# PARASOL Effort Progresses to Address Clinical Trial Endpoints in FSGS

By Howard Trachtman and Melissa West

Focal segmental glomerulosclerosis (FSGS) is a rare, primary glomerular disorder with a disproportionate impact on health outcomes, especially in socially disadvantaged populations. It is a significant cause of kidney failure in children and adults. Most importantly, there are no approved treatments for FSGS. Prompted by the urgent need to develop safe and effective therapies for people with FSGS, the Proteinuria and GFR [glomerular filtration rate] as Clinical Trial Endpoints in FSGS (PARASOL) initiative was conceived with the aim of defining a traditional or reasonably likely surrogate endpoint for use in FSGS clinical trials. A surrogate endpoint will enable accelerated approval of novel therapies and expedite access to effective treatments for this rare but devastating glomerular disorder. PARASOL represents a partnership among NephCure, the National Kidney Foundation, the International Society of Glomerular Disease, and the Kidney Health Initiative and brings together all of the relevant parties—patients, clinical nephrologists, industry sponsors, basic scientists, biostatisticians, and regulatory authorities.

After a successful meeting in December 2023 to launch the PARASOL initiative (1), the group reconvened this year on June 8th and 9th in Reykjavik, Iceland, for an interim assessment of the effort. The meeting was held at the former home of Iceland's first prime minister in a historic Nordic building that was just the right size to allow the participants to breathe easily and mingle comfortably. The weather was cold and breezy but rain-free throughout. There were 63 in-person attendees and 40 online participants, including 31 adult nephrologists, 8 pediatric nephrologists, 35 industry representatives, 9 biostatisticians, 15 patient and kidney health nonprofit organization advocates, as well as representatives from US and European regulatory agencies.

Under the leadership of Josh Tarnoff (NephCure); Laura H. Mariani, MD, MS, FASN (University of Michigan); Matthias Kretzler, MD (University of Michigan); and Tobias B. Huber, MD, FASN (International Society of Glomerular Disease), the meeting opened with a brief review of the unmet clinical need, PARASOL operations, and the features of the individual patient-level data that are required for inclusion and ultimate success of the initiative. An impressive 26 global patient cohorts and registries have confirmed that they have the required patient-level data and are able and willing to contribute to the effort (Table). Four cohorts are fully incorporated into the database and were used for the initial analysis: the Nephrotic Syndrome Study Network (NEPTUNE), Cure Glomerulonephropathy (CureGN), the Kidney Research Network (KRN), and the University of North Carolina at Chapel Hill Glomerular Disease Collaborative Network (GDCN). The additional cohorts were charged with completing the administrative requirements and approvals by August 15th for inclusion in the final analysis. "We are overwhelmed by the community response to PARASOL, including the enthusiasm of the nephrologists and teams that have agreed to share their data," Kretzler commented. "It was commonplace for each willing participant registry or patient cohort to identify another potential source of well-characterized patients with FSGS that could be approached to join PARASOL."

Significant time was spent reviewing characteristics of deidentified patients who have already been entered into the shared data repository. Since the focus of the PARASOL initiative is regulatory considerations of the aggregated data and their use in the development of an endpoint for use in clinical trials, it is important that the heterogeneity of FSGS is considered, and relevant subgroup analyses are addressed in the effort.

Three principle topics that are essential in understanding patients with FSGS and the application to clinical trial endpoints are: 1) the nature of the data regarding the estimated GFR (eGFR) trajectory, 2) the association of proteinuria and eGFR outcomes, and 3) the association of proteinuria and risk of progression to kidney failure. There was an understanding that additional follow-up work will be needed to define the clinical application of the findings by nephrologists in practice.

Following the overview and review of the patient-level data and data sources, Margaret Helmuth, MS, and Abigail Smith, PhD, members of the biostatistical team, presented a rich initial analysis supported by clear graphics. There were breakout groups to drill down deeper into key aspects of the data, deficiencies, and gaps and potential future research questions and analyses. "With an incredible group of experts in attendance, we spent time discussing how to optimize the endpoint(s) to meet the needs of patients, clinicians, and sponsors for feasible trial designs; analyze complex data from pediatric patients; incorporate information from medications; and identify additional specific patient subgroups to test the robustness of the model," said Mariani. "The feedback received is instrumental for the next phase of data analysis and presentation to the community in October 2024."

The atmosphere in Reykjavik was open and collegial, which promoted engaging conversation and interaction at all levels. The participants appreciated and respected the urgency of the task at hand. Defining a surrogate endpoint for immunoglobulin A nephropathy clinical trials has had an immediate impact for patients and families, with two drug approvals and ongoing interest from the pharmaceutical and biotech industry. The group in attendance in Iceland expressed the hope that achieving a successful outcome in PARASOL would similarly energize clinical research in FSGS and speed up the development of new treatments for people with FSGS. In addition, the successful implementation of a shared data resource to develop clinical trial endpoints in FSGS spurred enthusiasm for similar efforts in other rare kidney diseases such as membranous nephropathy and complement 3 glomerulopathy.

From its inception, the PARASOL initiative set an ambitious timeline of 11 months. The gathering of all participants at this interim meeting confirmed that the project is on schedule and moving full steam ahead and in the right direction. The next milestone is a public scientific workshop cosponsored by the US Food and Drug Administration to be held October 7–8, 2024, in Washington, DC. The goal of the workshop is to present the key findings of the PARASOL team and deliver a viable surrogate endpoint for traditional and/or accelerated approval use in FSGS clinical trials. Additional presentations will be offered for the larger community at ASN Kidney Week later that month in San Diego, CA.

To learn more about PARASOL, please visit https://www.is-gd.org/parasol, or contact Dr. Mariani at lmariani@med.umich.edu or Laurel Damashek, MA, at ldamashek@is-gd.org.

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**Reference**

1. West M. Community collaborates to address clinical trial endpoints for FSGS. *Kidney News*, February 2024; 16(2):14–15. https://www.kidneynews.org/view/journals/kidney-news/16/2/article-p14_7.xml

**Guiding principles of PARASOL data analysis**

- Nature of the data regarding the eGFR trajectory
- Association of proteinuria and eGFR outcomes
- Association of proteinuria and risk of progression to kidney failure

**Table. PARASOL contributors**

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| ACTION (Ph2 Study of the Efficacy and Safety of DMX-200 in Patients With FSGS Who Are Receiving an ARB) Trial |
| C-PROBE (Clinical Phenotyping and Resource Biobank) |
| CKiD (Chronic Kidney Disease in Children Study) |
| CureGN |
| DAPA-CKD (Dapagliflozin in Patients With Chronic Kidney Disease) Trial[a] |
| DUET (Dual Endothelin Receptor and Angiotensin Receptor Blocker, in Patients With Focal Segmental Glomerulosclerosis [FSGS]: A Randomized, Double-Blind, Active-Control, Dose-Escalation Study) Trial |
| EMPA-Kidney (Study of Heart and Kidney Protection With Empagliflozin) Trial |
| ERKNet (The European Rare Kidney Disease Reference Network)[a] |
| FSGS Clinical Trial |
| GDCN |
| Glosen Cohort (Spain) (Glomerular Diseases Working Group of the Spanish Society of Nephrology) |
| Hamburg Glomerulonephritis Registry |
| I-TANGIBLE (Indian Translational Glomerulonephritis Biology Network) |
| Indiana University Registry/Regenstrief Institute |
| Istituto Giannina Gaslini |
| Kaiser Permanente Southern California[a] |
| Karolinska Institute[a] |
| KRN |
| NEPTUNE |
| Ottawa Registry |
| PodoNET Registry |
| RaDaR (UK National Registry of Rare Kidney Diseases) |
| Toronto Glomerulonephritis Registry |
| University of Bari Aldo Moro cohort (Italy) |
| University of Ioannina cohort (Greece) |
| Uruguay National Glomerulonephritis Registry |

ARB, angiotensin receptor blocker.
[a]Potential contributor.