**Dear FDA: Allow Individuals with focal segmental glomerulosclerosis (FSGS) Access to sparsentan**

We, the members of the focal segmental glomerulosclerosis (FSGS) patient, caregiver, and advocacy community, write to you at a pivotal moment in history addressing our disease.

After decades of failed clinical drug development programs, we continue to rely on a limited number of severe, off-label medications with unpredictable efficacy and safety. We continue to face debilitating disease burden and progression, and all too often, recurrence of disease even after kidney transplantation. We continue to have more questions than answers about what our future, and the future for our children, holds with this complex and variable disease.

Our community, including the researchers, doctors, and many others who have devoted their lives to finding answers for this disease, have finally reached a critical moment in our combined efforts: the decision point regarding the first drug to complete a phase 3 study for FSGS. Through the DUPLEX study, sparsentan demonstrated profound and sustained reductions in proteinuria in a population with no FDA-approved treatment options.

As a crucial player in our journey to conquer FSGS, we want to acknowledge and thank the FDA for its longstanding and meaningful commitment to patients with rare kidney diseases. We recognize the agency's thoughtful research stewardship, scientific rigor and efficiency, and emphasis on incorporating the patient voice into regulatory decision-making. This commitment has given our community hope during years when progress felt out of reach.

Why are we coming to you now? Because despite the collective community's passionate efforts, time is running out for people living with FSGS.

**Background on Focal Segmental Glomerulosclerosis (FSGS)**

FSGS is a devastating, heterogeneous, and often episodic disease that remains one of the leading individual causes of kidney failure in both children and adults, accounting for up to 11%

of the adult kidney transplant population and 15% of kidney failure in children. For people with FSGS, receiving a kidney transplant does not mean a cure: the disease reoccurs after transplant approximately 50% of the time, forcing patients back on dialysis indefinitely. Although designated as a rare disease, its burden is profound and lifelong, and it affects individuals of all racial and ethnic backgrounds. Most patients are diagnosed in childhood, adolescence, or early adulthood—years that should be defined by education, career development, and family formation, not dialysis, transplantation, and chronic immunosuppression.

For decades, FSGS patients have had no approved medicines and few meaningful options for treatment. Current clinical management relies heavily on off-label immunosuppressive drugs that often provide limited benefit while imposing significant short- and long-term toxicity. Many patients endure cycles of remission and relapse that unpredictably derail their lives; others progress rapidly to kidney failure within just one to two years of diagnosis. Both paths carry extraordinary physical, emotional, and financial costs.

Against this backdrop, sparsentan represents a long-awaited inflection point.

**Proteinuria: Statistically Significant and Meaningful to Patients' Lived Experience**

The DUPLEX trial demonstrated statistically significant, profound, and sustained proteinuria reduction against an active comparator—using pre-specified and prospectively collected data points. While the eGFR endpoint was not met, subsequent insights from the groundbreaking PARASOL (Proteinuria and GFR as Clinical Trial Endpoints in Focal Segmental Glomerulosclerosis) initiative clarified and confirmed that change in eGFR over two years in an inclusive population (such that enrolled in DUPLEX) may not capture a protective therapeutic effect in a rare disease trial.

Proteinuria reduction, by contrast, has emerged through rigorous research, patient data, and regulatory dialogue as a meaningful and appropriate endpoint in FSGS studies. Patients themselves have emphasized reduction of proteinuria as the leading clinical trial outcome that they felt was most important to their experience with FSGS, higher even than eGFR, through opportunities like the 2020 Externally Led Patient-Focused Drug Development Meeting on FSGS. Had the field known a decade ago what PARASOL has now conclusively validated, proteinuria reduction would likely have been selected as the primary study endpoint from the beginning.

Importantly, the DUPLEX trial was conducted during the COVID-19 pandemic and still achieved a 91% retention rate—an extraordinary outcome for any rare kidney disease trial, and

particularly for one as complex as FSGS. This study recruited patients from the broad spectrum of FSGS diagnoses, including individuals with disease caused by genetic variants. In addition, families and community members advocated for pediatric inclusion, and this study remains one of the few in pivotal kidney disease studies to include participants as young as eight years of age. Patients participated, remained enrolled, and adhered because we are acutely aware of the stakes.

**Rationale for Approval**

Since the phase 3 program for sparsentan began, as many as half of all individuals with FSGS and unmitigated nephrotic-range proteinuria have likely progressed to kidney failure. For FSGS patients, delay represents not caution, but loss: loss of kidney function, independence, opportunity, and in some cases, life itself.

As patients, we live with the daily realities behind the endpoints and statistics. We are young adults forced to abandon schooling or careers, children who endure dialysis, repeated transplants, and prolonged hospitalizations before adulthood, and families navigating life with constant uncertainty. The cumulative burden of dialysis, transplant failure, and potentially life-altering side effects from unstudied treatments shape our willingness to accept uncertainty and risk in exchange for the possibility of preserving our kidney function and gaining time.

We ask for the opportunity to access the first therapy successfully studied and shown to meaningfully reduce proteinuria in FSGS. We are prepared to use this treatment responsibly, in partnership with our healthcare providers, and discontinue use if clinical benefit is not achieved.

The FDA has emphasized the importance of incorporating the patient voice, particularly in rare diseases with no approved therapies and high disease burden. The 21st Century Cures Act and the FDA's patient-focused drug development initiatives recognize that patients are uniquely positioned to contextualize benefit, risk, and unmet need. We respectfully ask that our voices be fully considered in the evaluation of sparsentan for FSGS.

As you deliberate, we ask that you remember us. We are the patients behind the data—those who enrolled, those who sacrificed, and those who today would give anything for five to ten more years before dialysis. For some, that time means finishing school or starting families; for many, it simply means living with hope and a future measured in years and decades rather than months.

We ask that our community not be penalized for the inherent variability of this disease nor for the diversity of clinical experiences it produces. We have stepped forward repeatedly and with urgency to participate in research and advance the field. We ask that our contributions not be made in vain. With innovation rapidly advancing across other kidney diseases, FSGS patients are waiting for the same progress to reach us—and not be held back due to the complexity of our disease.

Based on the totality of evidence from DUPLEX, the insights provided by PARASOL, and the severe, longstanding unmet needs of the FSGS community, we respectfully and urgently request that sparsentan be allowed to move forward as the first FDA-approved therapy for FSGS. We hope that this will be the first step of many in the development of a full range of novel therapeutics that will be needed to safely and effectively treat the full range of our experiences with FSGS.

We remain deeply grateful for your dedication to patients with rare kidney diseases and for your thoughtful consideration of this petition.

Sincerely,

NephCure on behalf of the FSGS Patient, Caregiver, and Advocacy Community