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# A Phase 2, Double-Blind, Placebo-Controlled, Randomized Study of Fresolimumab in Patients With Steroid-Resistant Primary Focal Segmental Glomerulosclerosis

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**Introduction:** Steroid-resistant focal segmental glomerulosclerosis (SR-FSGS) is a common glomerulopathy associated with nephrotic range proteinuria. Treatment goals are reduction in proteinuria, which can delay end-stage renal disease.

**Methods:** Patients with SR-FSGS were enrolled in a randomized, double-blind placebo-controlled trial of fresolimumab, a monoclonal anti–transforming growth factor–β antibody, at 1 mg/kg or 4 mg/kg for 112 days, followed double-blind for 252 days (NCT01665391). The primary efficacy endpoint was the percentage of patients achieving partial (50% reduction) or complete (< 300 mg/g Cr) remission of proteinuria.

**Results:** Of 36 enrolled patients, 10, 14, and 12 patients received placebo, fresolimumab 1 mg/kg, and fresolimumab 4 mg/kg, respectively. The baseline estimated glomerular filtration rate (eGFR) and urinary protein/creatinine ratio were 63 ml/min/1.73 $m^2$ and 6190 mg/g, respectively. The study was closed before reaching its target of 88 randomized patients. None of the prespecified efficacy endpoints for proteinuria reduction were achieved; however, at day 112, the mean percent change in urinary protein/creatinine ratio (a secondary efficacy endpoint) was –18.5% ($P = 0.008$), +10.5% ($P = 0.52$), and +9.0% ($P = 0.91$) in patients treated with fresolimumab 1 mg/kg, fresolimumab 4 mg/kg, and placebo, respectively. There was a nonsignificant trend toward greater estimated glomerular filtration rate decline in the placebo group compared to either of the fresolimumab-treated arms up to day 252.

**Discussion:** The study was underpowered and did not meet the primary or secondary endpoints. However, fresolimumab was well tolerated and is appropriate for continued evaluation in larger studies with adequate power.

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Primary focal segmental glomerulosclerosis (FSGS) is a major cause of nephrotic syndrome in adults worldwide,[1] with a profound negative impact on quality of life, morbidity, and mortality. Nephrotic syndrome, which may be severe, can be both debilitating and associated with complications, including

anasarca, cardiovascular, and thromboembolic events. If untreated, FSGS typically results in a relatively rapid decline in renal function and end-stage renal disease (ESRD), with a need for either dialysis or transplantation in the majority of patients.

The incidence of FSGS is reported as being higher, and the rate of renal survival as being worse, in African Americans when compared with non−African Americans.[1] This risk has been linked to 2 allelic variants in the APOL1 gene, namely *APOL1 G1* and *APOL1 G2*, carried by patients of African but not European descent.[2] Irrespective of the racial predilection for FSGS, however, no proven treatment exists for FSGS, with failure to respond to empiric therapy with steroids or calcineurin inhibitors (CNIs) portending progression to ESRD and renal replacement therapy. To date, remission of proteinuria is the only factor that predicts delayed progression to ESRD.[3]

CNIs are used off-label as an alternative or second-line therapy to corticosteroids in FSGS patients[4] and in patients with steroid-resistant idiopathic nephrotic syndrome.[5] However, many patients fail to respond to CNIs, and the use of these agents is associated with a high relapse rate.[6] As such, there is a high unmet medical need for new therapies that can induce sustained remission of proteinuria in FSGS and slow progression to ESRD.[2,7–11]

Transforming growth factor−β (TGF-β) is a cytokine involved in normal homeostasis[12]; however, sustained overproduction of TGF-β has been implicated in the pathogenesis of fibrosis in many animal models,[13] and in humans with fibrotic kidney diseases, including FSGS.[14–16] Preclinical models of FSGS have demonstrated prevention of proteinuria and glomerular pathology, as well as reduction in proteinuria, with inhibition of TGF-β.[17] To this end, fresolimumab, an engineered human monoclonal Ig that neutralizes the 3 major isoforms of TGF-β, namely, β1, β2, and β3, was developed with the aim to slow and potentially reverse fibrosis. Thus, fresolimumab may represent a new therapy with a novel mechanism of action for fibrotic kidney disease, including primary FSGS.

The purpose of this clinical study was to evaluate the safety and efficacy of fresolimumab in patients with steroid-resistant FSGS (NCT01665391).

## MATERIALS AND METHODS

### Trial Design

This was a phase 2, multicenter, double-blind, parallel-dosing, randomized study of 4 i.v. infusions of fresolimumab or placebo on days 1, 28, 56, and 84 in patients with steroid-resistant FSGS. The study was divided into 3 periods: screening (visit 1, up to 6 weeks prior to day 1/visit 2); treatment period (day 1/visit 2, day 28/visit 3, day 56/visit 4, day 84/visit 5, and day 112/visit 6); and follow-up period (day 140/visit 7, day 168/visit 8, and day 252/visit 9). A patient was considered to have completed the treatment period when assessments scheduled for day 112 had been completed. Fresolimumab doses of 1 mg/kg and 4 mg/kg were selected to assess dose–response and dose–safety relationships in these patients, with 4 mg/kg selected as the highest dose, as it was the highest dose used in the phase 1 FSGS study that was expected to represent a pharmacodynamically active dose.[18] The dosing interval of 28 days was selected based on the ∼14-day terminal elimination half-life of fresolimumab seen in the phase 1 study to prevent significant accumulation while providing sustained exposure to the study drug.[18]

### Randomization and Masking

At day 1, eligible patients who met all inclusion and exclusion criteria were randomly assigned, stratified by race (black versus nonblack) and prior CNI therapy (yes, no), to 1 of 3 treatment groups in a 3:3:2 allocation: fresolimumab 1 mg/kg total body weight; fresolimumab 4 mg/kg total body weight; or placebo, delivered via 30-minute i.v. infusions at 4-week intervals for a total of 4 doses. Patients were allowed treatment with immunosuppressive agents after day 112 at the clinicians' discretion and then were followed up for a total of 252 days, with patients and investigators remaining blinded to treatment assignment.

### Ethical Considerations

The protocol complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments, and with the laws and regulations, as well as any applicable guidelines, of the countries in which the study was conducted. Informed consent was obtained prior to the conduct of any study-related procedures. The patient informed consent form was modified according to local regulations and requirements, and the protocol and consent forms were reviewed and approved by independent ethics committees and/or the institutional review board at each participating site. This research was carried out in approximately 40 centers in 5 countries in accordance with Good Clinical Practice guidelines and applicable regulations.

### Inclusion and Exclusion Criteria

Inclusion and key exclusion criteria are listed in Table 1.