Sparsentan vs Irbesartan in Patients With Immunoglobulin A Nephropathy (IgAN): Subgroup Analyses of 2-Year Results From the Pivotal Phase 3 PROTECT Trial

TRAVERE THERAPEUTICS

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RESULTS

- A total of 404 patients were randomized to and received study drug (sparsentan, n=202; irbesartan, n=202)
- In the sparsentan group, 28 patients discontinued treatment (AE, n=19; patient decision, n=5; physician decision, n=0), and 174 (86.1%) completed treatment
- In the irbesartan group, 48 patients discontinued treatment (AE, n=18; patient decision, n=21; physician decision, n=7), and 154 (76.2%) completed treatment
- More patients discontinued irbesartan than sparsentan treatment due to patient or physician decision; nearly all patients completed the double-blind study period (sparsentan, 98.0%; irbesartan, 94.1%)
- The majority of patients enrolled in PROTECT were at high risk of disease progression, with elevated proteinuria and reduced kidney function (**Table 1**)
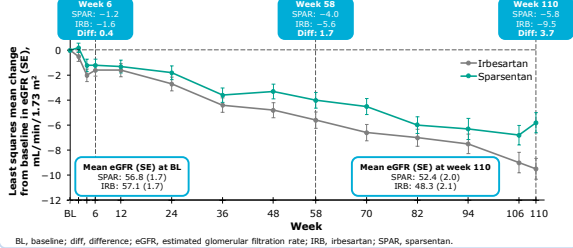
Table 1. Baseline Demographics and Clinical Characteristics

	Sparsentan (n=202)	Irbesartan (n=202)
Age at IgAN diagnosis, mean (SD), years	40.2 (13.4)	39.0 (12.4)
Time from initial kidney biopsy to informed consent, median (IQR), years	4.0 (1.0-10.0)	4.0 (1.0-10.0)
Male sex, n (%)	139 (69)	143 (71)
Blood pressure, mean (SD), mm Hg		
Systolic	128.0 (14.4)	129.9 (12.4)
Diastolic	81.6 (10.6)	83.2 (10.6)
Maximum labeled ACEi or ARB dose at screening, n (%)	130 (64)	125 (62)
eGFR, mean (SD), mL/min/1.73 m²	56.8 (24.3)	57.1 (23.6)
Subgroups: baseline proteinuria quartiles		
UPCR <0.80 g/g	57.3 (24.0)	61.9 (27.3)
UPCR ≥0.80 to <1.25 g/g	60.6 (25.0)	59.3 (25.2)
UPCR ≥1.25 to <1.80 g/g	55.9 (24.0)	55.1 (21.9)
UPCR ≥1.80 g/g	53.6 (24.5)	52.1 (18.8)
Urine protein excretion, median (IQR), g/day	1.8 (1.2-2.9)	1.8 (1.3-2.6)
UPCR, median (IQR), g/g	1.3 (0.8-1.8)	1.2 (0.9-1.7)
Hematuria, n (%)	111 (55)	114 (56)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; UPCR, urine protein-to-creatinine ratio.

Efficacy

- The 36-week interim primary analysis endpoint was met, with a 41% relative reduction in proteinuria (P<.0001)
- Significant proteinuria reduction was sustained over 110 weeks, with a 40% relative reduction in proteinuria at week 110
- Sparsentan preserves kidney function more than irbesartan (**Figure 2**)

Figure 2. eGFR Change Over 110 Weeks

Week 6: SPAR: −1.2; IRB: −1.6; Diff: 0.4
Week 58: SPAR: −4.0; IRB: −5.6; Diff: 1.7
Week 110: SPAR: −5.8; IRB: −9.5; Diff: 3.7

Mean eGFR (SE) at BL: SPAR: 56.8 (1.7); IRB: 57.1 (1.7)
Mean eGFR (SE) at week 110: SPAR: 52.4 (2.0); IRB: 48.3 (2.1)

BL, baseline; diff, difference; eGFR, estimated glomerular filtration rate; IRB, irbesartan; SPAR, sparsentan.

- More patients achieved complete proteinuria remission (<0.3 g/day) with sparsentan vs irbesartan (**Figure 3**)
- Absolute change in eGFR from baseline to week 110 was −5.8 mL/min/1.73 m² for sparsentan vs −9.5 mL/min/1.73 m² for irbesartan (difference, 3.7 mL/min/1.73 m²) (**Figure 4**)

Figure 3. Patients Achieving Complete Proteinuria Remission

Relative risk (95% CI) 2.5 (1.6 to 4.1)
Sparsentan: 31; Irbesartan: 11
Complete remission (urine protein excretion <0.3 g/day)

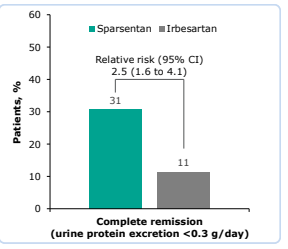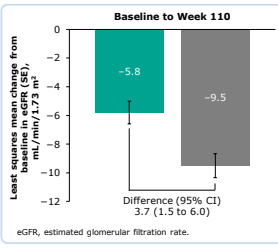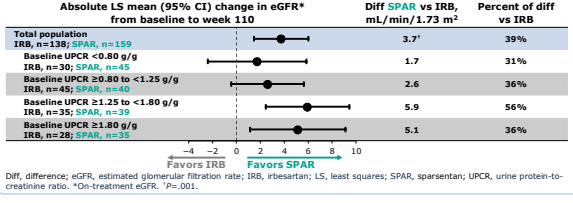### Figure 4. Absolute Change in eGFR From Baseline to Week 110

Baseline to Week 110: −5.8 (Sparsentan); −9.5 (Irbesartan)
Difference (95% CI) 3.7 (1.5 to 6.0)
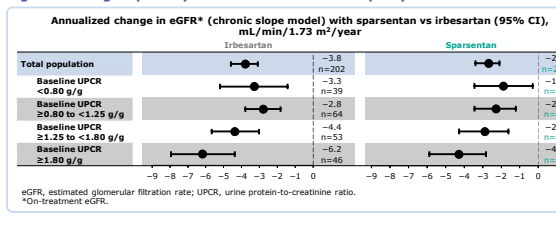
eGFR, estimated glomerular filtration rate.

- Subgroup analyses demonstrate a consistent treatment benefit across baseline urine protein-to-creatinine ratio subgroups in absolute eGFR change (**Figure 5**) and chronic eGFR slope (**Figure 6**)

Figure 5. Subgroup Analyses of Absolute Change in eGFR* by Baseline Proteinuria

	Absolute LS mean (95% CI) change in eGFR* from baseline to week 110	Diff SPAR vs IRB, mL/min/1.73 m²	Percent of diff vs IRB
Total population IRB, n=138; SPAR, n=159		3.7†	39%
Baseline UPCR <0.80 g/g IRB, n=30; SPAR, n=45		1.7	31%
Baseline UPCR ≥0.80 to <1.25 g/g IRB, n=45; SPAR, n=40		2.6	36%
Baseline UPCR ≥1.25 to <1.80 g/g IRB, n=35; SPAR, n=39		5.9	56%
Baseline UPCR ≥1.80 g/g IRB, n=28; SPAR, n=35		5.1	36%

Favors IRB / Favors SPAR

Diff, difference; eGFR, estimated glomerular filtration rate; IRB, irbesartan; LS, least squares; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio. *On-treatment eGFR. †P=.001.
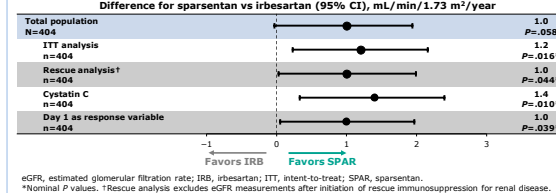
Figure 6. Subgroup Analyses of Chronic eGFR* Slope by Baseline Proteinuria

Annualized change in eGFR* (chronic slope model) with sparsentan vs irbesartan (95% CI), mL/min/1.73 m²/year

	Irbesartan	Sparsentan
Total population	−3.8 n=202	−2.7 n=202
Baseline UPCR <0.80 g/g	−3.3 n=39	−1.9 n=54
Baseline UPCR ≥0.80 to <1.25 g/g	−2.8 n=64	−2.3 n=47
Baseline UPCR ≥1.25 to <1.80 g/g	−4.4 n=53	−2.9 n=49
Baseline UPCR ≥1.80 g/g	−6.2 n=46	−4.3 n=52

eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio. *On-treatment eGFR.

- Sensitivity analyses confirm long-term kidney function preservation with sparsentan vs irbesartan (**Figure 7**)
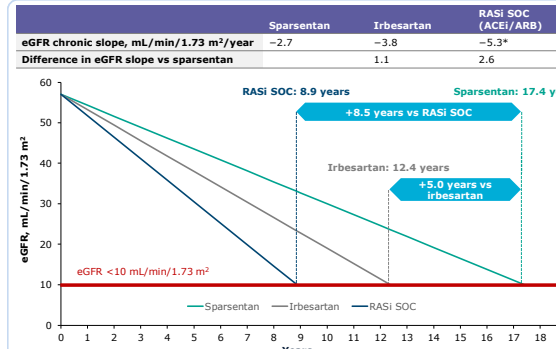
Figure 7. Total eGFR Slope Sensitivity Analyses

Annualized change in eGFR (total slope model) Difference for sparsentan vs irbesartan (95% CI), mL/min/1.73 m²/year

	Difference	
Total population N=404	1.0	P=.058
ITT analysis n=404	1.2	P=.016*
Rescue analysis† n=404	1.0	P=.044*
Cystatin C n=404	1.4	P=.010*
Day 1 as response variable n=404	1.0	P=.039*

Favors IRB / Favors SPAR

eGFR, estimated glomerular filtration rate; IRB, irbesartan; ITT, intent-to-treat; SPAR, sparsentan. *Nominal P values. †Rescue analysis excludes eGFR measurements after initiation of rescue immunosuppression for renal disease.

- Fewer sparsentan-treated patients progressed to composite kidney failure endpoints of confirmed 40% or 50% eGFR reduction, end-stage kidney disease, or death vs irbesartan
- Patients initiated immunosuppressive therapy sooner and more frequently with irbesartan vs sparsentan
- Improved eGFR slope suggests that sparsentan could delay the need for dialysis or kidney transplant (**Figure 8**)

Figure 8. Potential Long-Term Impact of Improved eGFR Slope

	Sparsentan	Irbesartan	RASi SOC (ACEi/ARB)
eGFR chronic slope, mL/min/1.73 m²/year	−2.7	−3.8	−5.3*
Difference in eGFR slope vs sparsentan		1.1	2.6

RASi SOC: 8.9 years; Sparsentan: 17.4 years; +8.5 years vs RASi SOC
Irbesartan: 12.4 years; +5.0 years vs irbesartan
eGFR <10 mL/min/1.73 m²

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; RASi, renin-angiotensin system inhibitor; SOC, standard of care. Baseline (0 years) eGFR = 57 mL/min/1.73 m² based on the mean eGFR of all patients (N=404) reported in this study. *Mean of observed slopes for maximized ACEi/ARB as reported in 5 clinical trials.[5-9]

Safety

- Sparsentan was well tolerated, with a consistent safety profile comparable to irbesartan (**Table 2**)
- Peripheral edema was similar in both groups, with no increases in body weight
- Low incidence of alanine aminotransferase/aspartate aminotransferase of >3x upper limit of normal that was comparable with irbesartan; no cases of drug-induced liver injury with sparsentan

Table 2. Treatment-Emergent Adverse Events

Patients with TEAEs, n (%)	Sparsentan (n=202)	Irbesartan (n=202)
Any TEAEs	187 (93)	177 (88)
Most common TEAEs (≥10% of patients in either group)		
COVID-19	53 (26)	46 (23)
Hyperkalemia	32 (16)	26 (13)
Peripheral edema	31 (15)	24 (12)
Dizziness	30 (15)	13 (6)
Headache	27 (13)	26 (13)
Hypotension	26 (13)	8 (4)
Hypertension	22 (11)	28 (14)
Transaminase elevations	5 (2)	7 (3)
Serious TEAEs	75 (37)	71 (35)
Serious TEAEs in ≥5 patients in either group		
COVID-19	42 (21)	38 (19)
Chronic kidney disease	6 (3)	6 (3)
TEAEs leading to treatment discontinuation	21 (10)	18 (9)
TEAEs leading to death	0	1 (<1)

TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Sparsentan treatment causes a sustained reduction in proteinuria and a clear benefit in eGFR over 110 weeks
- eGFR decline in proteinuria subgroups all favor sparsentan
- Patients with IgAN treated with sparsentan over 2 years had one of the slowest annual rates of kidney function decline seen in phase 3 IgAN clinical trials
- Sparsentan is well tolerated, with a consistent safety profile comparable to irbesartan

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INTRODUCTION

- Sparsentan is an orally active dual endothelin angiotensin receptor antagonist (DEARA) that reduces proteinuria and preserves estimated glomerular filtration rate (eGFR) in patients with IgAN[1,2]
- Sparsentan molecules bind individually to either endothelin type A (ET$_A$R) or angiotensin type 1 (AT$_1$R) receptors and inhibit intracellular signaling[3]
- In IgAN, the endothelin system is activated along with the renin-angiotensin-aldosterone system
- Both systems mediate kidney injury through multiple mechanisms, including inflammation and fibrosis
- Sparsentan has received accelerated approval in the US for treatment of patients with IgAN who are at risk of rapid disease progression[4]
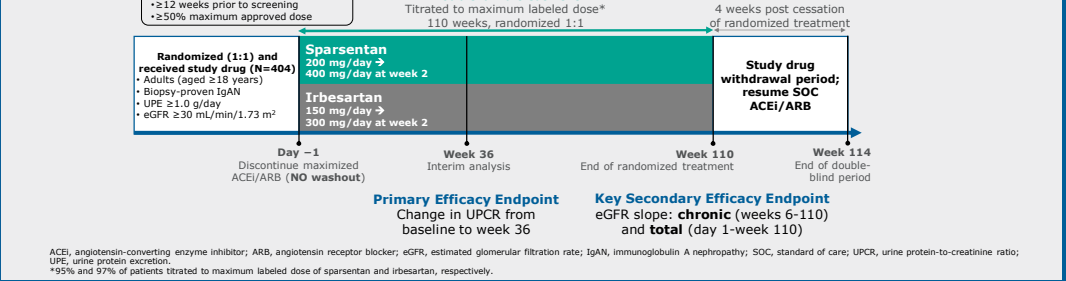
Objective

- Test the efficacy and safety of sparsentan vs active control (irbesartan) in patients with IgAN, including across different levels of baseline proteinuria

METHODS

- PROTECT is a randomized, double-blind, parallel-group, 110-week trial of sparsentan (n=202) vs irbesartan (n=202) in adults with IgAN with urine protein excretion of ≥1.0 g/day and eGFR of ≥30 mL/min/1.73 m² (**Figure 1**)

Figure 1. PROTECT Trial Design (NCT03762850)

Maximized ACEi/ARB
- ≥12 weeks prior to screening
- ≥50% maximum approved dose

Double-blind treatment
Titrated to maximum labeled dose* 110 weeks, randomized 1:1

4 weeks post cessation of randomized treatment

Randomized (1:1) and received study drug (N=404)
- Adults (aged ≥18 years)
- Biopsy-proven IgAN
- UPE ≥1.0 g/day
- eGFR ≥30 mL/min/1.73 m²

Sparsentan 200 mg/day → 400 mg/day at week 2
Irbesartan 150 mg/day → 300 mg/day at week 2

Study drug withdrawal period; resume SOC ACEi/ARB

Day −1: Discontinue maximized ACEi/ARB (NO washout)
Week 36: Interim analysis
Week 110: End of randomized treatment
Week 114: End of double-blind period

Primary Efficacy Endpoint Change in UPCR from baseline to week 36
Key Secondary Efficacy Endpoint eGFR slope: chronic (weeks 6-110) and total (day 1-week 110)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; SOC, standard of care; UPCR, urine protein-to-creatinine ratio; UPE, urine protein excretion. *95% and 97% of patients titrated to maximum labeled dose of sparsentan and irbesartan, respectively.

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