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Urinary Biomarker Analysis Reveals Rapid Intrarenal Anti-inflammatory and Anti-fibrotic Effects of Sparsentan in IgA Nephropathy in the SPARTAN Study

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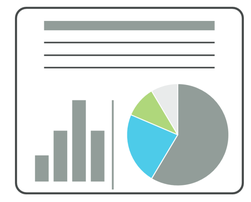

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CONCLUSIONS

- Interim findings from the SPARTAN trial show that sparsentan, as a first-line treatment in patients with IgAN, led to rapid and sustained reductions in proteinuria (≈70% from baseline)
- The biomarker results show evidence of the anti-inflammatory and anti-fibrotic actions of sparsentan in the clinical setting, consistent with extensive preclinical data[8,9]
- Sparsentan reduces urinary BAFF and C5b9, suggesting downregulation of B-cell and complement activation pathways
- This enhances the scope of sparsentan's mode of action to cellular effects well beyond hemodynamic actions

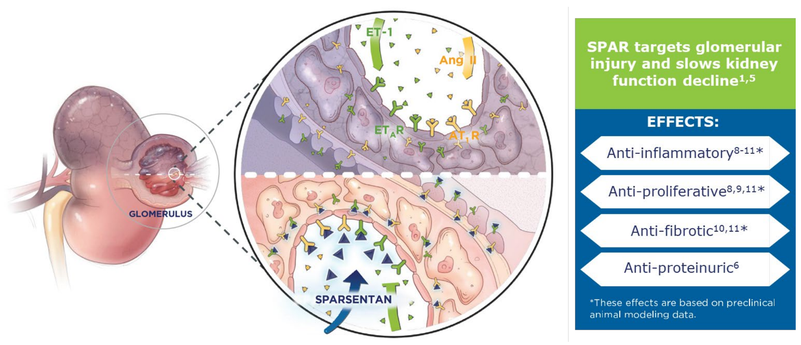
KEY TAKEAWAY

Sparsentan treatment resulted in rapid and sustained reductions in proteinuria and urinary biomarkers of inflammation and fibrosis, suggesting disease-modifying effects in IgAN

INTRODUCTION

- Sparsentan is a non-immunosuppressive, novel, dual endothelin angiotensin receptor antagonist (DEARA) (**Figure 1**), approved in the US and Europe, and indicated to slow kidney function decline in adults with IgAN[1-6]
- SPARTAN (NCT04663204) is a phase 2, open-label, single-arm multicenter trial designed to study the efficacy and safety of sparsentan as first-line therapy in patients with IgAN[7]
- The study also examines the effects of sparsentan on the underlying pathophysiology in IgAN, incorporating a biomarker-focused approach

Figure 1. Sparsentan Mechanism of Action



OBJECTIVE

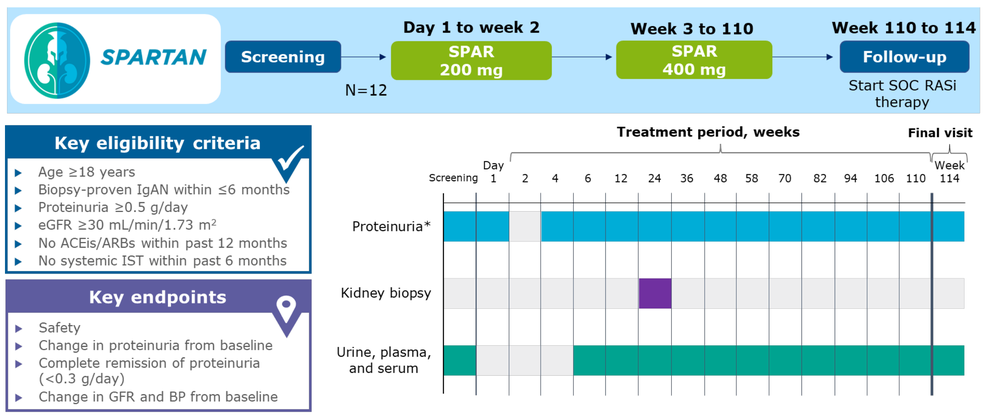
- Here, we report interim clinical findings for proteinuria and urinary biomarkers over the first 24 weeks of treatment with sparsentan from SPARTAN

METHODS

SPARTAN Study Design (NCT04663204)

- The SPARTAN study is being conducted at 5 participating sites in the UK (**Figure 2**)
- Changes in urinary biomarkers were measured by ELISA and normalized to creatinine concentration

Figure 2. Study Design and Patient Assessment Schedule



*24-hour collection.

RESULTS

Patient Population

- As of the data cutoff (February 15, 2024), 12 patients participated in the SPARTAN trial for 24 weeks; 1 patient discontinued treatment after week 6 (**Table 1**)

Table 1. Demographics and Baseline Characteristics of Patients in the SPARTAN Trial

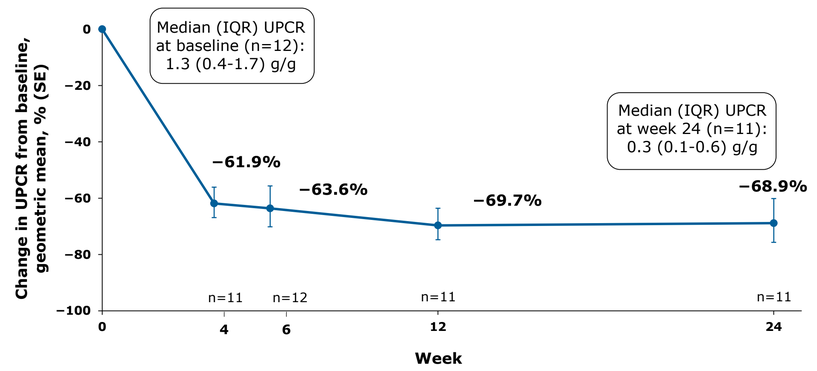
	SPARTAN (N=12)
RASi use, %	0*
IST use, %	0†
Time from initial kidney biopsy to informed consent, median (IQR), years	0.25 (0.14-0.39)‡
Age at informed consent, mean (SD), years	35.8 (12.2)
Male sex, %	58
White race, %	83
UPE, median (IQR), g/day	1.7 (0.6-3.3)
UPCR, median (IQR), g/g	1.3 (0.4-1.7)
eGFR, mean (SD), mL/min/1.73 m²	70.2 (25.0)
BP, mean (SD), mm Hg§	
Systolic	125 (10)
Diastolic	78 (10)
Weight, mean (SD), kg	83.1 (24.7)

*Eligibility criteria for SPARTAN did not allow ACEis/ARBs use within ≤12 months. †Eligibility criteria for SPARTAN did not allow systemic IST within ≤6 months. ‡n=11. §Office BP.

Proteinuria

- Proteinuria reductions were rapid and sustained over 24 weeks of sparsentan treatment (**Figure 3**)

Figure 3. Proteinuria Change (UPCR) From Baseline*

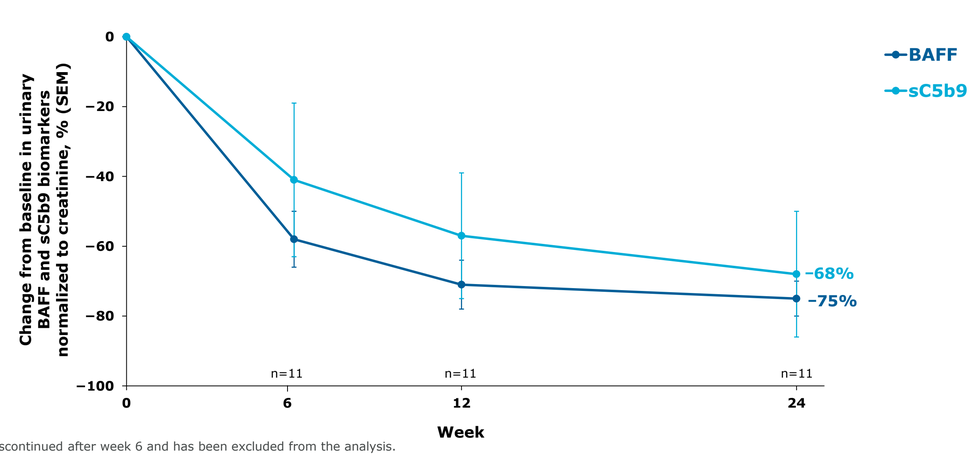


*On-treatment analysis; 1 patient discontinued after week 6.

Urinary biomarkers

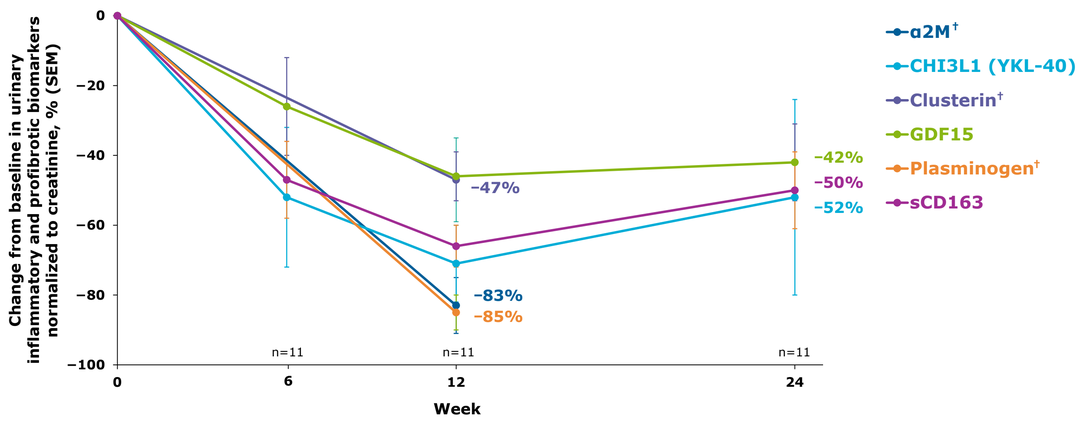
- Rapid and sustained reductions in urinary biomarkers of inflammation, immune cell recruitment/modulation, and fibrosis were observed after starting sparsentan (**Figures 4-6**)
- Protein-protein network mapping reveals a close relationship between affected biomarkers, suggesting a coordinated effect of sparsentan on modulation of intrarenal inflammatory and fibrotic pathways within multiple nephron segments (**Supplementary Figure**)

Figure 4. Urinary BAFF and sC5b9 Biomarker Change From Baseline*



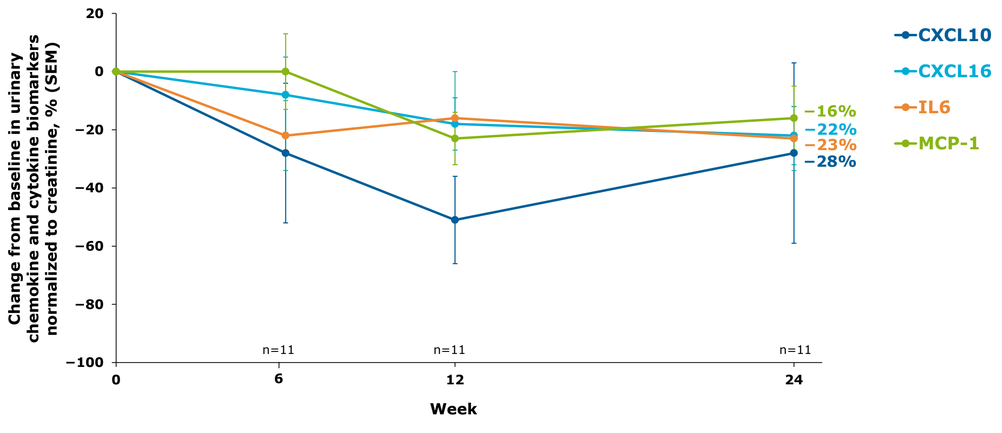
*1 patient discontinued after week 6 and has been excluded from the analysis.

Figure 5. Urinary Inflammatory and Profibrotic Biomarker Change From Baseline*



*1 patient discontinued after week 6 and has been excluded from the analysis. †α2M, clusterin, and plasminogen analysis was performed only at baseline and week 12.

Figure 6. Urinary Chemokine and Cytokine Biomarker Change From Baseline*



*1 patient discontinued after week 6 and has been excluded from the analysis.

Safety

- Sparsentan was well tolerated with no new safety signals

ABBREVIATIONS

α2M, alpha-2-macroglobulin; **ACEi**, angiotensin-converting enzyme inhibitor; **AE**, adverse event; **Ang II**, angiotensin II; **ARB**, angiotensin receptor blocker; **AT$_1$R**, angiotensin II type 1 receptor; **BAFF**, B-cell activating factor; **BP**, blood pressure; **CH13L1**, chitinase-3-like protein 1; **CXCL10**, C-X-C motif chemokine ligand 10; **CXCL16**, C-X-C motif chemokine ligand 16; **DEARA**, dual endothelin angiotensin receptor antagonist; **eGFR**, estimated glomerular filtration rate; **ELISA**, enzyme-linked immunosorbent assay; **ET-1**, endothelin-1; **ET$_A$R**, endothelin-1 type A receptor; **GDF15,** growth/differentiation factor 15; **GFR**, glomerular filtration rate; **IgAN**, immunoglobulin A nephropathy; **IL6,** interleukin 6; **IST**, immunosuppressive therapy; **MCP-1,** monocyte chemoattractant protein-1 **RASi**, renin-angiotensin system inhibitor; **sC5b9**, soluble C5b9; **sCD163,** soluble CD163; **SE,** standard error; **SEM,** standard error of the mean; **SOC**, standard of care; **SPAR**, sparsentan; **UPCR**, urine protein-to-creatinine ratio; **UPE**, urine protein excretion.

For more information about the trial, please visit https://www.clinicaltrials.gov/study/NCT04663204

REFERENCES

1. Filspari (sparsentan). Prescribing information. Travere Therapeutics, Inc.; September 2024. 2. Filspari (sparsentan). Summary of product characteristics. Vifor France; May 2024. 3. Filspari (sparsentan). Summary of product characteristics. Vifor France; October 2024. 4. Filspari (sparsentan). Summary of product characteristics. Vifor France; November 2024. 5. Kohan DE, et al. *Clin Sci.* 2024;138:645-662. 6. Rovin BH, et al. *Lancet.* 2023;402(10417):2077-2090. 7. ClinicalTrials.gov. Accessed May 14, 2025. https://clinicaltrials.gov/study/NCT04663204. 8. Jenkinson C, et al. Poster presented at: ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. SAT-010. 9. Reily C, et al. *Am J Physiol Renal Physiol.* 2024;326:F862-F875. 10. Nagasawa H, et al. *Nephrol Dial Transplant.* 2024;39:1494-1503. 11. Jenkinson C, et al. Presentation at: International Symposium on IgA Nephropathy; September 27-29, 2018; Buenos Aires, Argentina.

ACKNOWLEDGMENTS

This study was funded by Travere Therapeutics, Inc.

Medical writing assistance was provided under the direction of the authors by Taryn Ralph, PhD, of Nucleus Global, an Inizio company, in accordance with Good Publication Practice 2022 guidelines, and was funded by Travere Therapeutics, Inc. The authors thank all the patients, families, and investigators who made this study possible.

DISCLOSURES

CKC has received consulting fees from Alexion Pharmaceuticals, Boehringer Ingelheim, Calliditas Therapeutics, CSL Vifor, Dimerix Limited, George Clinical, Novartis, Otsuka Pharmaceuticals, Roche, Stada Arzneimittel AG, Travere Therapeutics, Inc., and Vera Therapeutics; and research funding from Travere Therapeutics, Inc. ND has received consulting fees from Travere Therapeutics, Inc.; research funding from Pfizer, and Travere Therapeutics, Inc.; and serves as an advisor for Travere Therapeutics, Inc. SG has received consulting fees from Alexion Pharmaceuticals, Bayer, CSL Vifor, Eledon Pharmaceuticals, Inc., Hansa Biopharma, and Takeda Pharmaceuticals; honoraria from Bayer, CSL Vifor, and Travere Therapeutics, Inc.; and serves as part of speakers bureaus for CSL Vifor and Travere Therapeutics, Inc. BH and RK are employees and stockholders of Travere Therapeutics, Inc. WJ has received consulting fees from Travere Therapeutics, Inc. AM is an employee of JAMCO Pharma Consulting AB; reports consulting fees from Dimerix, HJ-Bio, Timberlyne Therapeutics, Travere Therapeutics, Inc., and Vera Therapeutics; and has ownership interest in JAMCO Pharma Consulting AB. MS has received research funding from Travere Therapeutics, Inc. SS has received consulting fees from Inozyme Pharma and Sanifit Therapeutics S.A.; research funding from AstraZeneca, CSL Vifor, Johnson and Johnson, and Sanofi Genzyme; honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, CSL Vifor, GSK, Medscape, Menarini Group, Napp Pharmaceuticals, Novartis, and Sanofi Genzyme; is the National Clinical Director of Renal Medicine for NHS England; and is a trustee of the Kidneys for Life Charity. LW has received consulting fees from CSL Vifor, Novartis, and Travere Therapeutics, Inc.; research funding from the National Institute for Health and Care Research; honoraria from Otsuka Pharmaceuticals; has been part of advisory boards for Eledon Pharmaceuticals, Inc.; and serves as part of speakers bureaus for CSL Vifor, Novartis, and Otsuka Pharmaceuticals. MK has received consulting fees from the Alport Foundation, Boehringer Ingelheim, Certa, Chan Zuckerberg Initiative, Chinook Therapeutics, Dimerix Limited, European Union Innovative Medicine Initiative, Maze Therapeutics, National Institute of Health, Novo Nordisk, Renalytix AI, Regeneron Pharmaceuticals, Roche (Genentech), Sanofi, Travere Therapeutics, Inc., and Vera Therapeutics. JB has received consulting fees from Alnylam Pharmaceuticals, argenx, Astellas Pharma, Inc., BioCryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, Dimerix Limited, Galapagos, Novartis, Omeros, Otsuka (Visterra) Pharmaceuticals, Travere Therapeutics, Inc., and Vera Therapeutics; and research funding from argenx, Calliditas Therapeutics, Chinook Therapeutics, Galapagos, GSK, Novartis, Omeros, Otsuka (Visterra) Pharmaceuticals, and Travere Therapeutics, Inc. WAB, S Chaki, S Chinnakotla, AAAJ, IK, VN, and NN have no conflicts of interest.

Presented at the International Podocyte Conference & ISGD Meeting; June 10-13, 2025; Hamburg, Germany

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