Nefrologia xx (2026) 501596

Sociedad Española de Nefrología

nefrología
Revista de la Sociedad Española de Nefrología
journal homepage: www.revistanefrologia.com

Brief review

Sparsentan after approval: Defining the treatment boundary in FSGS without nephrotic syndrome

Sparsentan tras su aprobación: definición del límite terapéutico en la glomeruloesclerosis focal y segmentaria (GEFS) sin síndrome nefrótico

Lucas Maciel de Almeida Corrêa [a,*], Luiggi Kevin Virgino Brandão [b], Yan Roberth Delmiro Silva [c], Camilla Cristina Silva Fernandes [d], Isabela Malerba Pinheiro [e], Éverton Victor Belmiro da Silva [f], Gabriela Wander Fossati [g], Maria Clara do Nascimento Meneses [h], Sicilia Lins Peixoto Arruda [a]

[a] *Faculdade de Medicina de São José do Rio Preto (FAMERP), São José do Rio Preto, São Paulo, Brazil*
[b] *Centro Universitário Uninorte (UNINORTE), Rio Branco, Acre, Brazil*
[c] *Universidade Federal de Alagoas (UFAL), Arapiraca, Alagoas, Brazil*
[d] *Universidade do Estado da Bahia (UNEB), Salvador, Bahia, Brazil*
[e] *Pontifícia Universidade Católica de Minas Gerais (PUC Minas), Poços de Caldas, Minas Gerais, Brazil*
[f] *Universidade Federal de Pernambuco (UFPE), Recife, Pernambuco, Brazil*
[g] *Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Rio Grande do Sul, Brazil*
[h] *Centro Universitário Maurício de Nassau (UNINASSAU), Teresina, Piauí, Brazil*

ARTICLE INFO

Keywords:
Focal segmental glomerulosclerosis
Sparsentan
Proteinuria
Nephrotic syndrome
Endothelin receptor antagonists
Precision nephrology

ABSTRACT

The US Food and Drug Administration approval of sparsentan to reduce proteinuria in adults and children aged 8 years or older with focal segmental glomerulosclerosis (FSGS) without nephrotic syndrome represents a regulatory and therapeutic milestone, but also creates a new clinical challenge: how to translate a US proteinuria-based indication into phenotype-driven practice without treating FSGS as a single disease. DUPLEX established a robust antiproteinuric effect compared with irbesartan, but did not demonstrate a statistically significant between-group difference in eGFR slope at 108 weeks, underscoring the need for careful patient selection. This perspective argues that the main post-approval task is to define a treatment boundary. Accordingly, sparsentan is best positioned not as a broad FSGS therapy, but as a nonimmunosuppressive antiproteinuric strategy for a delimited phenotype: biopsy-confirmed FSGS, persistent clinically relevant proteinuria, absence of overt nephrotic syndrome, and no clear indication for intensive immunosuppression. Primary nephrotic, secondary/adaptive, genetic, and advanced chronicity-dominant phenotypes require different therapeutic reasoning. We propose a practical framework integrating syndrome definition, exclusion of secondary drivers, genetic assessment, histologic chronicity, early proteinuria response, and safety monitoring. The clinical value of sparsentan in FSGS will depend less on broad adoption than on careful identification of patients in whom proteinuria reduction is likely to reflect a meaningful therapeutic target rather than a nonspecific pharmacodynamic effect.

Palabras clave:
Glomeruloesclerosis focal y segmentaria
Sparsentan
Proteinuria
Síndrome nefrótico

RESUMEN

La aprobación por la Administración de Alimentos y Medicamentos de los Estados Unidos de sparsentan para reducir la proteinuria en adultos y niños de 8 años o más con glomeruloesclerosis focal y segmentaria (GEFS) sin síndrome nefrótico representa un hito regulatorio y terapéutico, pero también plantea un nuevo reto clínico: cómo trasladar una indicación estadounidense basada en la proteinuria a una práctica guiada por fenotipos sin tratar la GEFS como una única enfermedad. El estudio DUPLEX demostró un efecto

* Corresponding author.
E-mail address: lucasmacielll@icloud.com (L.M.A. Corrêa).

https://doi.org/10.1016/j.nefro.2026.501596
Received 11 May 2026; Accepted 1 June 2026
Available online xxx
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Please cite this article in press as: L.M. de A. Corrêa, L.K.V. Brandão, Y.R. Delmiro Silva et al., Sparsentan after approval: Defining the treatment boundary in FSGS without nephrotic syndrome, Nefrologia, https://doi.org/10.1016/j.nefro.2026.501596

Antagonistas del receptor de endotelina
Nefrología de precisión

antiproteinúrico robusto en comparación con irbesartán, pero no mostró una diferencia estadísticamente significativa entre grupos en la pendiente del filtrado glomerular estimado a las 108 semanas, lo que subraya la necesidad de una selección cuidadosa de los pacientes. Esta perspectiva sostiene que la principal tarea tras la aprobación es definir un límite terapéutico. En consecuencia, sparsentan se posiciona mejor no como un tratamiento amplio para la GEFS, sino como una estrategia antiproteinúrica no inmunosupresora para un fenotipo delimitado: GEFS confirmada por biopsia, proteinuria persistente clínicamente relevante, ausencia de síndrome nefrótico manifiesto y ausencia de una indicación clara para inmunosupresión intensiva. Los fenotipos primario nefrótico, secundario/adaptativo, genético y con predominio de cronicidad avanzada requieren un razonamiento terapéutico diferente. Proponemos un marco práctico que integra la definición sindrómica, la exclusión de factores secundarios, la evaluación genética, la cronicidad histológica, la respuesta proteinúrica temprana y la monitorización de la seguridad. El valor clínico de sparsentan en la GEFS dependerá menos de su adopción generalizada que de la identificación cuidadosa de los pacientes en quienes la reducción de la proteinuria probablemente refleje un objetivo terapéutico significativo, y no simplemente un efecto farmacodinámico inespecífico.

Approval changed the treatment landscape, not the diagnostic problem

In April 2026, the US Food and Drug Administration (FDA) approved sparsentan to reduce proteinuria in adults and children aged 8 years or older with focal segmental glomerulosclerosis (FSGS) without nephrotic syndrome, closing a historic US regulatory gap but not simplifying the clinical problem.[1,2] The indication – to reduce proteinuria in patients aged 8 years or older with FSGS without nephrotic syndrome – was supported by DUPLEX, in which sparsentan achieved higher rates of partial proteinuria remission than maximally dosed irbesartan, although no statistically significant difference in the estimated glomerular filtration rate (eGFR) slope was observed at 108 weeks.[1–3] This dissociation makes a simplified interpretation of the trial untenable.[3–5] A drug that reduces proteinuria more effectively than an active comparator, without demonstrating a corresponding benefit on kidney function decline, should not be framed as a universal standard for FSGS; its clinical value depends on how carefully the eligible phenotype is defined.[3–5] Approval therefore ended the era in which no therapy was approved for FSGS, but inaugurated the era of phenotypic selection.[1,2] The central post-approval question is not whether sparsentan reduces proteinuria, but where its use should define a new treatment boundary between nonimmunosuppressive antiproteinuric therapy, conventional immunosuppression, and optimized supportive care.[1–5]

The need for selection does not arise from approval itself, but from the biological heterogeneity concealed beneath the diagnostic umbrella of FSGS.[6–8] FSGS is not a single disease, but rather a histologic pattern in which biologically distinct processes converge on podocyte injury and segmental sclerosis.[6–8] Primary, genetic, secondary/adaptive, and undetermined forms may overlap morphologically, yet differ in pathogenesis, clinical trajectory, and plausibility of response to a dual endothelin and angiotensin receptor antagonist.[6–8] The post-approval clinical problem, therefore, is not simply to choose a drug; it is to avoid treating patients with fundamentally different disease mechanisms as though they shared the same therapeutic substrate.[6–8] A regulatory indication identifies a population in which the benefit–risk profile was judged acceptable; it does not eliminate the need to define the biological substrate of FSGS at the bedside.[1,2,6–8] Any prescribing algorithm that incorporates sparsentan without first clarifying phenotype, mechanism, and chronicity risks converting a specific proteinuria-based approval into a nonselective therapeutic standard.[6–8]

Non-nephrotic FSGS is a treatment boundary, not a benign category

Following sparsentan approval, the distinction between nephrotic-range proteinuria and overt nephrotic syndrome has gained renewed practical importance in the evaluation of FSGS.[9] Pathophysiologically, primary FSGS is associated with the abrupt presentation of the full syndrome – characterized by hypoalbuminemia, edema, and diffuse podocyte foot process effacement – reflecting extensive cellular injury.[6,9] By contrast, maladaptive and secondary forms arise from hemodynamic overload, manifesting with high-grade proteinuria but only rarely with the complete nephrotic syndrome.[6,7,9] This distinction prevents management from being reduced to a numerical UPCR threshold.[6,7,9] In FSGS, the syndrome-level phenotype – proteinuria, serum albumin, edema, tempo of presentation, and extent of foot process effacement – determines whether the lesion is more consistent with acute primary podocytopathy, maladaptive stress, genetic disease, or an undetermined-cause phenotype.[6,7,9]

The absence of nephrotic syndrome should not be interpreted as synonymous with low risk or a benign course.[10,11] Although this presentation has historically been regarded as less aggressive, contemporary data indicate that these patients may experience kidney outcomes as severe as those observed in syndromic disease, with progression to renal replacement therapy (RRT) occurring in approximately 26.8% of cases.[10,11] This adverse outcome is concentrated among cases with substantial chronicity and tubulointerstitial fibrosis on biopsy, encompassing secondary and genetic forms with insidious progression.[6,10] Because organ failure is driven by the sustained burden of proteinuria, persistent levels above 1.5–3.5 g/day predict kidney deterioration.[12] Thus, non-nephrotic FSGS is clinically dangerous for two opposing reasons: it may be undertreated when interpreted as benign proteinuria, but overtreated when histologic FSGS is equated with primary immune-mediated disease.[6,10,12] This dual risk is precisely what makes the non-nephrotic phenotype the key post-approval treatment boundary.[6,10,12]

The sparsentan candidate: persistent proteinuria, phenotypic coherence, and no clear immunosuppressive target

The evidence base for sparsentan in FSGS is strong enough to change the therapeutic conversation, but not strong enough to remove the need for phenotype-based selection.[3–5] In DUET, sparsentan produced greater short-term proteinuria reduction than irbesartan and increased the proportion of patients reaching the FSGS partial remission endpoint.[13] DUPLEX confirmed a sustained antiproteinuric advantage, with higher partial remission at 36 weeks and greater UPCR reduction through 108 weeks, but did not demonstrate a statistically significant between-group difference in total eGFR slope at 108 weeks.[3,14] This pattern supports sparsentan as a potent antiproteinuric therapy, while leaving unresolved the central post-approval question: in this setting, proteinuria reduction should be interpreted as a necessary pharmacodynamic signal, but not as sufficient proof that dual endothelin–angiotensin receptor antago-

nism will produce durable kidney protection across biologically heterogeneous FSGS phenotypes.[4,5]

In post-approval practice, sparsentan should be framed as a boundary-defining therapy rather than a category-wide FSGS therapy.[3–5] The most defensible candidate is the patient in whom four conditions converge: biopsy-confirmed FSGS; persistent clinically relevant proteinuria, typically aligned with the DUPLEX threshold of UPCR ≥1.5 g/g; absence of overt nephrotic syndrome; and no clear clinical indication for intensive immunosuppression after exclusion of primary nephrotic, maladaptive, viral, drug-induced, and other secondary drivers.[3,6,7,14] Patient selection should also be understood as dynamic rather than static.[4,15,16] DUET extension and remission analyses suggest that early achievement of partial or complete proteinuria remission may identify patients with a more favorable subsequent kidney trajectory; however, no threshold has been validated as a mandatory stop-or-continue rule in post-approval practice.[4,13,15,16] A pragmatic, explicitly nonvalidated reassessment point is to evaluate treatment response after approximately 8–12 weeks, asking whether UPCR has fallen by roughly ≥40% and/or is moving toward the FSGS partial remission endpoint, defined as UPCR ≤1.5 g/g with >40% reduction from baseline.[4,13,15,16] Failure to meet this threshold should not automatically mandate discontinuation, but it should trigger reassessment of adherence, blood pressure and sodium control, competing mechanisms of proteinuria, safety, and whether continued therapy remains biologically plausible and clinically worthwhile.[4,15,16] Thus, sparsentan use after approval should be framed not only as phenotype-conditioned initiation, but also as response-conditioned continuation.[4,15,16] It is a pragmatic post-approval framework designed to prevent two errors: reflexive immunosuppression in non-nephrotic disease and reflexive sparsentan use in biologically discordant FSGS phenotypes.[6–8] In light of contemporary data, the most consistent clinical niche for sparsentan appears to lie in an intermediate population: patients with FSGS and persistent proteinuria, but without nephrotic syndrome, in whom immunosuppression is not clearly indicated and whose long-term risk may remain clinically consequential despite optimized supportive care.[7,12]

The post-approval era makes untenable the simplistic view that genetic FSGS is equivalent to therapeutic futility.[8,17] A recent exploratory analysis of DUPLEX in patients with pathogenic or likely pathogenic genetic variants demonstrated a consistent antiproteinuric signal with sparsentan: at 36 weeks, the median reduction in UPCR was 56% in the sparsentan group versus 26% in the irbesartan group, with a treatment difference of −47% (95% CI, −72% to −5%; $P = 0.03$).[17] At 108 weeks, the median reduction was 64% versus 38%, respectively, with a treatment difference of −40% (95% CI, −68% to 2%; $P = 0.06$), a nominally non-significant result that should be interpreted as exploratory rather than guideline-directive.[17] However, this was a post hoc, exploratory analysis of the DUPLEX subset with genetic-associated FSGS, in which next-generation sequencing identified 31 patients with podocyte gene variants, 25 with COL4A3–COL4A5 variants, and 14 with apolipoprotein L1 (APOL1) high-risk genotypes. Because baseline characteristics varied across genetic subgroups and the analysis was exploratory, these findings should not be overinterpreted as definitive evidence of uniform benefit across all type IV collagen, podocyte-gene, and APOL1-risk contexts.[8,17] The post-approval question is no longer whether genetics excludes treatment by definition, but which genotypes and clinical contexts remain plausible for antiproteinuric benefit.[7,8,17] This does not authorize gene-agnostic extrapolation: patients with genetic FSGS should avoid unnecessary immunosuppression, but may be reasonable candidates for sparsentan when they have persistent proteinuria and preserved kidney function.[7,8,17] The value of these preliminary data is not to justify genotype-agnostic prescribing, but to move the field beyond the false binary in which genetic FSGS is either automatically untreatable or treated as biologically equivalent to primary disease.[7,8,17] Genotypic precision should determine whether sparsentan is a plausible antiproteinuric strategy, whether immunosuppression should be avoided, and which outcomes should be considered realistic.[7,8,17]

What sparsentan should – and should not – replace

The traditional FSGS algorithm remains strongly anchored in KDIGO guidelines, which recommend high-dose glucocorticoids as first-line therapy for primary disease, reserving calcineurin inhibitors (CNIs) as an alternative or rescue strategy in specific settings of resistance or intolerance.[7] However, this deeply entrenched clinical tradition coexists with an evidence base that is considerably less robust than many nephrologists assume.[18,19] A Cochrane Database systematic review demonstrated the scarcity of randomized clinical trials directly comparing corticosteroids with placebo or strictly conservative supportive care in adults with FSGS.[18] In addition, recent meta-analyses highlight profound uncertainty regarding the true efficacy of immunosuppressive therapy in preserving long-term hard kidney outcomes in nonspecific settings, in stark contrast to the well-documented cumulative toxicity of these regimens.[19] Systemic adverse effects, ranging from incident diabetes to osteoporosis and infectious morbidity, are highly prevalent and substantially compromise overall patient health in proteinuric kidney diseases, thereby driving the current nephrology-wide effort toward global glucocorticoid minimization.[20,21] It is within this landscape of evidentiary fragility and toxicity that dual endothelin and angiotensin receptor antagonism is positioned.[3,18–21] Sparsentan does not enter an empty therapeutic field; it enters a field in which the boundary between immune-mediated podocytopathy and nonimmune proteinuric progression is often clinically blurred.[3,7,18,19] Its most important post-approval contribution may therefore be not the replacement of immunosuppression, but the requirement that nephrologists define more explicitly when immunosuppression is biologically justified, when it is avoidable, and when supportive antiproteinuric therapy is the more coherent strategy.[3,7,18,19]

In this sense, recalibrating the therapeutic armamentarium requires refined pathophysiologic reasoning in daily clinical practice.[6,7,22] The residual role of immunosuppression remains well established in adult patients with a clinical presentation highly suggestive of acute primary podocytopathy, provided that secondary causes have been excluded through coherent clinicopathologic assessment.[22] Historically, it is in this restricted population that immunosuppressive intensity has shown the greatest capacity to induce complete remission, with consequent effects on functional preservation.[23] Conversely, within the clinical spectrum of non-nephrotic FSGS, particularly when phenotypic features point toward a maladaptive, genetic, or undetermined etiology, the rationale for early exposure to prolonged courses of corticosteroids or CNIs becomes less automatic and fundamentally less defensible, supporting the growing incorporation of systematic genetic testing to avoid futile therapies.[6,24] In these more insidiously progressive patients, in whom subnephrotic proteinuria reflects secondary glomerular scarring and mechanical stress more than acute immune-mediated inflammation, sustained reduction of proteinuric and hemodynamic stress becomes a central priority of nephroprotective management.[25] In this context, targeting pathways that modulate intrarenal hemodynamics may help reduce proteinuric stress without the heavy burden of immunosuppression.[3,25] Thus, sparsentan approval should not be interpreted as an argument against immunosuppression in primary nephrotic FSGS.[7,22,23] Rather, it sharpens the question of where immunosuppression remains justified.[7,22,23] In non-nephrotic FSGS with maladaptive, genetic, chronicity-dominant, or undetermined features, prolonged corticosteroid or CNI exposure should require a higher evidentiary threshold, whereas nonimmunosuppressive antiprotei-

nuric therapy becomes a more coherent initial strategy when safety conditions are met.[6,7,22–25]

Operationalizing the treatment boundary at the bedside

The first post-approval step should not be prescription, but classification.[6,7] Clinicians should confirm that the biopsy shows true FSGS rather than focal global glomerulosclerosis, define whether the patient has overt nephrotic syndrome, and integrate electron microscopy, serum albumin, edema, tempo of presentation, and tubulointerstitial chronicity before assigning a therapeutic path.[6,7,26] Secondary and adaptive drivers – including obesity, reduced nephron mass, long-standing hypertension, reflux nephropathy, viral infection, drug exposure, hyperfiltration injury, and early type IV collagen disease – should be systematically assessed because they change both the rationale for immunosuppression and the expected meaning of proteinuria reduction.[6–8,24,25] Only after this classification step should clinicians choose among three paths: immunosuppression for convincing primary nephrotic disease; sparsentan or other optimized antiproteinuric therapy for persistent non-nephrotic proteinuria without a clear immune target; or driver-directed supportive care when a secondary mechanism dominates.[3–7,24,25] This sequence converts sparsentan approval from a drug-centered event into a phenotype-centered decision framework.[3–5,7] Because the regulatory indication includes children aged 8 years or older, this framework should be applied across age groups with age-specific and developmental caution.[1,2,7,14,24] In pediatric patients, treatment selection should additionally account for weight-based dosing and titration, growth and pubertal development, school-age medication routines, caregiver capacity, reproductive counseling when applicable, adherence during adolescence, and transition to adult care.[1,2,7,14,24] Pediatric use should therefore not be treated as simple extrapolation of adult FSGS practice; it requires family-centered monitoring of blood pressure, edema and volume status, kidney function, potassium, liver enzymes, and early proteinuria response.[1,2,7,14,24] Fig. 1 summarizes this post-approval treatment-boundary framework by separating FSGS heterogeneity, the most plausible sparsentan niche, and the corresponding therapeutic implications.[3–7] Table 1 translates this framework into common post-approval clinical scenarios and decision safeguards.[3–8,14,24,25]

Safety conditions for real-world use

A treatment-boundary framework is incomplete without safety boundaries.[2,3] Before initiating FILSPARI, renin–angiotensin–aldosterone system (RAAS) inhibitors and endothelin receptor antagonists (ERAs) should be discontinued. FILSPARI should not be coadministered with angiotensin receptor blockers (ARBs), ERAs, or aliskiren, because such combinations may increase the risks of hypotension, syncope, hyperkalemia, and changes in renal function, including acute renal failure. Monitoring should include blood pressure, volume status, serum creatinine/eGFR, potassium, serum aminotransferases and total bilirubin according to current Risk Evaluation and Mitigation Strategy (REMS) requirements, and pregnancy testing and contraception precautions when applicable.[2] Monitoring should include blood pressure, volume status, serum creatinine/eGFR, potassium, liver aminotransferases, bilirubin, and reproductive safety according to current REMS requirements.[2] This distinction matters because the post-approval candidate is defined by two sequential filters: biological plausibility first, operational safety second.[2,3] In real-world practice, this operational filter should also include monitoring capacity, access, reimbursement, and patient-level feasibility, because a biologically coherent treatment strategy may still fail if it cannot be delivered safely, continuously, and equitably.[2,3,7]

These operational constraints also have equity implications. A high-cost specialty drug that requires phenotype clarification, genetic testing in selected patients, laboratory monitoring, pregnancy-prevention safeguards, and sustained reimbursement may be preferentially accessible to patients treated in experienced centers, whereas patients in less resourced settings may face delayed initiation, interrupted access, or incomplete monitoring. In diverse

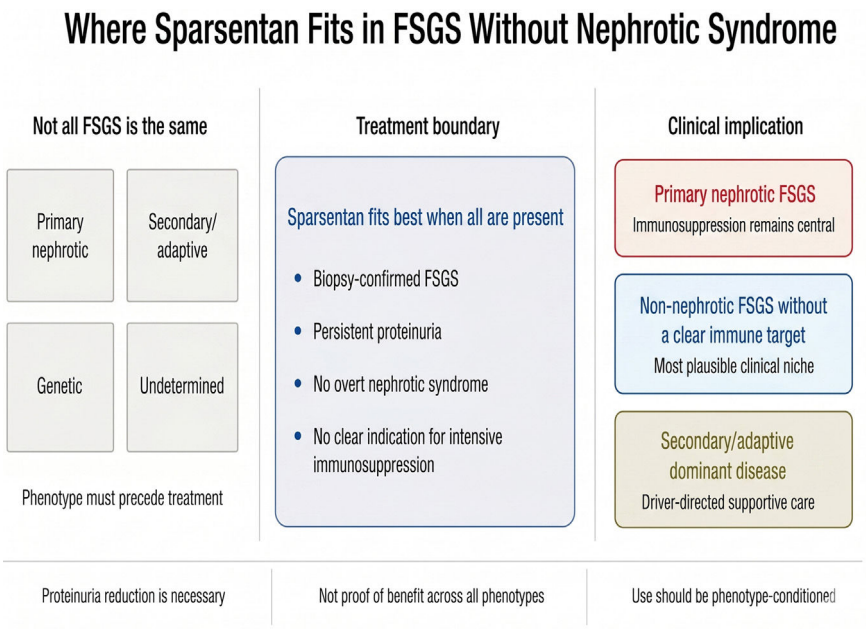

Fig. 1. Where sparsentan fits in focal segmental glomerulosclerosis without nephrotic syndrome. Sparsentan approval creates a need for phenotype-driven treatment selection rather than category-wide prescribing. The framework emphasizes that focal segmental glomerulosclerosis (FSGS) is biologically heterogeneous and that phenotype should precede treatment selection. Sparsentan is best positioned as a nonimmunosuppressive antiproteinuric strategy when biopsy-confirmed FSGS, persistent proteinuria, absence of overt nephrotic syndrome, and no clear indication for intensive immunosuppression coexist. Patients with convincing primary nephrotic FSGS remain candidates for immunosuppression, whereas patients with secondary/adaptive dominant disease require driver-directed supportive care. Proteinuria reduction supports therapeutic relevance but should not be interpreted as proof of durable kidney benefit across all FSGS phenotypes.

Table 1
Clinical scenarios and decision safeguards for sparsentan use after approval in FSGS without nephrotic syndrome.

Clinical situation	Most defensible role of sparsentan	Main decision error to avoid
Persistent non-nephrotic proteinuria; biopsy-confirmed FSGS; no dominant secondary driver[3,6,7,12,14]	Most plausible niche if safety and access conditions are met; use as nonimmunosuppressive antiproteinuric therapy within an individualized supportive platform, with early response assessment.[3,4,7,13–16]	Do not treat regulatory eligibility as proof of durable kidney protection. Reassess if response is absent or transient.[3–5,15,16]
Abrupt full nephrotic syndrome with hypoalbuminemia, edema, and diffuse foot process effacement[6,7,9,22]	Not a substitute for immunosuppression when primary nephrotic FSGS is convincing; consider only as individualized supportive therapy.[7,19,22,23]	Do not delay appropriate immunosuppression or reduce primary FSGS to a proteinuria-only indication.[6,7,19,22,23]
Obesity, reduced nephron mass, reflux nephropathy, long-standing hypertension, viral infection, or drug exposure[6–8,25]	Role uncertain and likely adjunctive; prioritize driver-directed care, nephroprotective platform, and correction of modifiable causes.[6,7,25]	Do not convert histologic FSGS into an immune diagnosis or use sparsentan to bypass causal evaluation.[6–8,25]
Pathogenic or likely pathogenic variant, including podocyte, type IV collagen, or APOL1-risk context[8,17,24,31]	Possible antiproteinuric option in selected patients with persistent proteinuria and preserved operational safety.[7,8,17]	Avoid unnecessary immunosuppression, but also avoid genotype-agnostic extrapolation of sparsentan benefit.[7,8,17,24,31]
Advanced chronicity, tubulointerstitial fibrosis, low kidney reserve, or long-standing stable scarring[6,10,26,28]	Benefit uncertain; consider only when residual modifiable proteinuric activity and a safety window remain plausible.[4,6,10,26,28]	Do not mistake irreversible scarring for active treatment failure or expect proteinuria response to prove renal salvage.[4,6,10,26,28]
No meaningful early proteinuria response despite adherence and adequate exposure[4,15,16,32]	Reassess phenotype, trajectory, competing proteinuria mechanisms, and benefit–risk before continuing therapy.[4,15,16,32]	Do not continue reflexively without response-conditioned reassessment.[4,15,16,32]
Hyperkalemia, hypotension, edema/fluid retention, liver risk, pregnancy potential, or concomitant therapy requiring discontinuation or avoidance, including RAAS inhibitors, ERAs, ARBs, or aliskiren.[2,3]	Defer, avoid, or monitor closely depending on risk; before initiation, discontinue RAAS inhibitors and ERAs, and do not coadminister FILSPARI with ARBs, ERAs, or aliskiren.[2]	Do not confuse biological plausibility with operational eligibility or overlook label-based discontinuation and coadministration restrictions; safety, monitoring capacity, access, and continuity of treatment are implementation filters after phenotype.[2,3,7]

This table provides a pragmatic decision matrix for postapproval sparsentan use in FSGS without nephrotic syndrome. It is intended to support phenotype-driven clinical reasoning and should not be interpreted as a validated treatment rule. *Abbreviations*: APOL1, apolipoprotein L1; ARB, angiotensin receptor blocker; ERA, endothelin receptor antagonist; FSGS, focal segmental glomerulosclerosis; RAAS, renin–angiotensin–aldosterone system; UPCR, urinary protein-to-creatinine ratio.

European healthcare systems, implementation should therefore be judged not only by biological precision, but also by whether selection, monitoring, and reimbursement pathways can be delivered without widening disparities in FSGS care.[2,3,7]

Although DUPLEX demonstrated superior proteinuria reduction compared with irbesartan, sparsentan should not be interpreted as replacing an individualized supportive nephroprotective platform.[3,7,27] Sodium–glucose cotransporter 2 (SGLT2) inhibitors should be viewed as part of supportive nephroprotection rather than as substitutes for phenotype-specific treatment decisions in FSGS.[3,7,27] In the prespecified DAPA-CKD FSGS analysis, dapagliflozin was associated with a slower chronic eGFR decline in a small biopsy-confirmed subgroup, but event numbers were limited and the analysis did not resolve how SGLT2 inhibitors should be sequenced against dual endothelin–angiotensin receptor antagonism.[27] In practice, SGLT2 inhibitors may be optimized when indicated by eGFR, albuminuria/proteinuria, cardiovascular risk, and tolerability, whereas sparsentan may be considered when persistent non-nephrotic proteinuria remains the dominant actionable target after phenotype clarification and safety conditions are met.[3,7,27] Because sparsentan replaces ACE inhibitor or ARB therapy rather than being added to it, any combination with an SGLT2 inhibitor should be individualized and monitored for blood pressure, volume status, eGFR trajectory, and potassium.[2,3,7,27]

The post-approval evidence agenda

In the post-approval setting, the introduction of sparsentan shifts the focus from isolated efficacy to a more decisive question: which patients with FSGS without nephrotic syndrome should receive it, at what point, and in place of which potentially avoidable immunosuppressive exposure.[3,18–21,28] In this context, the evidence agenda should prioritize comparisons across subphenotypes to avoid inappropriate extrapolation.[3,28,29] It also requires validation of clinicopathologic selection criteria and integration of genetic data and biomarkers to refine risk stratification.[30,31] Therefore, endpoints must move beyond proteinuria, incorporating kidney disease progression, toxicity, and quality of life.[4,32]

A further post-approval gap is the absence of validated response-enrichment tools.[4,32] Genetic testing can prevent inappropriate immunosuppression and refine expectations, but genotype alone is unlikely to capture the full biological substrate of sparsentan responsiveness.[6,8,17,24,31] Experimental and translational studies suggest that dual endothelin–angiotensin receptor antagonism may influence glomerular hemodynamics, podocyte and endothelial cell function, inflammatory signaling, and tissue-repair pathways; however, these observations remain hypothesis-generating for clinical selection.[33,34] Future studies should therefore test whether clinical phenotype, genotype, histologic chronicity, and noninvasive biomarkers can be integrated into a response-enrichment model rather than applied as isolated variables.[4,5,30–32]

Real-world observational data will therefore be essential to determine whether – and in which scenarios – specific immunosuppressive exposures can be safely avoided.[28,32] If the pre-approval era was defined by the absence of an approved therapy, the post-approval era should be judged by the precision of its use.[3–5,28,32] The success of sparsentan in FSGS will depend less on how broadly it is prescribed than on whether nephrologists can identify the phenotype in whom proteinuria reduction is a meaningful surrogate for durable kidney benefit – and avoid exposing biologically discordant patients to either unnecessary immunosuppression or poorly targeted drug adoption.[4,5,28,32]

Finally, translation of the FDA approval into European practice should be explicitly jurisdiction-specific. At the time of revision, the European Medicines Agency (EMA) public product information listed Filspari as authorised in the European Union for adults with primary IgA nephropathy, whereas an EMA-authorised FSGS indication was not publicly listed.[35] Thus, for Spanish and European nephrologists, the FDA label is clinically informative but should not be treated as a European prescribing authorisation. Until an EMA decision, national availability, reimbursement, and any FSGS-specific risk-minimisation

measures are clarified, use in Europe should be limited to locally authorised pathways, clinical trials, compassionate or managed-access mechanisms where available, and institutionally approved off-label frameworks.[35] Potential European implementation may also differ from the US label in age range, indication wording, pharmacovigilance requirements, additional monitoring, and reimbursement criteria.[35] This regulatory gap reinforces, rather than weakens, the central argument of this review: sparsentan should be implemented through phenotype-driven selection, response reassessment, safety monitoring, and equitable access pathways rather than diagnosis-wide adoption.[1,2,35]

This evidence agenda is also consistent with the fact that KDIGO has initiated renewed FSGS-focused discussion after the 2021 Glomerular Diseases guideline, including a dedicated FSGS summit in May 2026, although no formal FSGS guideline update has yet replaced the 2021 KDIGO recommendations.[7,36]

Box 1. Practice statements after sparsentan approval

These statements summarize principle-level practice implications; Table 1 provides scenario-specific operational safeguards, so the two elements are intended to be complementary rather than duplicative.

1. FSGS should not be treated as a single therapeutic entity after sparsentan approval.[1,3,6–8]
2. Absence of nephrotic syndrome should trigger phenotypic clarification, not reassurance.[6,7,9,10,12]
3. Sparsentan is most compelling when persistent proteinuria exists without a clear indication for intensive immunosuppression.[3,6,7,14,18,19]
4. Genetic FSGS should not mean automatic therapeutic futility, but genotype-agnostic extrapolation is unsafe.[7,8,17,24,31]
5. The unresolved question is not whether sparsentan reduces proteinuria, but in whom proteinuria reduction predicts durable kidney benefit.[3–5,12,15,16,32]

Authors' contributions

Research idea and study design: LMAC and SLPA; literature acquisition: LKVB, YRDS, CCSF, IMP, EVBS, GWF, MCNM; data analysis/interpretation: LMAC, LKVB, YRDS, CCSF, IMP, EVBS, GWF, MCNM; statistical analysis: not applicable; supervision or mentorship: LMAC and SLPA. Each author contributed important intellectual content, approved the final manuscript for submission, and agrees to be accountable for their own contributions.

Ethics approval

Not applicable.

Informed consent

Not applicable.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interests

None declared.

Data availability

No new data were generated or analysed for this article.

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