Sparsentan Shows Clinically Meaningful Treatment Effects vs Irbesartan in Patients With IgA Nephropathy (IgAN) in the Phase 3 PROTECT Trial

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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

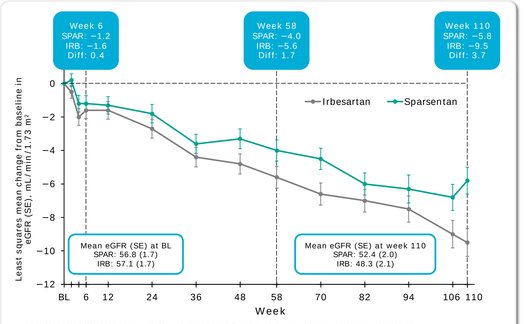
	Sparsentan (n=202)	Irbesartan (n=202)
Age at IgAN diagnosis, mean (SD), years	40.2 (13.4)	39.0 (12.4)
Time from initial kidney biopsy to informed consent, median (IQR), years	4.0 (1.0-10.0)	4.0 (1.0-10.0)
Male sex, n (%)	139 (69)	143 (71)
Blood pressure, mean (SD), mm Hg		
Systolic	128.0 (14.4)	129.9 (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 m^2	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



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 m^2 for sparsentan vs −9.5 mL/min/1.73 m^2 for irbesartan (difference, 3.7 mL/min/1.73 m^2) (Figure 4)

Figure 3. Patients Achieving Complete Proteinuria Remission

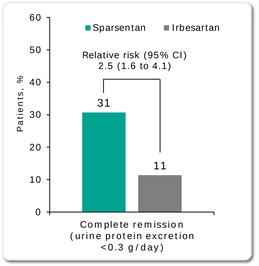
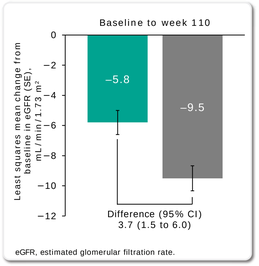


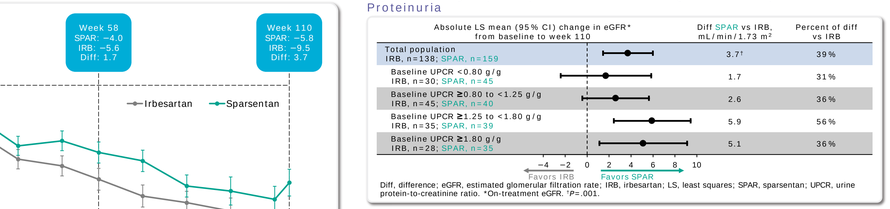
Figure 4. Absolute Change in eGFR From Baseline to Week 110



eGFR, estimated glomerular filtration rate.

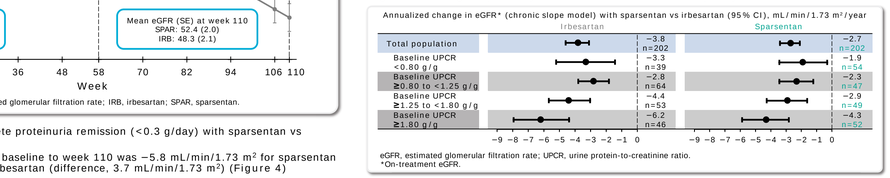
- Subgroup analyses demonstrate a consistent treatment benefit across baseline urine protein-to-creatinine ratio subgroups in absolute eGFR change (Figure 5) and chronic eGFR slope (Figure 6)

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



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



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)

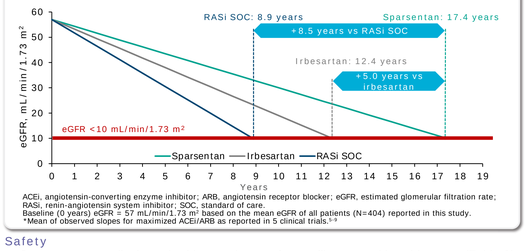
Figure 7. Total eGFR Slope Sensitivity Analyses

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 m^2/year	−2.7	−3.8	−5.3*
Difference in eGFR slope vs sparsentan, mL/min/1.73 m^2/year		1.1	2.6



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 m^2 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 >3× 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

DISCLOSURES

BR reports consulting fees from Alexion Pharmaceuticals, Alpine Pharma, BioCryst Pharmaceuticals, Calliditas Therapeutics, Novartis, Q32 Bio, Omeros, Otsuka Pharmaceuticals, Travere Therapeutics, Inc., and Vera Therapeutics and has a leadership role at NephroNet, Lupus ABC/LRA, and Lupus Foundation of America. JB reports a research grant and consulting fees from Travere Therapeutics, Inc. EM, RG, RK, and DRF are employees and stockholders of Travere Therapeutics, Inc. VP is an employee of UNSW Sydney and serves as a board director for St. Vincent's Health Australia and several medical research institutes; has led or served on the steering committees of trials funded by AbbVie, Bayer, Boehringer Ingelheim, Chinook Therapeutics, Gilead Sciences, GSK, Janssen, Lilly, Novartis, Novo Nordisk, Otsuka Pharmaceuticals, Pfizer, Travere Therapeutics, Inc., and Tricida; and reports honoraria for steering committee roles, scientific presentations, and/or advisory board attendance from AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook Therapeutics, Gilead Sciences, GSK, Janssen, Lilly, Merck, Mitsubishi Tanabe Pharma, Mundipharma, Novartis, Novo Nordisk, Otsuka Pharmaceuticals, Pfizer, Travere Therapeutics, Inc., and Tricida.

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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_AR) or angiotensin type 1 (AT_1R) 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]

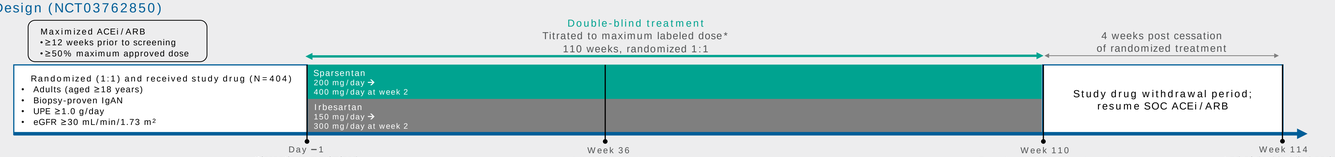
Objective

- 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 m^2 (Figure 1)

Figure 1. PROTECT Trial Design (NCT03762850)



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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