Examples of potentially eligible study participants

EXAMPLE 1:

Never achieved partial or complete remission

- 54-year-old Hispanic male

1 year ago:

- Edema, biopsy confirmed primary FSGS
- Started on tacrolimus 2 mg twice daily

3 months later:

- Reduction of UPCR:
- 10 → 4 g/g
- → diarrhea, hyperkalemia and hypomagnesemia

Currently:

- Max dose losartan and dapagliflozin
- **UPCR between 4 to 6 g/g for the past 2 months**
- eGFR 60 mL/min/1.73 m^2

EXAMPLE 2:

Achieved partial/complete remission but developed recurrence- adolescent

- 16 yr old Caucasian female

2 years ago:

- Fatigue, anasarca, UPCR 10 g/g
- Started on 2 mg/kg/day of prednisone

Weeks later:

- Full remission

→ Prednisone tapered → relapsed

Next 3 mos:

- Remission, followed by relapse during taper x3
- Biopsy → minimal change disease
- Started on tacrolimus

12 months later:

- Nonadherent to trough monitoring

Currently:

- **UPCR 3.5 g/g**, eGFR 61 mL/min/1.73m^2
- Family interested in other steroid sparing agent

EXAMPLE 3:

Achived partial/complete remission but developed recurrence

- 43 year-old African American female

4 years ago:

- Sudden onset swelling
- UPCR 16 g/g
- Biopsy confirmed primary FSGS
- Prednisone 80 mg daily

→ Partial remission

→ UPCR < 3 g/g

- Insomnia, weight gain, acne, irritability

6 months later:

→ Prednisone tapered off

Next 2 years:

→ UPCR continued in 1.5-2.5 g/g

→ Maintained on lisinopril and dapagliflozin

- Rapid weight gain (10 lbs over preceding mos)

Currently:

- **UPCR increased to 6 g/g**
- eGFR 67 mL/min/1.73 m^2

EXAMPLE 4:

Achieved partial/complete remission, developed recurrence on taper, need to regularly re-evaluate UPCR for eligibility

- 51-year-old male

10 months ago:

- Anasarca,, UPCR 6.5 g/g
- Biopsy with primary FSGS
- Started on high dose steroids at 60 mg daily

4 months later:

- Complete remission, UPCR 0.1 g/g so steroid tapered over 2 months
- 2 weeks after completion of taper, UPCR rose to 3.6 g/g
- Steroids increased again to 60 mg daily

3 months later:

- Complete remission again, UPCR 0.1 g/g
- 6 weeks into steroid taper UPCR rose again to 2.7 g/g
- Not tolerating steroids
- Noted UPCR was not eligible for trial at that time (2.7 g/g < 3 g/g)
- Asked to return to clinic in 2 weeks
- UPCR noted then to be 3.1 g/g, eGFR 55 ml/min/1.73 m^2 so he is referred to this clinical trial.

References

1. Maas RJ, Deegens JK, Smeets B, Moeller MJ, Wetzels JF. Minimal change disease and idiopathic FSGS: manifestations of the same disease. Nat Rev Nephrol. 2016 Dec;12(12):768-776. doi: 10.1038/nrneph.2016.147. Epub 2016 Oct 17. PMID: 27748392.
2. Carlozzi NE, Massengill SF, Trachtman H, Walsh L, Singhal N, LaVigne JM, et al. Health- Related Quality of Life in Focal Segmental Glomerular Sclerosis and Minimal Change Disease: A Qualitative Study of Children and Adults to Inform Patient-Reported Outcomes. Kidney Med. 2021;3(4):484-97.e1.
3. Delville M, Sigdel TK, Wei C, Li J, Hsieh SC, Fornoni A, et al. A circulating antibody panel for pretransplant prediction of FSGS recurrence after kidney transplantation. Sci Transl Med. 2014;6(256):256:1-12.
4. Doublier S, Zennaro C, Musante L, Spatola T, Candiano G, Bruschi M, et al. Soluble CD40 ligand directly alters glomerular permeability and may act as a circulating permeability factor in FSGS. PLoS One. 2017;12(11):1-21.
5. Ye Q, Zhou C, Li S, Wang J, Liu F, Liu Z, et al. The immune cell landscape of peripheral blood mononuclear cells from PNS patients. Sci Rep. 2021;11(1):13083:1-9.
6. Mariani LH, Eddy S, AlAkwaa FM, McCown PJ, Harder JL, Nair V, et al. Precision nephrology identified tumor necrosis factor activation variability in minimal change disease and focal segmental glomerulosclerosis. Kidney Int. 2023;103(3):565-79.

sanofi

MAT-US-2409557 v1.0 - P
Expiration Date: 09/25/2026

RESULT

Renal **E**fficacy **S**ignaling **U**mbrel**L**a **T**rial

In Primary Focal Segmental Glomerulosclerosis (FSGS) or Minimal Change Disease (MCD)

Brochure for healthcare provider use

sanofi

Primary focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) are clinico-pathologic diagnoses that are glomerular patterns of injury mediated by a common underlying immunologic pathway [1]. This pathway culminates in progressive loss of the glomerular filtration barrier function, leading to nephrotic range proteinuria and nephrotic syndrome, the clinical hallmark of primary FSGS/MCD. The current standard of care consists of high dose corticosteroids or non-steroid immunosuppressive therapies, all of which are associated with significant toxicity and variable effectiveness [2].

The efficacy of immunosuppressive therapies and numerous studies on the molecular and cellular pathogenesis of primary FSGS/MCD have highlighted the critical role for T-cell, B-cell, and cytokine-mediated pathways within the immune system. Specifically, multiple lines of evidence suggest that CD40 ligand (CD40L), OX40 ligand (OX40L), Tumor necrosis factor alpha (TNf α), and Bruton's tyrosine kinase (BTK) each play a significant role in the cell signaling pathways that underlie pathogenesis [3,4,5, 6]

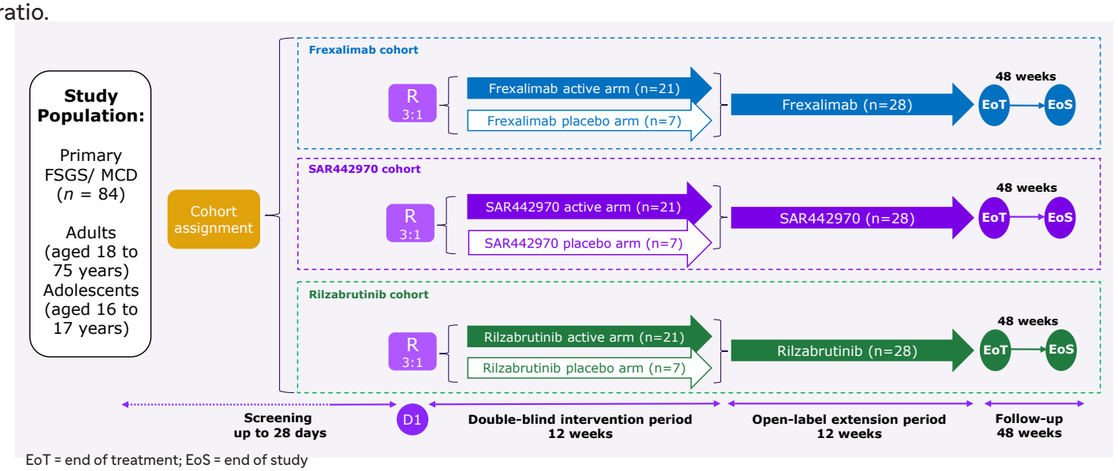
Frexalimab
is a monoclonal antibody that inhibits T-cell-dependent B-cell activation by blocking the costimulatory CD40/CD40L pathway.

SAR442970
is a novel bispecific NANOBODY® molecule that inhibits both TNFα, which plays a role in a variety of inflammatory processes, and OX40L, which plays a role in costimulation and maintenance of effector T cells.

Rilzabrutinib
is a small molecule that inhibits BTK signaling, which is expected to inhibit B cell maturation and reduce pathogenic autoantibody production.

Each of these investigative agents inhibit downstream signaling and/or immune cell differentiation, proliferation, and survival and are in various stages of development by Sanofi for other immune-mediated conditions.

RESULT is a Phase 2a, randomized, double-blind, placebo-controlled trial to simultaneously evaluate the efficacy, tolerability and safety of Frexalimab, SAR442970, and Rilzabrutinib in participants with biopsy-proven FSGS or MCD. These target specific aspects of the adaptive immune response that drive the underlying pathogenesis of disease, and they have the potential to decrease the urine protein-to-creatinine ratio.



EoT = end of treatment; EoS = end of study

The study is planned to include approximately *84 participants worldwide*

(in approximately 20 countries) and will be divided into 4 periods: screening, double blind intervention period, open label extension period, and follow-up period.

KEY INCLUSION CRITERIA:

- Aged 16-75 years at time of screening
- Biopsy-proven primary FSGS or MCD
- Urinary Protein Creatinine Ratio ≥3 g/g
- eGFR * ≥45 mL/min/1.73 m2
- Documented history of response to corticosteroid or other immunosuppressive therapy
- Stable dose of prednisone or equivalent ≤ 10 mg/day

*eGFR = estimated glomerular filtration rate

KEY EXCLUSION CRITERIA:

- Genetic or secondary FSGS or MCD
- Current or prior ESKD requiring dialysis or transplantation
- History, clinical evidence, suspicion, or significant risk for thromboembolic events, myocardial infarction, stroke, and/or antiphospholipid syndrome
- High-dose of steroids (> 10 mg/day prednisone or equivalent), or change in disease within 1-week prior to randomization

IMPORTANT POTENTIAL RISKS:

Based on the review of available non-clinical, clinical and literature data, these are considered as important potential risks for the respective study drugs.

Frexalimab:

- Infections
- Immunogenicity/ hypersensitivity
- Thromboembolic events
- Injection site reactions/ local tolerability at injection site

SAR442970:

- Infections
- Malignancies
- Anaphylaxis or serious allergic reactions including hypersensitivity reactions
- Hepatitis B virus reactivation
- Demyelinating disease
- Cytopenia, pancytopenia
- Heart failure
- Lupus-like syndrome
- Reduced antibody response to vaccination

Rilzabrutinib:

- Infections
- Liver enzyme elevation
- Uveitis