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Sparsentan As First-Line Treatment of Incident Patients With IgA Nephropathy (IgAN): Interim Analysis of the SPARTAN Trial

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Leicester IgA Nephropathy Research Group

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DISCLOSURES

- **CKC** has received consulting fees and research funding from Travere Therapeutics, Inc.
- **SM** is an employee and stockholder of Travere Therapeutics, Inc.
- **ND** and **JB** have received consulting fees and research funding from Travere Therapeutics, Inc.
- **SG** has received consulting fees from CSL Vifor and Alexion; honoraria from Bayer and Travere Therapeutics, Inc.; travel support from Alexion; and has been part of advisory boards for Emmes and ICON plc.
- **RK** is an employee and shareholder of Travere Therapeutics, Inc.
- **AM** has received consulting fees from Travere Therapeutics, Inc., Vera Therapeutics, and HI-Bio.
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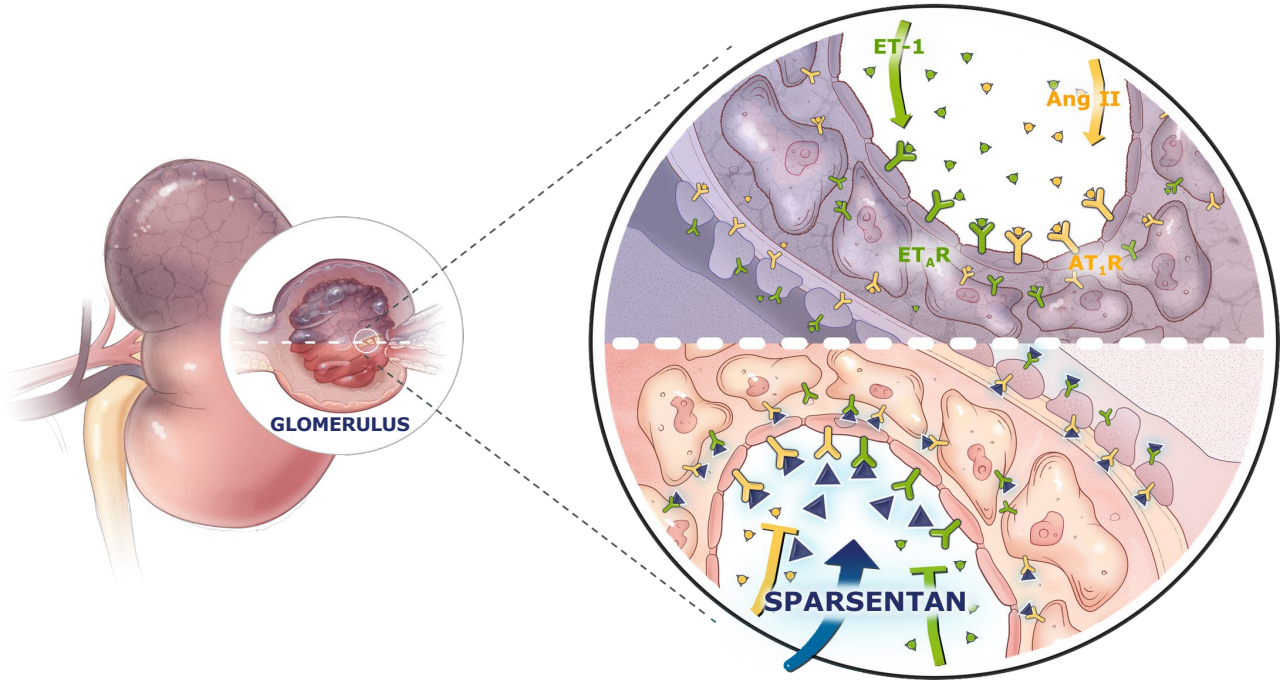
- **LW** has received consulting fees from Travere Therapeutics, Inc., Novartis, Chinook, and Goldfinch Bio; honoraria from Travere Therapeutics, Inc., Novartis, and Otsuka; and has been part of advisory boards for Eledon Pharmaceuticals.
- **AH** and **MS** have no conflicts of interest.

- Sparsentan, a non-immunosuppressive novel dual endothelin and angiotensin receptor antagonist (DEARA), is approved in the US and the EU to treat adults with IgAN based on data from the Phase 3 PROTECT trial[1-4]



Sparsentan targets glomerular injury and slows kidney function decline[1,5]

EFFECTS:

- Anti-inflammatory[6-9*]
- Anti-proliferative[6,7,9*]
- Anti-fibrotic[8,9*]
- Anti-proteinuric[4]

*These effects are based on pre-clinical animal modeling data.

Ang II, angiotensin II; AT_1R, angiotensin II type 1 receptor; ET-1, endothelin 1; ET_AR, endothelin-1 type A receptor.

1. FILSPARI (sparsentan). Prescribing Information. September 2024. Travere Therapeutics, Inc. San Diego, CA, USA; 2. FILSPARI (sparsentan). European Medicines Agency (EMA). https://www.ema.europa.eu/en/medicines/human/EPAR/filspari (Accessed October 2, 2024); 3. Heerspink HJL, et al. *Lancet.* 2023;401(10388):1584-1594; 4. Rovin BH, et al. *Lancet.* 2023;402(10417):2077-2090; 5. Kohan DE, et al. *Clin Sci.* 2024;138:645-6625; 6. Jenkinson C, et al. Poster presented at: ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. SAT-010; 7. Reily C, et al. *Am J Physiol Renal Physiol*. 2024;326:F862-F875; 8. Nagasawa H, et al. *Nephrol Dial Transplant*. 2024;39:1494-1503; 9. Jenkinson C, et al. Presentation at: International Symposium on IgANephropathy; September 27-29, 2018; Buenos Aires, Argentina.

- In the PROTECT trial, sparsentan showed reduced proteinuria and long-term kidney function preservation in prevalent IgAN patients vs maximally titrated irbesartan[1,2]
- The effect in newly diagnosed, RASi-naive patients remains unknown
- SPARTAN (NCT04663204) is a Phase 2, open-label, single-arm, multicenter trial investigating the safety, efficacy, and mechanistic actions of sparsentan as first-line therapy in patients newly diagnosed with IgAN[3]

Objective

- Here we report interim clinical findings over the first 24 weeks of treatment with sparsentan from SPARTAN

1. Rovin BH, et al. *Lancet*. 2023;402(10417):2077-2090; 2. Heerspink HJL, et al. *Lancet*. 2023;401(10388):1584-1594;
3. ClinicalTrials.gov. Accessed October 2, 2024. https://clinicaltrials.gov/study/NCT04663204.

SPARTAN Study Design (NCT04663204)

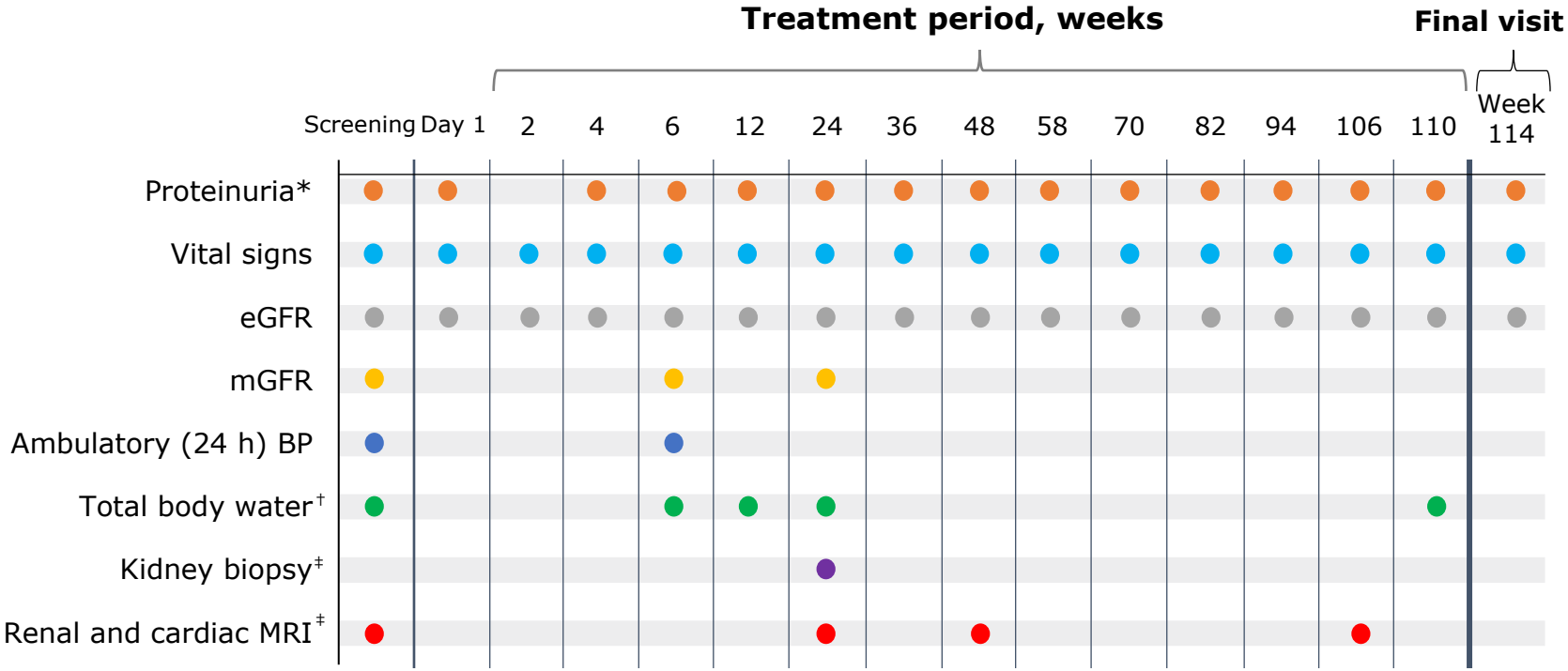
- The SPARTAN study is being conducted at 5 participating sites in the UK

Key Eligibility Criteria

- Age ≥18 years
- Biopsy-proven IgAN within ≤6 months
- Proteinuria ≥0.5 g/day
- eGFR ≥30 mL/min/1.73 m^2
- No ACEIs/ARBs within ≤12 months
- No systemic IST within ≤6 months

Key Endpoints

- Safety
- Change in proteinuria from baseline
- Complete remission of proteinuria (<0.3 g/day)
- Change in GFR and BP from baseline



mGFR, measured glomerular filtration rate; SOC, standard of care; SPAR, sparsentan.
*24-hour collection. †Measured by bioimpedance spectroscopy. ‡For future analyses.

RESULTS

Demographics and Baseline Characteristics of Patients in the SPARTAN vs PROTECT Trials

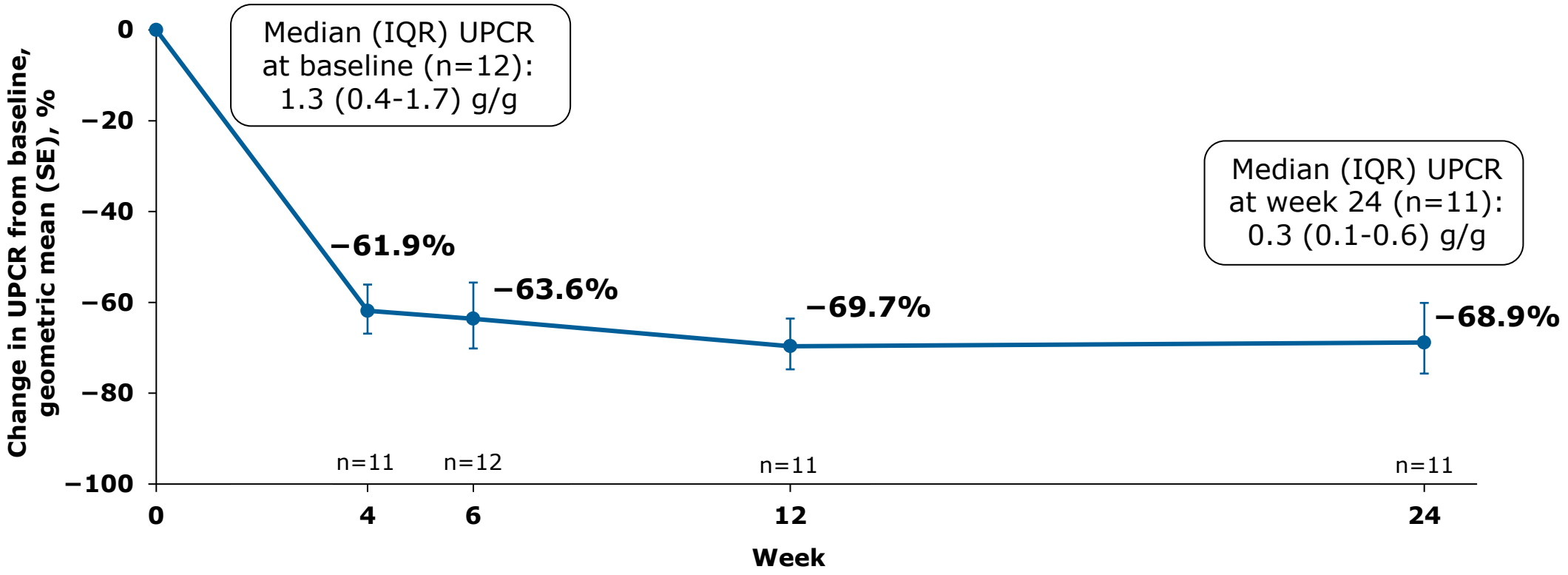
	SPARTAN (N=12)	PROTECT[1,2] (N=402)
RASi use, %	0*	>99†
IST use, %	0‡	5§
Time from initial kidney biopsy to informed consent, median (IQR), years	0.25 (0.14-0.39)‖	4.0 (1.0-10.0)
Age at informed consent, mean (SD), years	35.8 (12.2)	46.0 (12.44)
Male sex, %	58	70
White race, %	83	67
UPE, median (IQR), g/day	1.7 (0.6-3.3)	1.8 (1.3-2.8)
UPCR, median (IQR), g/g	1.3 (0.4-1.7)	1.2 (0.8-1.8)
eGFR, mean (SD), mL/min/1.73 m²	70.2 (25.0)	56.9 (24.0)
BP, mean (SD), mm Hg¶		
Systolic	125 (10)	129 (14)
Diastolic	78 (10)	82 (11)
Weight, mean (SD), kg	83.1 (24.7)	84.4 (19.8)

*Eligibility criteria for SPARTAN did not allow ACEIs/ARBs use within ≤12 months. †At screening. ‡Eligibility criteria for SPARTAN did not allow systemic IST within ≤6 months. §For renal indication. ‖n=11. ¶Office BP.

1. Rovin BH, et al. *Lancet*. 2023;402(10417):2077-2090. 2. Data on file. Travere Therapeutics, Inc.

Proteinuria Change (UPCR) From Baseline*

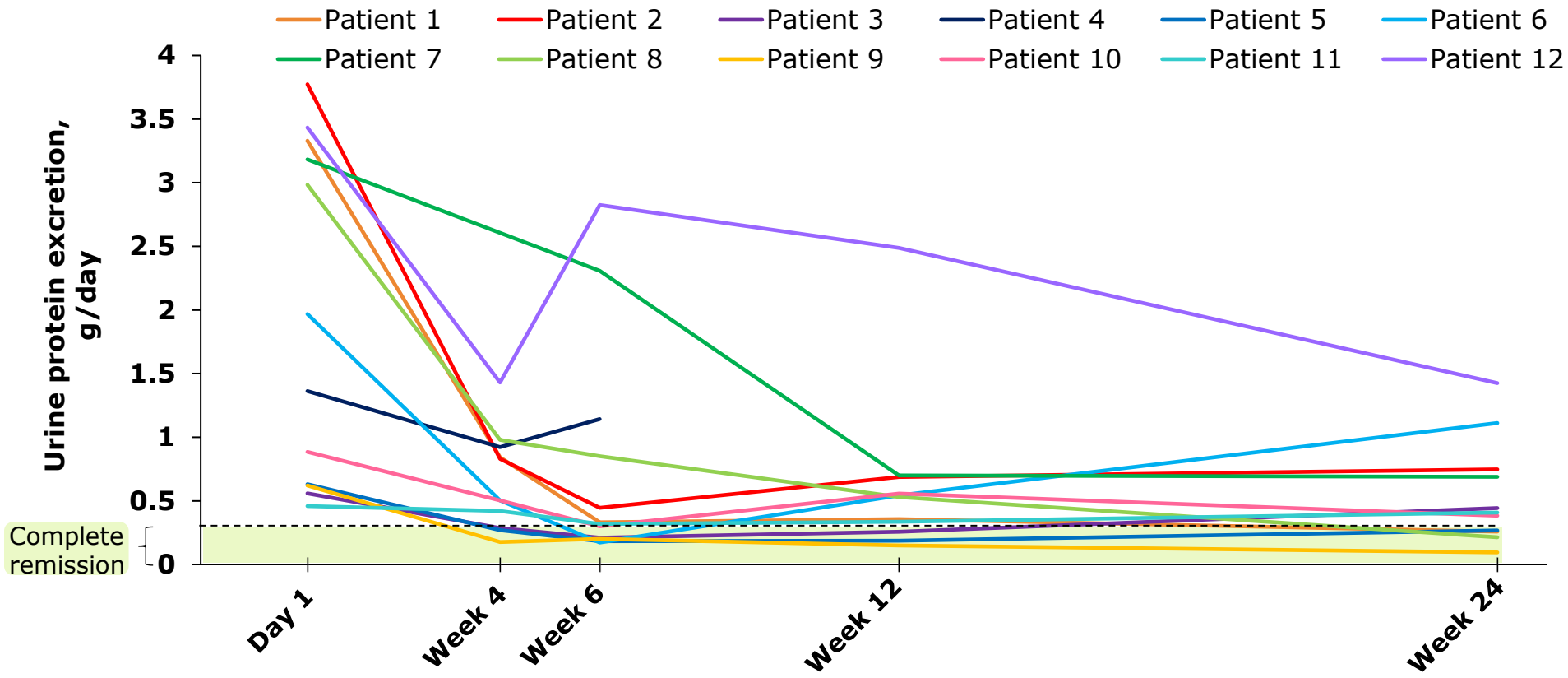
- Proteinuria reductions were rapid (≈60% from baseline at week 4) and sustained over 24 weeks of sparsentan treatment



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

Proteinuria Per Individual Patient*

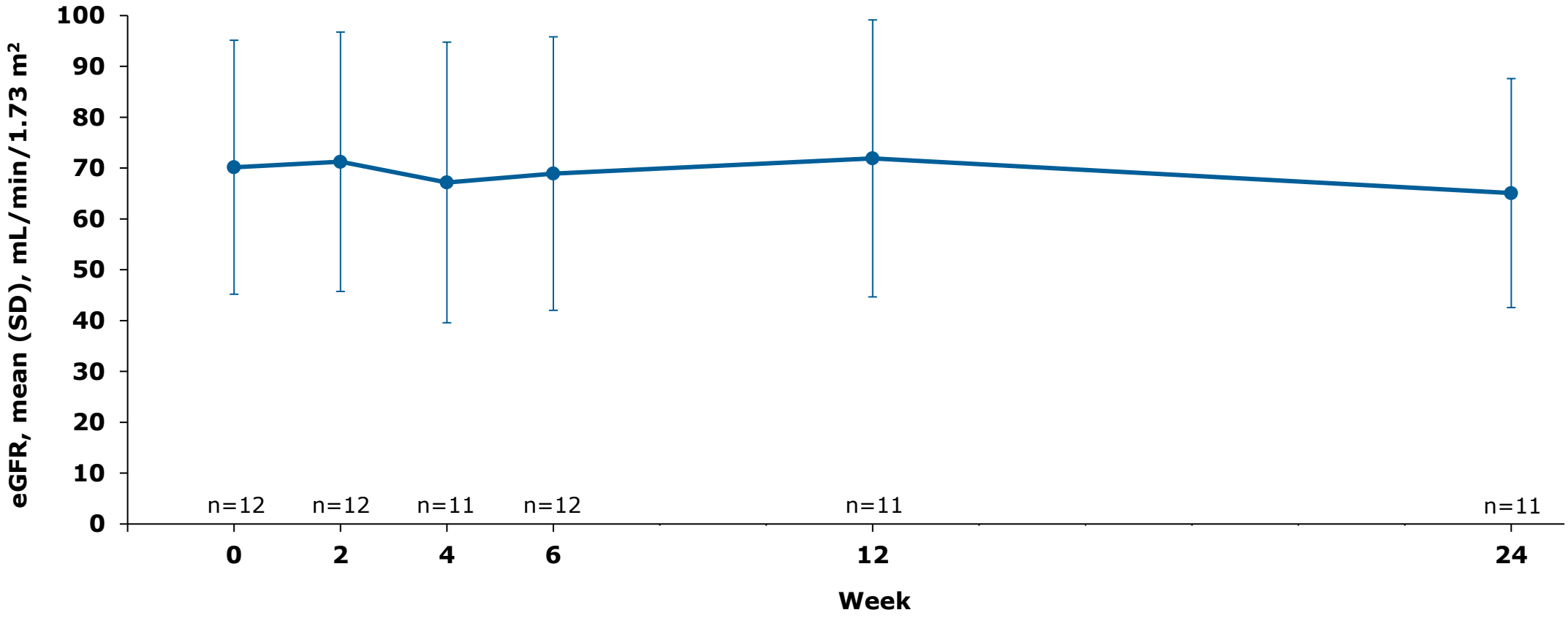
- Among the 5 patients with protein excretion of >2 g/day at baseline, 4 had proteinuria reductions of ≥75% at any time during the first 24 weeks of treatment
- 58% of patients (7/12) achieved complete remission (<0.3 g/day) at any time during the 24-week treatment period



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

RESULTS

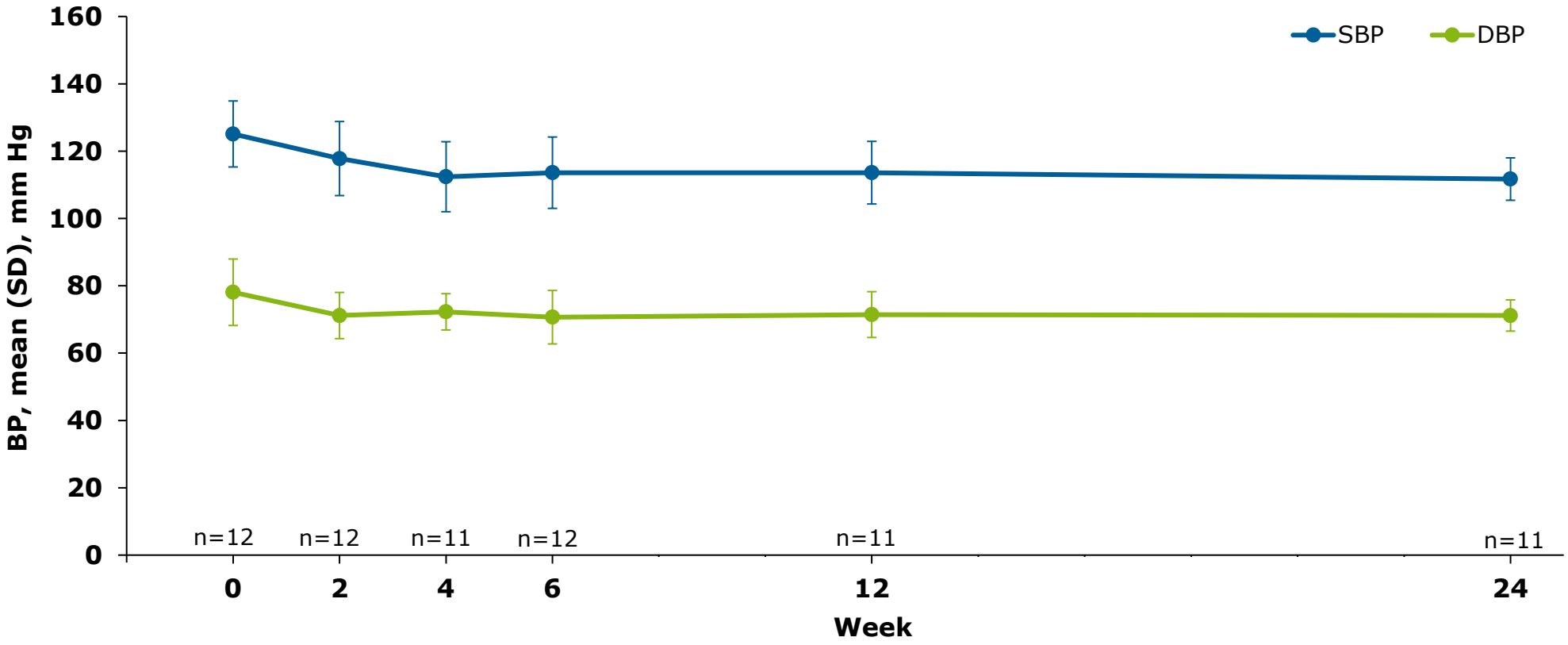
Mean eGFR at Each Visit Over 24 Weeks*



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

Mean Office BP at Each Visit Over 24 Weeks*

- After an initial slight decrease, BP remained stable during the rest of the treatment period as measured by office and ambulatory BP



DBP, diastolic blood pressure; SBP, systolic blood pressure.
*On-treatment analysis; 1 patient discontinued after week 6.

Mean Weight and Total Body Water Change From Baseline*

- There were no meaningful changes in body weight over 24 weeks
- Mean total body water change from baseline showed modest reductions during the treatment period

Mean (SD) change from baseline	Week				
	2	4	6	12	24
n	12	11	12	11	11
Weight, kg	−0.3 (0.7)	−0.2 (1.4)	0.3 (1.4)	0.1 (2.7)	−1.0 (3.3)
Total body water, L†	–	–	−2.0 (7.2)	−2.0 (7.5)	−2.4 (7.4)

*On-treatment analysis; 1 patient discontinued after week 6. †Measured by bioimpedance spectroscopy.

Safety Over 24 Weeks of Treatment

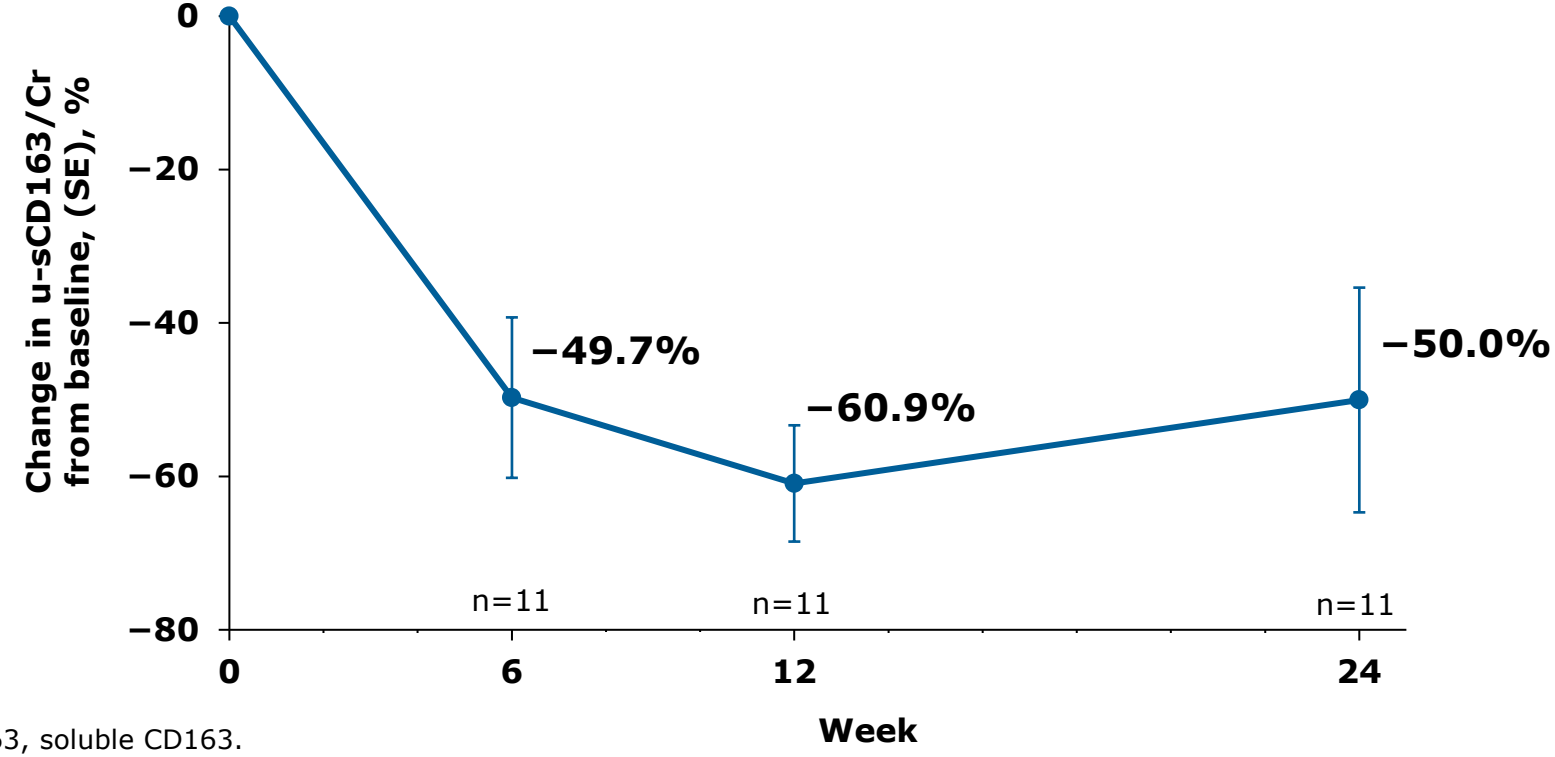
- Sparsentan was generally well tolerated
- 1 patient permanently discontinued treatment due to hypotension after week 6

	Sparsentan (N=12)
	n (%)
Any AE	12 (100)
Any serious AE*	1 (8)
Most common AEs (>2 patients)	
Dizziness	6 (50)
Urinary tract infection	3 (25)
Dyspepsia	3 (25)
Vomiting	3 (25)

AE, adverse event.
*Serious AE was an abscess (limb).

Urinary sCD163 Levels*

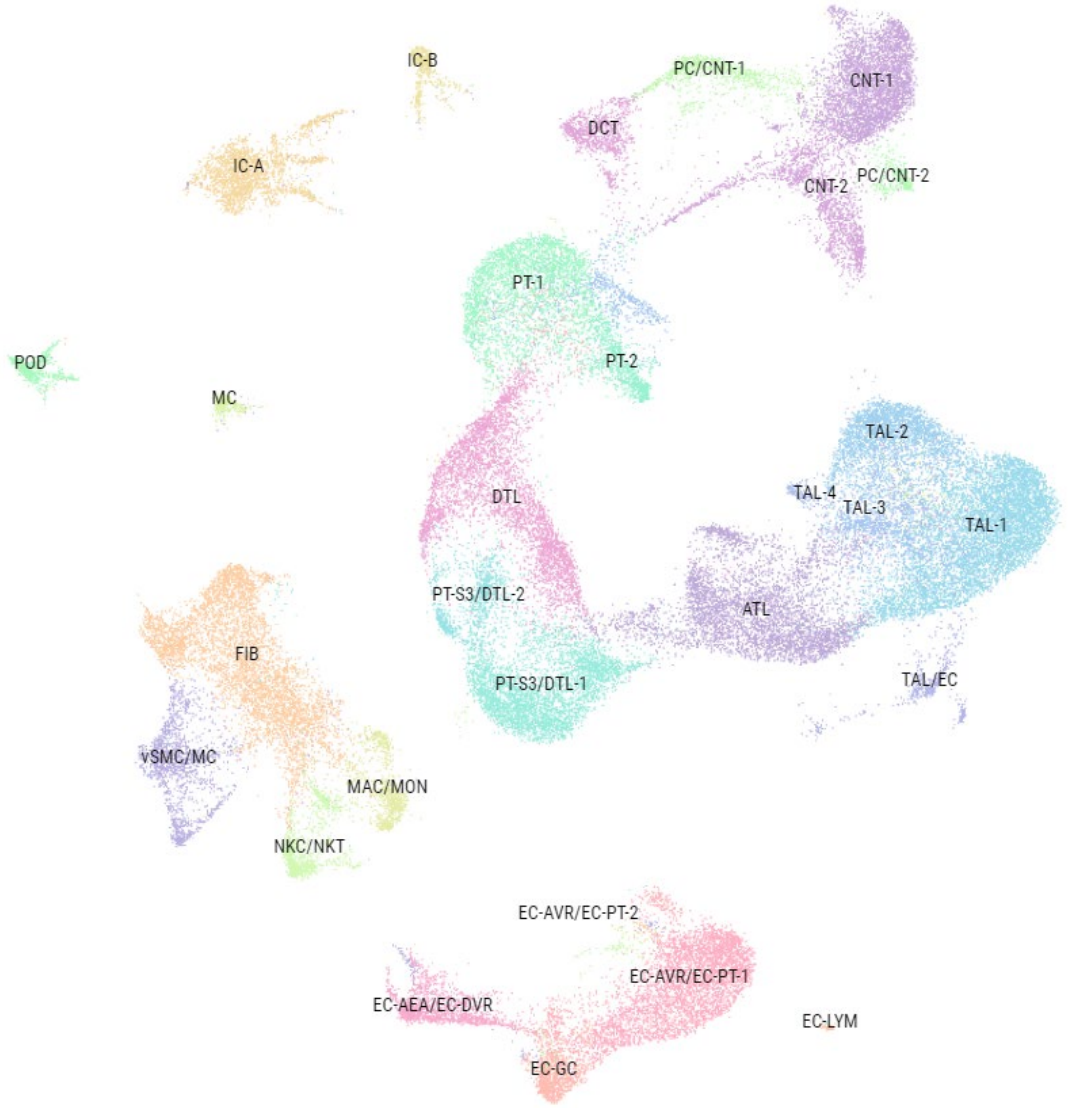
- Urinary sCD163 (u-sCD163) is a marker for alternatively activated macrophages that has been correlated with kidney macrophage infiltration and active lesions in IgAN. In the TESTING study, a ≥50% reduction of u-sCD163 from baseline was associated with a reduced risk of the composite kidney end points[1]
- Rapid and sustained reduction of u-sCD163 was observed with sparsentan treatment



CR, creatinine; sCD163, soluble CD163.
*1 patient discontinued after week 6 and has been excluded from analysis.
1. Li J, et al., *Kidney Int Rep.* 2024;9:3016-3026.

RESULTS

Kidney Biopsy Single-Cell Nuclear RNA-seq Gene Expression Profile to Define the Impact of Sparsentan on Kidney Cell Populations



ATL	4538
CNT-1	3884
CNT-2	2147
DCT	1119
DTL	4353
EC-AEA/EC-DVR	1432
EC-AVR/EC-PT-1	4184
EC-AVR/EC-PT-2	600
EC-GC	1077
EC-LYM	99
FIB	5222
IC-A	2221
IC-B	529
MAC/MON	942
MC	385
NKC/NKT	1139
PC/CNT-1	975
PC/CNT-2	309
POD	764
PT-1	3325
PT-2	837
PT-S3/DTL-1	3782
PT-S3/DTL-2	973
TAL-1	6523
TAL-2	2872
TAL-3	2164
TAL-4	343
TAL/EC	621
vSMC/MC	1633

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CONCLUSIONS

- These 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)
- Within 24 weeks of starting sparsentan, ~60% of patients achieved complete remission of proteinuria, a treatment goal recommended in the draft 2024 KDIGO guidelines[1]
- Sparsentan was generally well tolerated over 24 weeks of treatment, with no evidence of fluid retention. Safety was consistent with the Phase 3 PROTECT study[2,3]
- Rapid reductions in urinary sCD163 were observed. The reduction in this biomarker is the first demonstration of sparsentan's anti-inflammatory effect in humans and supports preclinical data that also showed attenuation of immune and proinflammatory signaling with sparsentan[4,5]
- Further analysis of transcriptomics, kidney biopsies, and additional serum, plasma, and urinary biomarkers is planned to investigate the mechanistic actions of sparsentan and its potential nephroprotective effects

KDIGO, Kidney Disease: Improving Global Outcomes.

1. KDIGO Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV). https://kdigo.org/wp-content/uploads/2024/08/KDIGO-2024-IgAN-IgAV-Guideline-Public-Review-Draft.pdf (accessed September 2024); 2. Heerspink HJL, et al. *Lancet*. 2023;401(10388):1584-1594; 3. Rovin BH, et al. *Lancet*. 2023;402(10417):2077-2090; 4. Nagasawa H, et al. *Nephrol Dial Transplant*. 2024;39:1494-1503; 5. Reily C, et al. *Am J Physiol Renal Physiol*. 2024;326:F862-F875.

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Questions?

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