertal, premenopausal, not surgically sterilized). Urine pregnancy testing will be preformed at the central lab.
4. Laboratory studies including glycosylated hemoglobin and fructosamine will be analyzed at the central laboratory, Spectra East. The blood sample for the in vitro glomerular permeability (Palb) assay will be sent to the laboratory of Virginia Savin MD (Kansas City, KS) and the blood for determination of serum galactose concentration will be sent to the laboratory of Daniel Stein PhD (Bronx NY).
5. Testing at local labs may be utilized if adverse events occur.

NOTE: Although there is a formal requirement to repeat a pregnancy test at specified follow-up visits, it is advised that the test be repeated as often as deemed clinically necessary to avoid unanticipated teratogenic effects of the drugs used in the treatment protocol.

See the Schedule of Events in Section 6.5 for the timing of laboratory tests.

Estimation of Glomerular Filtration Rate

The purposes of estimating glomerular filtration rate (GFR) are to:

1. Determine eligibility for the study AND
2. Provide an estimate of renal function for longitudinal analyses of the effects of the treatment intervention on GFR as a side effect of therapy or progression of disease.

To determine GFR:

1. The average of serum creatinine values at the Screening visits (B01 and B02) will be used for the calculation of the study estimated GFR baseline.
2. GFR will be estimated by the Schwartz formula for subjects age < 18 years and by the Cockcroft Gault formula for subjects age is ≥ 18 years.
3. The local investigator should use the formulas (see Manual of Operations for formulas) when calculating the GFR to determine eligibility during the Screening Evaluation.

Additional Samples for Special Studies at the Screening Assessment

Testing for HIV, Hepatitis B and C if not done in the previous 12 months. (The site must provide documentation of the result of these tests if they are not being repeated). In

cases where there is a low clinical suspicion of HIV, serology results may be reported as negative within the previous 36 months.

Biorepository Samples:
Additional biological samples will be obtained at screening (B01 or B02) and Week 26. The biological samples will be stored for use in future studies of the pathobiology of FSGS. A separate materials consent will be obtained to specifically address the collection of these specimens. Among those subjects who consent for storage of biological specimens, urine, serum and plasma specimens will be shipped to the National Institutes of Health Biosample Repository at Fisher BioServices. In addition, whole blood specimens for DNA will be shipped to the National Institutes of Health Genetics Initiative at Rutgers University Cell and DNA Repository. In subjects who enroll in FONT who were participants in the FSGS Clinical Trial, DNA testing will **not** be repeated.

Collection of biosamples and DNA will be fully coordinated with the FSGS-CT and FONT NIDDK sponsored Biorepositories. DNA samples will be stored in the Rutgers University Biorepository under the auspices of the NIDDK under the direction of Rebekah Rasooly MD. Storage of materials in the NIDDK Biorepository will facilitate future studies into the mechanism of action and laboratory correlates of response to novel therapies. Sample storage and investigational use will be conducted under the Ancillary Studies Protocol of the FSGS-CT (see section 14 of the FSGS-CT Protocol). This document is available on the FSGS-CT website, www.fsgstrial.org.

PPD (tuberculosis skin test)
Potential subjects without a history of a previously positive PPD skin test (tuberculosis skin test) must receive a PPD test during the screening period unless the subject has a documented negative PPD test in the 12 months prior to enrollment. PPD must be negative. In the case of a historically positive PPD, confirmation of previous therapy for tuberculosis and a negative chest radiograph is an acceptable alternative.

Kidney Biopsy Review
The existing kidney biopsy that documents the diagnosis of FSGS will be reviewed by the FONT study pathologist unless previously reviewed and approved by an FSGS clinical trial pathologist. See detailed description of pathology procedures in Section 9.

History and Physical Examination
A full history and physical examination should be done at all required visits (see the Schedule of Events in Section 6.5) including measurement of including height, weight, and vital signs.

Participant Questionnaires
The TSQM questionnaire should be administered at the Week 26 visit. Satisfaction with the novel therapy regimen will be assessed using the Treatment Satisfaction Questionnaire for Medication (use authorized by S. Colman, Quintiles Late Phase, San Francisco, CA). It yields valid information in four areas – effectiveness, side effects, convenience and global satisfaction. This index contains 14 questions, scored on a Likert scale and requires approximately 10 minutes to complete. The results are scored on a 0-100 scale.

Quality of life questionnaires will be self administered at the B02 visit, week 26, week 52 and year 2 visits.

a. The SF-36 is a 36 item quality of life questionnaire self-reported for adults age 18 and above (108).
b. The PedsQL is a 23 item quality of life questionnaire self-reported for children ages 5 to 17 years and parent proxy-reported for ages 2-17 years (92)
c. The Patient Reported Outcome Measurement Information System (PROMIS) (17.9) will be completed by study subjects age 8 and above (83). This permits the assessment of patient reported outcomes across the life span.

Validated translations of the SF-36 and the PedsQL will be provided in English, Spanish, and French. PROMIS is an English only instrument

Additional QOL assessment will be conducted at study year 2 if additional funding is acquired.

General Standard of Medical Care

The study protocol does not define the specific care to be provided for the following problems that are likely to arise in the subjects identified during the Screening Period or the Treatment and Follow-up Periods: (1) hypertension; (2) hyperlipidemia; (3) edema. All participating PIs are encouraged to treat these problems in the best manner possible, in accordance with the prevailing practice patterns at their institution. The therapy for these problems can be initiated during the Baseline period.

1. For hypertension medications should be prescribed to maintain the blood pressure below the 90th percentile for gender by age and height for children and ≤ 130/80 for adults. Additional medications to control blood pressure can be prescribed if needed, after maximizing the ACEi and ARB dosing in the screening phase.
2. Modification of diet and the use of cholesterol lowering medications are encouraged to achieve target lipid levels. These can include statins or cholesterol binding agents, whatever is deemed appropriate for the specific subject.
3. It is anticipated that edema may be a persistent or recurrent problem in subjects enrolled in the clinical trial. This may be managed using dietary sodium restriction, diuretics as single agents or in combination therapy, and/or alternative medication supplements. It is advised, if possible, that diuretic medication should not be changed within one week of a scheduled visit.
4. Dietary advice and the use of antacids and H2 blockers to prevent gastritis will be left to the discretion of the Participating Site PI. However, cimetidine must be held for 48 hours before each follow-up visit in order to enable accurate measurement of the serum creatinine concentration and Up/c ratio. Therefore an alternate H2 Blocker may be more compatible with trial subjects.

6.5 – Schedule of Events: The following table summarizes the evaluations during the Phase II Trial

	Screening Run-In		Wk 0	Wk 2	Wk 8	Wk 16	Wk 26	Mo 7	Mo 9	Mo 12	Mo 18	q 6mo[7]
	B 01	B 02*										
Physical Exam [1]	X	X		X	X	X	X	X	X	X	X	X[8]
History	X	X		X	X	X	X	X	X	X	X	X
Pre-visit telephone contact [2]		X		X	X	X	X	X	X	X	X	
QOL and PROMIS	X [11]	X[11]					X			X		X[9]
TSQM							X					
Up/c	XX[3]	X		X	X	X	XX[3]	X	X	X	X	X[8][10]
GFR	X	X		X	X	X	X	X	X	X	X	X[8][10]
Serum Creatinine	X	X		X	X	X	X	X	X	X	X	X[8][10]
Serum Na, K, CO3, Cl, BUN	X	X[4]		X	X	X	X	X	X	X	X	X[8][10]
Serum fructosamine[5]	X				X[5]		X[5]					
Serum galactose[5]	X				X[5]		X[5]					
HbA1c [5]	X				X[5]		X[5]					
Palb [5]	X				X[5]		X[5]					
Glucose, Albumin	X			X	X	X	X	X	X	X	X	
Uric Acid	X			X	X	X	X	X	X	X	X	
AST/ALT/ alk phos	X			X	X	X	X	X	X	X	X	
LDH	X			X	X	X	X	X	X	X	X	
CPK	X				X		X					
CBC	X	X		X	X	X	X	X	X	X	X	
ANA/C3/Cholesterol	X					X	X					
Pregnancy test	X	X			X	X	X					
HIV[6]	X											
Hep B/C[6]	X											
PPD [6]	X											
Biorepository-blood	X						X					
Biorepository-DNA	X											
Biorepository-Urine	X						X					
Randomized Intervention			X	X	X	X	X					
Cancer screening	X											
Assessment of AE	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X

[1]Physical exam includes examination of lymph nodes, liver and spleen and measurement of height, weight and vital signs.
[2]Recommended.
[3]Two first morning urine samples to be submitted at the visit and collected a minimum of 24 hours apart
[4]Serum potassium only.
[5]Baseline samples for serum galactose levels, serum fructosamine, HbA1c and Palb will be done in all subjects. Samples at weeks 8 and 26 will only be collected in subjects randomized to galactose .The 26-wk Palb sample will be run in all galactose subjects and the 8 wk Palb sample will be stored for future assay.
[6]HIV, Hep B/C and PPD if not performed in the 12 months prior to screening
[7]Long term follow up after Month 18 may be conducted in person or by telephone interview
[8]Optional protocol procedure
[9]Final QOL assessment at month 24
[10]Local lab testing will be acceptable for these visits
[11] QOL and PROMIS must be completed at B01 if the subject does not require a B02

7: STUDY MEDICATIONS AND DOSE ADJUSTMENT PROTOCOLS

7.1: Drug Supply and Allocation

In July 2008, IND # 103,147 was issued authorizing the performance of the complete protocol including the use of the two experimental drugs, rosiglitazone and adalimumab and the three components of standard medical therapy, lisinopril, losartan, and atorvastatin. An application was submitted to the FDA on 3/29/10 for an IND to authorize the administration of all study agents including galactose that would be administered in this modified Phase II clinical trial. The four arm protocol modification was approved by the FDA and was incorporated into the existing IND #103,147 that currently is active for the FONT trial. In August 2010, a second major revision was made in the protocol to remove the rosiglitazone arm and revert to a 3-arm study (standard conservative therapy, adalimumab, and galactose). This revision has been submitted to the FDA along with an updated IND application. No new IND number has been issued.

Aptuit, Inc. will serve as a central pharmacy and drug distribution system. This facility will receive the drug assignments after randomization from the DCC and ship the appropriate study drug to participating sites for provision to the subject.

Formulation and Administration of the Experimental Novel Therapies:

Adalimumab (Humira®): *TNF-α antibody*

This medication will be provided by Abbott Laboratories and will be available as a liquid in single use vials. It will be administered as a subcutaneous injection every other week. The therapeutic dose of adalimumab will be 24 mg/m^2 to a maximum of 40 mg/dose every other week for the entire treatment period. Although the PK data from the FONT I Study indicated enhanced clearance of adalimumab in subjects with FSGS and nephrotic-range proteinuria the dose will not be increased above the standard amount given to treat rheumatoid arthritis because of safety concerns related to malignancies that might be associated with the administration of anti-TNF agents.

Subjects should be instructed to rotate the site of injection. In order to reduce the pain associated with the biweekly adalimumab injections, subjects can apply EMLA crème or steroid inhaler spray prior to administration of the medication. After the injection is completed, the subject can take Tylenol as needed or apply ice to the site for symptomatic pain relief.

Subjects receiving Humira® will be required to write down dates and times of drug administration and bring the administration log to each study visit (see Manual of Operations for administration log). In addition, when a subject is assigned to the Humira® arm, a per protocol dose schedule listing the week and the optimal date of drug administration will be sent with the medication to the site. This sheet can be used to facilitate scheduling of visits and it can be shared with the subject.

<u>Instructions for Administration of Humira® to Pediatric Subjects</u>

Children participating in this study may require less than the contents of the vial of Humira® (40 mg/0.8 mL) provided by Abbott. In order to calculate the correct dose of study drug to be administered, obtain the subject's height and weight and calculate body surface area. The treatment dose is 24 mg/m^2 and the maximum dose is 40 mg.

The dose is calculated exactly and the volume of Humira to be administered is determined to the closest 0.01 ml.

For children who require less than the contents of the complete vial of Humira®, the following procedure should be followed. Using a 1 cc tuberculin syringe with a 25 or 27 gauge needle, draw back the syringe to the mark indicating the correct dose of study medication. Place the needle of the syringe into the vial of Humira® and inject the air into the vial. Holding the vial and syringe upright, withdraw the required amount of medication. Before removing the needle from the bottle, check the syringe for any air bubbles which may reduce the amount of medication in it. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose. Administer this dose as a subcutaneous injection immediately. Discard any unused drug immediately after giving the injection using standard hospital procedures for drug waste. Discard the used needle and syringe in a "Sharps" container.

Galactose: *sugar*
This medication will be purchased from Ferro Pfanstiehl (Waukegan, IL).It will be dispensed as a powder and each jar will contain 500 g. The sugar will be administered orally in two divided daily doses. The therapeutic dose of galactose will be 0.2 g/kg per dose administered twice a day. The maximum single dose will be 15 g. The sugar will be dissolved in 15-30 ml and the liquid will be ingested 15-30 minutes before breakfast and dinner. 5 ml of the galactose powder is equal to 4 grams of the sugar. Appropriate size measuring spoon will be sent to the site once a subject is randomized to galactose.

Conservative Medical Therapy:
All subjects will receive optimal conservative medical therapy consisting of a combination of the following three agents: (1) ACEi, lisinopril: (2) ARB, losartan; and (3) statin, atorvastatin. The doses of the ACEi and ARB will be maximized during the Screening/Run-In period (2-12 weeks).The maximum target doses for subjects weighing <40 kg are: lisinopril 10 mg and losartan 25 mg. For subjects weighing >40 kg, the maximum target doses are: lisinopril 20 mg and losartan 50 mg. A steady state dose for each of these agents must be achieved by the end of the Screening/Run-in period and remain unchanged for the duration of the Treatment Period barring any clinical or laboratory side effects.

DRUG	WT ≤ 40 KG Maximum Dose	WT > 40 KG Maximum Dose
Lisinopril	10 mg	20 mg
Losartan	25 mg	50 mg
Atorvasatin	10 mg	20mg

These target doses can be adjusted downward for reasons of safety and/or tolerance. If a subject requires additional treatment for hypertension, additional antihypertensive agents may be used for blood pressure control as needed. If a subject is intolerant of lisinopril because of cough, then the losartan dose can be doubled if necessary.

Treatment with the HMG CoA reductase inhibitor, atorvastatin, will be at a dose of 0.5 mg/kg/day, maximum 20 mg/day. This third component of conservative medical therapy will be initiated at the Week 0 visit, which constitutes the start of the treatment period.

The site investigator should instruct the subject to achieve the target dose by the first visit after 2 weeks of the Treatment Period.

Subjects who require steroid treatment to maintain clinical stability will have the dose tapered to the lowest effective level, preferably given every other day, during the Run-In Period. All medication doses defined at the end of the Run-In Period will be unchanged during the 6-month Treatment Period except for safety indications.

7.2: Therapeutic Interventions

7.2.1: Conservative Medical Therapy

The following are common toxicities for lisinopril:

a. Decline in eGFR which is 30% or more below the baseline value and ≤100 mL/min/1.73m^2 which is repeated and confirmed in a well-hydrated subject will require modification of study medications.
b. Hyperkalemia: If serum potassium concentration is 5.5-6.0 mmol/L the value will be confirmed then, alterations in diet and administration of diuretics should be attempted. If hyperkalemia persists with serum potassium greater than 6 mmol/L, dosage modification should be instituted.
c. Hypotension or orthostasis
d. Cough: Persistent cough unrelated to other causes.
e. Angioedema: Lisinopril and losartan should be discontinued and a Serious Adverse Event Form should be completed. A Study Medication Termination Form should be filed for lisinopril. The Clinical Coordinating Center should be informed. Losartan can be reintroduced at the discretion of the site investigator.

Dosage Modifications for Lisinopril / Losartan Toxicity:
If a, b, or c above pertain, the dose of lisinopril should be reduced to 50% of the original dose for 2 weeks. If the indication for dosage modification persists, the lisinopril should be discontinued.

If the toxicity persists, the losartan should be reduced to 50% of the original dose for 2 weeks.

The dose of lisinopril or losartan at which the toxicity is corrected should be maintained for the remainder of the study. If lisinopril is discontinued because of toxicity of cough (see dosage modification above), treatment with ARB may continue and toxicity monitored.

If lisinopril or losartan have to be discontinued to achieve resolution of toxicity a, b or c, then the drug may be restarted at a lower dose at the discretion of the local investigator with monitoring for return of toxicity.

7.2.2: Adalimumab

Dose adjustment protocols

The following Table outlines the expected adverse events for the novel therapies and the responses that will be taken to each adverse event.

Adalimumab (Humira®): Event rate is based on dose of 24 mg/m^2 or maximum 40 mg

ANTICIPATED ADVERSE EVENT	SEVERITY GRADE CTC 0-5	EXPECTED FREQUENCY % OF PTS	TREATMENT OR ACTION TO BE TAKEN
Lupus-like syndrome	4	Rare	D/C drug
Confusion	4	Rare	D/C drug
Multiple sclerosis	4	Rare	D/C drug
Subdural hematoma	4	Rare	D/C drug
Serious infection/Sepsis	4	1%	D/C drug
Malignancy/lymphoma	4	<2%	D/C drug
Tuberculosis	4	Rare	D/C drug
Antibodies (ANA)	3	12%	D/C drug
Paresthesia	3	Rare	Reduce dose by 50%
↑alkaline phosphatase	2	Common	Symptomatic Rx, continue drug
Hypertension	2	Common	Symptomatic Rx, continue drug
Allergic reaction	1-2	<1%	Hold drug, try to restart
Tremor	1-2	Rate	Reduce dose by 50%
Injection site reaction	1-2	20%	Symptomatic Rx, continue drug
Local Infection	1-2	Common	Symptomatic Rx, continue drug
Headache	1-2	Common	Symptomatic Rx, continue drug
Rash	1-2	Common	Symptomatic Rx, continue drug
Nausea	1-2	Common	Symptomatic Rx, continue drug
Hyperlipidemia	1-2	Common	Symptomatic Rx, continue drug
Abdominal pain/ Back pain	1-2	Common	Symptomatic Rx, continue drug

7.2.3: Galactose

Galactose. Event rate is based on a dose of 20 mg per day

ANTICIPATED ADVERSE EVENTS	SEVERITY GRADE CTC 0-5	EXPECTED FREQUENCY % OF PATIENTS	TREATMENT OR ACTION TO BE TAKEN
Hepatotoxicity	4	Rare	Discontinue drug
Hyperglycemia	4	Rare	Discontinue drug
Abdominal pain, bloating, flatulence	1-3	Common	Reduce dose by 50%
Diarrhea	1-3	Common	Reduce dose by 50%
Headache	1-2	Common	Symptomatic Rx, continue drug
URI	1-2	Common	Symptomatic Rx, continue drug

8: ADVERSE EVENTS AND DEVIATIONS FROM ASSIGNED TREATMENT

Subject Safety:
In assessing safety of the novel therapies and the frequency of adverse events careful consideration will be given to the frequency of these events in subjects with resistant FSGS, as a consequence of their underlying disease. Thus, it is estimated that nearly 33% of the study subjects may develop CTC Grade 2-3 anemia, more than 50% are likely to develop CTC Grade 3 hypertension, and 5-10% may develop CTC Grade 3-4 infectious complications.

Serious Adverse Events
All serious adverse events (SAE) will be documented on the Adverse Event Report Form. This form will request that the participating site note whether or not the SAE was related to the study medication.

The 7 items listed below constitute the definition of an SAE:

a. Death
b. Life-threatening
c. Requires or prolonged hospitalization
d. Results in disability significant, persistent, or permanent
e. Pregnancy with or without resultant in a birth defect
f. Causes cancer
g. Overdose of a study medication. Overdose is retained as an SAE and is defined as ingestion of a study medication in a dose that requires hospitalization for evaluation or treatment.

After the subject has been off study drug for at least one year, only adverse events that are considered both serious and related to study intervention must be reported during the follow-up period.

If an SAE or unanticipated adverse effect occurs during the FONT study or in a post-study period of reasonable duration, the participating site investigator is required to inform the Study Principal Investigator (H Trachtman, beeper #888-732-4232, telephone number 718-470-3491) and an official at the local IRB within 2 business days (or within 72 hours if a weekend intervenes) of occurrence or knowledge of the event. If you are unable to reach Dr. Trachtman then please inform Dr. Gipson (telephone number 734-232-4852) of the SAE within the 48-72 hour allowable time window.

After this initial notification is done, the Adverse Event Report Form should be completed and Faxed to the Study Principal Investigator, FAX #718-470-0887. The Principal Investigator will report the SAE to the FONT Steering Committee and the DCC, which will inform all participating sites of the occurrence. In addition, if it is necessary to inform officials from the NIDDK or FDA, the Study Principal Investigator at the Steven and Alexandra Cohen Children's Medical Center of New York (CCMC) Clinical Coordinating Center will do this.

Other Adverse Events

These events will be recorded at each follow-up visit on the Adverse Event Report Form. These events will be reviewed by the FONT Steering Committee and summarized on an annual basis for the Data Safety Monitoring Board (DSMB).

Please note that information about all adverse events may be shared with the pharmaceutical companies that are supplying the study medication if they request this data.

Study Mandated Deviations from Assigned Treatment: Medication Stop Points

Definition

A stop point can only occur after the subject is randomized to a treatment arm and denotes the occurrence of an event, which necessitates altering the interventions of the study, i.e., cessation of galactose or adalimumab. Before a stop point is declared, all possible measures will be taken to reverse the problem necessitating the stop point. If there is a necessary deviation from the randomized intervention, we will minimize the degree if at all possible. If possible, the subject will resume the intervention at a later time.

The Participating Site will complete an Adverse Event Form noting the date and reason for discontinuation of the study medication. The FONT Steering Committee will confirm the indications for stopping the study medication.

Stop points for novel therapy:

- >50% decline from baseline eGFR and <60mL/min/1.73m^2 OR a final level <20 mL/min/1.73m^2
- ESRD, i.e., initiation of dialysis or receipt of a renal transplant
- SAE, i.e. grade 4 CTC toxicity
- Increase in ALT/AST to >2.5x the upper limit of normal
- Onset of congestive heart failure
- Clinical onset of SLE and/or positive ANA $\geq$ 1:160
- Serious infection/sepsis
- Malignancy
- Pregnancy

If any of these events occur, the Participating Site PI will complete an SAE form and notify Dr. Howard Trachtman as outlined earlier in this section.

NOTE: If a study subject becomes pregnant during the course of the clinical trial, then the study medication should be discontinued immediately. Second, the PI at the Steven and Alexandra Cohen Children's Medical Center of New York (CCMC) Administrative Center should be informed of this event. Third, the subject must be followed until the time of delivery (premature or full-term) to determine the outcome of the pregnancy and if there are any birth defects in the infant.

Follow-Up after reaching a Stop Point:

If the study medication is stopped, effort should be made to follow the subject according to the study protocol to permit adequate safety monitoring and intent to treat analysis.

During these visits, a history and complete physical examination will be performed. Laboratory testing should follow the study protocol. If the subject progresses to CKD 5 and is receiving dialysis, or has received a kidney transplant, this date should be recorded and long term follow up schedule should be followed.

9: PATHOLOGY SECTION

In order to confirm subject eligibility for the FONT trial, a biopsy review will be done by the FONT Pathologist for those subjects not previously found biopsy eligible in the FSGS-CT Study.

Renal biopsy

The following materials should be sent to the FONT Pathologist:

- Representative light microscopy slides containing a minimum of 1 glomerulus demonstrating segmental sclerosis on light microscopy will be required to confirm the diagnosis. A minimum of one H & E and one PAS slide or unstained slide is required. An H&E optimal shipment will include one of each:
    A. 1 Hematoxylin & eosin (H&E) slide
    B. 1 Periodic acid-Schiff (PAS) slide
    C. 1 Silver stain slide
    D. 1 unstained slide if possible

- A copy of the immunofluorescence and electron microscopy reports (describing the staining pattern and appearance of at least 1 glomerulus)

- Representative photomicrographs (1-5 per subject) of the electron microscopy containing at least 1 glomerulus and demonstrating the FSGS lesion)

If electron microscopy cannot be performed at a participating site, then arrangements can be made by the FONT pathologist to process and review electron microscopy from an existing specimen prior to randomization. The FONT Pathologist will store these materials until completion of the study.

For subjects in the FONT study who require confirmation of the diagnosis of FSGS, renal histopathological slides and photographs should be sent by courier. The contact information for the person in which these materials should be sent to is located in the Manual of Operations.

The FONT Pathologist will review all biopsy specimens within 5 business days of receipt. The review will be communicated to the local site Principal Investigator. Reports of the FONT Pathologist review will be completed and returned to the Participating Site's PI and DCC. Subjects with a history of biopsy confirmed FSGS from the NIH Sponsored FSGS Clinical Trial Pathology Committee will not require additional biopsy review. The FSGS Clinical Trial identification number or FSGS Clinical Trial Biopsy Report will need to be submitted to FONT for confirmation of biopsy eligibility.

10: CENTRAL PHARMACY

The Central Pharmacy (Drug Distribution Center) for the FONT II Study will be set up by Aptuit, Inc. They will be responsible for storage of all study medications and shipping them to participating sites once a subject is enrolled and randomized. All shipments will be secure and designed to insure stability of the individual medications during transport.

The contact information for the Central Pharmacy is listed in the Address Directory.

Drug Returns
The Participating Sites should use their own approved local procedures for disposal of any unused study medications.

11. Study Monitoring and Quality Assurance

Recruitment will be assessed on a monthly basis though the DCC and study Executive Committee. Recruitment reports will be discussed monthly during the Executive Committee Conference Calls and disseminated to all participating sites on a monthly basis.

Data Integrity and Quality – will be reviewed on a quarterly basis by the Quality Assurance and Clinical Management Committee. In addition, an Independent External Monitor will review the performance of the study in accords with regulations covering clinical trials in which the same person holds the IND and is the PI of the project.

Withdrawals are reviewed by the Executive Committee during the biweekly conference calls.

Adverse Events are reviewed as follows. Serious Adverse Events are reviewed within 24 hours of reporting by the Study PI, Howard Trachtman and Co-Investigator and Chair of the Clinical Management Committee, Debbie Gipson. Reporting to IRB, FDA as indicated, and the NIH program officer will follow. All other adverse events are reviewed on a quarterly basis by the Clinical Management Committee who are blinded to the randomized treatment assignment. Full Adverse Event reports are presented to the DSMB on an annual basis

Compliance with protocol procedures is reviewed during the monthly Clinical Management Committee conference calls. If protocol deviations are identified, communication requesting return to the protocol or submission of supporting documentation from the site principal investigator will be requested.

Data and Safety Monitoring Board (DSMB):
The FONT II Data and Safety Monitoring Board information can be found in the Charter Statement for the Safety and Monitoring Committee.

12: REFERENCES

1. Burgess E: Management of focal segmental glomerulosclerosis: Evidence-based recommendations. Kidney Int, 55:S26-S32, 1999.

2. Korbet SM. Angiotensin antagonists and steroids in the treatment of focal segmental glomerulosclerosis. Semin Nephrol 2003;23:219-28

3. Franceschini N, Hogan SL, Falk RJ. Primum non nocere: Should adults with idiopathic FSGS receive steroids? Semin Nephrol 2003;23:229-33

4. Benchimol C. Focal segmental glomerulosclerosis: pathogenesis and treatment. Curr Opin Pediatr 2003;15:171-80

5. Cattran DC, Rao P. Long-term outcome in children and adults with classic focal segmental glomerulosclerosis. Am J Kid Dis 1998;32:72-9

6. Tejani A, Stablein DH. Recurrence of focal segmental glomerulosclerosis posttransplantation: a special report of the North American Pediatric Renal Transplant Cooperative Study. J Am Soc Nephrol 1992; 2(12 Suppl):S258-S263

7. Senggutuvan P, Cameron JS, Hartley RB, et al: Recurrence of focal segmental lomerulosclerosis in transplanted kidneys: analysis of incidence and risk factors in 59 allografts. Pediatr Nephrol 1990;4:21-8

8. Huang K, Ferris ME, Andreoni KA, Gipson DS. The differential effect of race among pediatric kidney transplant recipients with focal segmental glomerulosclerosis. Am J Kidney Dis 2004;43:1082-1090.

9. Korbet SM. Treatment of primary focal segmental glomerulosclerosis. Kidney Int 2002;62:2301-10

10. Cattran DC. Outcomes research in glomerulonephritis Semin Nephrol 2003;23:340-354

11. Cattran DC. Cyclosporine in the treatment of idiopathic focal segmental glomerulosclerosis. Sem Nephrol 2003:23:234-41

12. Ponticelli C, Passerini P. Other immunosuppressive agents for focal segmental glomerulosclerosis. Semin Nephrol 2003;23:242-8

13. Jafar TH, Schmid H, Landa M, et al for the ACE Inhibition in Progressive renal Disease Study Group: Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. Ann Int Med 2001;135:73-87

14. Ruggenenti P, Perna A, Remuzzi G on behalf of the investigators of the GISEN group. Retarding progression of chronic renal disease: The neglected issue of residual proteinuria. Kidney Int 2003;63:2254-61

15. Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC, Toronto Glomerulonephritis Registry Group. Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. J Am Soc Nephrol 2005;16:1061-1068

16. Gipson DS, Chin H, Presler TP, Jennette C, Ferris ME, Massengilll S, Gibson K, Thomas DB. Differential risk of remission and ESRD in childhood FSGS. Pediatr Nephrol 2006;21:344-349

17. Fogo A. Progression and potential regression of glomerulosclerosis. Nephrology Forum. Kidney Int 2001;59:804-19

18. Fogo AB. The role of angiotensin II and plasminogen activator inhibitor-1 in progressive glomerulosclerosis. Am J Kid Dis 2000;35:179-88

19. Eddy AA. Molecular basis of renal fibrosis. Pediatr Nephrol 2000;15:290-301

20. Eddy AA. Proteinuria and interstitial injury. Nephrol Dial Transplant 20045;19:277-81

21. Bakir AA, Bazilinski NG, Rhee HL, Ainis H, Dunea G: Focal segmental glomerulosclerosis. A common entity in nephrotic black adults. Arch Intern Med 1989;149:1802-4

22. Pontier PJ, Patel TG. Racial differences in the prevalence and presentation of glomerular disease in adults. Clin Nephrol 1994;42:79-84

23. Korbet SM, Genchi RM, Borok RZ, Schwartz MM. The racial prevalence of glomerular lesions in nephrotic adults. Am J Kidney Dis 1996; 27:647-51

24. Suthanthiran M,. Khanna A, Cukran D, et al. Transforming growth factor-beta 1 hyperexpression in African American end-stage renal disease patients. Kidney Int 1998;53:639-44

25. Jafar TH, Stark PC, Schmid CH, et al for the AIPRD Study Group. Angiotensin-converting enzyme inhibition and progression of renal disease. Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. Kidney Int 2001;60:1131-40

26. Gansevoort RT, Sluiter WJ, Hemmelder MH, de Zeeuw D, de Jong PE. Antiproteinuric effect of blood-pressure-lowering agents: a meta-analysis of comparative trials. Nephrol Dial Transplant 1995;10:1963-74

27. Lama G, Luongo I, Piscitelli A, Salsano ME: Enalapril: Antiproteinuric effect in children with nephrotic syndrome. Clin Nephrol 2000;53:432-6

28. McLaughlin K, Jardine AG. Angiotensin converting enzyme inhibitors and angiotensin receptor (AT1) antagonists: Either or both for primary renal disease? Nephrol Dial Transplant 1999;14:25-8

29. Milliner DS, Morgenstern BZ: Angiotensin converting enzyme inhibitors for reduction of proteinuria in children with steroid-resistant nephrotic syndrome. Pediatr Nephrol 1991;5:587-90

30. Navis G, de Zeeuw D, de John PE. ACE-inhibitors: Panacea for progressive renal disease? Lancet 1997; 349:1852-3

31. Proesmans W, Van Wambeke I, Van Dyck M. Long-term therapy with enalapril in patients with nephrotic-range proteinuria. Pediatr Nephrol 1996;10:587-9

32. Stiles KP, Abbott KC, Welch PG, Yuan CM. Effects of angiotensin-converting enzyme inhibitor and steroid therapy on proteinuria in FSGS: A retrospective study in a single clinic. Clin Nephrol 2001;56:89-95

33. Russo D, Minutolo R, Pisani A, Esposito R, Signoriello G, Andreucci M, Balletta MM: Coadministration of losartan and enalapril exerts additive antiproteinuric effect in IgA nephropathy. Am J Kidney Dis 2001;38:18-25

34. Woo KT, Lau YK, Wong KS, Chiang GS. ACEi/ATRA therapy decreases proteinuria by improving glomerular permselectivity in IgA nephritis. Kidney Int 2000; 58:2485-91

35. Fried L, Orchard TJ, Kasiske BL for the Lipids and renal Disease Progression Meta-Analysis Study Group: effect of lipoid reduction on progression of renal disease: A meta-analysis. Kidney Int 2001;59:260-9

36. Schieppati A, Remuzzi G. the future of renoprotection: frustration and promises. Kidney Int 2003;63:1947-55.

37. Brenner BM. Retarding the progression of renal disease. Kidney Int 2003;63:370-8

38. Zoja C, Corna D, Camozzi D, Cattaneo D, et al. How to fully protect the kidney in a more severe model of progressive nephropathy: a multidrug approach. J Am Soc Nephrol 2002;13:2898-908

39. Hebert LA, Wilmer WA, Falkenhain ME, Ladson-Wofford SE, Nahman S, Rovin BH: Renoprotection: One or many therapies? Kidney Int, 59:1211-1226, 2001.

40. Bauid L., Fouqueray B, Philippe C, Amrani A. Tumor necrosis factorα and mesangial cells. Kidney Int 1992;41:600-3

41. Bemelmans MH, van Tits LJ, Buurman WA. Tumor necrosis factor: function, release and clearance. Crit Rev Immunol 1996;16:1-11

42. Reimold AN. TNF-alpha as therapeutic agent: new drugs, more applications. Curr Drug Targets Inflamm Allergy 2002;1:377-392.

43. McCarthy ET, Sharma R, Sharma M, Li JZ, Ge XL, Dileezpan KN, Savin VJ. TNF-alpha increases albumin permeability of isolated rat glomeruli through the generation of superoxide. J Am Soc Nephrol. 1998; 9: 433-8

44. Gertzberg N, Neumann P, Rizzo V, Johnson A. NAD(P)H oxidase mediates the endothelial barrier dysfunction induced by TNF-α. Am J Physiology 2004; 286:L37-L48

45. Wright SC, Zheng H, Zhong J, Torti FM, Larrick JW. Role of protein phosphorylation in TNF-induced apoptosis: phosphatase inhibitors synergize with TNF to activate DNA fragmentation in normal as well as TNF-resistant U937 variants. J Cell Biochem. 1993; 53: 222-33

46. Gaur U, Aggerwal BB. Regulation of proliferation, survival, and apoptosis by members of the TNF superfamily. Biochem Pharmacol 2003;66:1403-8

47. Ortiz A, Bustos C, Alonso J, Alcazar R, Lopez-Armada MJ, Plaza JJ, Gonzalez E, Egido J. Involvement of tumor necrosis factor-alpha in the pathogenesis of experimental and human glomerulonephritis. Adv Nephrol Necker Hosp 1995; 24: 53-77

48. Rodriguez-Iturbe B, Pons H, Herrera-Acosta J, Johnson RJ: Role of immunocompetent cells in nonimmune renal diseases. Kidney Int 2001; 59:1626-1640

49. Muller DN, Shagdarsuren E, Park, J, Dechend R, Mervaala E, Hampich F, Fiebeler A, Ju X, Finckenberg P, Theuer J, Viedt C, Kreuzer J, Heidecke H, Haller H, Zenke M, Luft F. Immunosuppressive Treatment Protects Against Angiotensin II-induced Renal Damage. Am J Pathol 2002;161:1679-93

50. Taal MW, Zandi-Nejad K, Weening B, et al. Proinflammatory gene expression and macrophage recruitment in the remnant kidney. Kidney Int 2000;58:1664-76

51. Nakamura T, Ebihara I, Fukui M, et al. Altered glomerular steady-state levels of tumor necrosis factor-alpha mRNA during nephrotic and sclerotic phases of puromycin aminonucleoside in rats. Clin Sci 1993;84:349-56

52. Pawluczyk IZ, Harris KP. Cytokine interactions promote synergistic fibronectin accumulation by mesangial cells. Kidney Int 1998;54:62-70

53. DiPetrillo K, Countermarsh B, Gesek FA. Urinary tumor necrosis factor contributes to sodium retention and renal hypertrophy during diabetes. Am J Physiol 2003;284:F113-F121

54. Kalantarina K, Awad AS, Siragy HM. Urinary and renal interstitial concentrations of TNF-α increase prior to the rise in albuminuria in diabetic rats. Kidney Int 2003;64:1208-13

55. Nakamura T, Fukui M, Ebihara I, et al. mRNA expression of growth factors in glomeruli from diabetic rats. Diabetes 1993;42:450-6

56. Suranyi MG, Guasch A, Hall BM, Myers BD. Elevated levels of tumor necrosis factor-alpha in the nephrotic syndrome in humans. Am J Kidney Dis. 1993; 21: 251-9

57. Bustos C, Gonzalez E, Muley R, Alonso JL, Egido J. Increase of tumour necrosis factor alpha synthesis and gene expression in peripheral blood mononuclear cells of children with idiopathic nephrotic syndrome. Eur J Clin Invest 1994; 24: 799-805

58. Bakr A, Shokeir M, El-Chenawi F, El-Husseni F, Abdel-Rahman A, El-Ashry R. Tumor necrosis factor-alpha production from mononuclear cells in nephrotic syndrome. Pediatr Nephrol. 2003 18: 516-20

59. Tain YL, Liu CA, Yang KD. Implications of blood soluble and cell surface tumor necrosis factor receptors in childhood nephrotic syndrome. Pediatr Nephrol 2002;17:926-32

60. Tanaka R, Yoshikawa N, Nakamura H, Ito H. Infusion of peripheral blood mononuclear cell products from nephrotic children increases albuminuria in rats. Nephron 1992; 60: 35-41

61Cattran D, Neogi T, McCarthy ET, Savin VJ, Sharma R. Serial estimates of serum permeability activity and clinical correlates in patients with native kidney focal segmental glomerulosclerosis. J Am Soc Nephrol.12003;4:448-53.

62Savin VJ, Sharma R, Lovell HB, Welling DJ. Measurement of albumin reflection coefficient in isolated rat glomeruli. J Am Soc Nephrol 1992;3:1260-1269..

63Artero ML, Sharma R, Savin VJ, Vincenti F. Plasmapheresis reduces proteinuria and serum capacity to injure glomeruli in-patients with recurrent focal glomerulosclerosis. Am J Kidney Dis 1994;23:574-581.

64Savin VJ, Sharma R, Sharma M, et al. Circulating factor increasing glomerular permeability in recurrent focal segmental glomerulosclerosis. N Engl J Med 1996;334: 878-883:1996.

65 Sharma M, Sharma R, McCarthy ET, Savin VJ. The focal segmental glomerulosclerosis permeability factor: biochemical characteristics and biological effects. Exp Biol Med 2004;229:85-98.

66Savin VJ, Sharma M, McCarthy ET, Sharma R, Reddy S, Dong JW, Hess S, Kopp JB. Cardiotropin-like cytokine-1: candidate for the focal glomerular sclerosis permeability factor. J Am Soc Nephrol 2008;19:59A (abstract)

67Savin VJ, McCarthy ET, Sharma R, Charba D, Sharma M. Galactose binds to focal segmental glomerulosclerosis permeability factor and inhibits its activity. Transl Res 2008;151:288-292

68De Smet E, Rioux JP, Ammann H, Begin LR, Deziel C, Querin S. FSGS permeability factor-associated nephrotic syndrome: remission and oral galactose therapy. Neph Dial Transplant 2009;24:2938-2940.

69Trachtman H, Futterweit S, Singhal PC, Franki N, Sharma M, Sharma R, Savin V. Circulating factor in patients with recurrent focal segmental glomerulosclerosis postrenal transplantation inhibits expression of inducible nitric oxide synthase and nitric oxide production by cultured rat mesangial cells. J Invest Med 1999;47:114-120

70Trachtman H, Futterweit S, Singhal PC. Nitric oxide modulates the synthesis of extracellular matrix proteins in cultured rat mesangial cells. Biochem Biophys Res Commun 1995;207:120-125

71Trachtman H, Futterweit S, Garg P, Reddy K, Singhal PC. Nitric oxide stimulates the activity of a 72-kDa neutral matrix metalloproteinase in cultured rat mesangial cells. Biochem Biophys Res Commun 1996;218:704-708

72. Cattran DC, Appel GB, Hebert LA, et al. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. North America Nephrotic Syndrome Study Group. Kidney Int 1999;56:2220-6

73. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, Rowland CR. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health and Quality Outcomes 2004;2:12 (http://www.hqlo.com/content/pdf/1477-7525-2-12.pdf)

74. Liu P. Phase II Selection Designs, Chapter 6, pp 119-127, in Handbook of Statistics in Clinical Oncology, John Crowley Ed, Marcel Dekker, 2001

75. Simon R, Wittes R, Ellenberg. Randomized phase II clinical trials. Cancer Treatment Rep 1985; 69:1375-81

76. Buyse M. Randomized designs for early trials of new cancer treatments – An overview. Drug Information Journal 2000; 34:387-396, 2000

77. Verbeke G, Molenberghs. Linear Mixed Models for Longitudinal Data. Springer, New York, 2000

78. Greene T, Lai J and Levey AS. Interpretation of Clinical Studies of Renal Disease. Chapter 40 in Immunologic Renal Diseases, Neilson EG and Couser WG (eds). Lippincott-Raven Publishers, Philadelphia, Pennsylvania, pp 887-914 (1997)

79. Liang KY and Zeger SL. Inference based on estimating functions in the presence of nuisance parameters. *Statistical Science* 1995;10:158-173

80. Toledano AY, Gatsonis C. Generalized estimating equations for ordinal categorical data: arbitrary patterns of missing responses and missingness in key covariates. *Biometrics* 1999; 55:488-496

81. Green S. Overview of Phase II Clinical Trials, Chapter 4, pp 93-103 in Handbook of Statistics in Clinical Oncology, John Crowley Ed, Marcel Dekker, 2001

82. Jennison C and Turnbull B. Confidence intervals for a binomial parameter following a multistage test with application to MIL-STD 105D and medical trials. *Technometrics*, 1983; 25:49-58

83. Patient Reported Outcomes Measurement Information System (PROMIS). www.nihpromis.org

84. Caridi G, Bertelli R, Carrea A, et al: Prevalence, genetics and clinical features of patients carrying podocin mutations in steroid resistant nonfamilial focal segmental glomerulosclerosis. J Am Soc Neph 2001;12:2742-6

85. Pollak MR: The genetic basis of FSGS and steroid-resistant nephrosis. Sem Nephrol, 23:141-146, 2003.

86. Ruf RG, Lichtenberger A, Karle SM, et al. Patients with mutations in NPHS2 (podocin) do not respond to standard steroid treatment of nephritic syndrome. J Am Soc Nephrol 2004;15:722-32

87. Caridi G, Bertelli R, DiDuca M, et al. Broadening the spectrum of diseases related to podocin mutations. J Am Soc Nephrol 2003;14:1278-86

88. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society Guidelines for the Early Detection of Cancer, 2003. CA Cancer J Clin 53:27-43

89. Nacional high blood pressure education working group on high blood pressure in children and adolescents. The fourth sport on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114:555-576.

90. Chobanian AV, Bakris GL, Black HR, et al. National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. JAMA 2003;289:2560-2572.

91. Varni JW, Seid M, Rode CA: The PedsQL™: Measurement model for the Pediatric Quality of Life Inventory. Medical Care 1999, 37**:**126-139

92. Varni JW, Seid M, Kurtin PS: PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 Generic Core Scales in healthy and patient populations. *Med Care* 2001, 39**:**800-812.

93. JE Ware, KK Snow, M Kosinski, B Gandek, SF-36 health survey: manual and interpretation guide. The Health Institute, New England Medical Center, 1993