PROTECT: Two-Year Efficacy and Safety Findings of Sparsentan

In September 2024, sparsentan was approved by the US FDA to slow kidney function decline in adults with primary IgA nephropathy who are at risk for disease progression.

- IgA nephropathy is a rare kidney disease that can lead to progressive kidney function decline and kidney failure within 10 to 20 years of diagnosis[1,2]
- Sparsentan was approved by the US FDA to slow kidney function decline in adults with primary IgA nephropathy who are at risk for disease progression[3]
- Sparsentan is a non-immunosuppressive, single-molecule, Dual Endothelin Angiotensin Receptor Antagonist (DEARA)[4]
- In the PROTECT study, sparsentan compared to irbesartan demonstrated[3,4]:
  - Superior reductions in proteinuria
  - Better preservation of kidney function that accrued over time
  - A comparable safety profile

Aim

The PROTECT study evaluates long-term efficacy and safety of sparsentan vs. irbesartan in IgA nephropathy[4]

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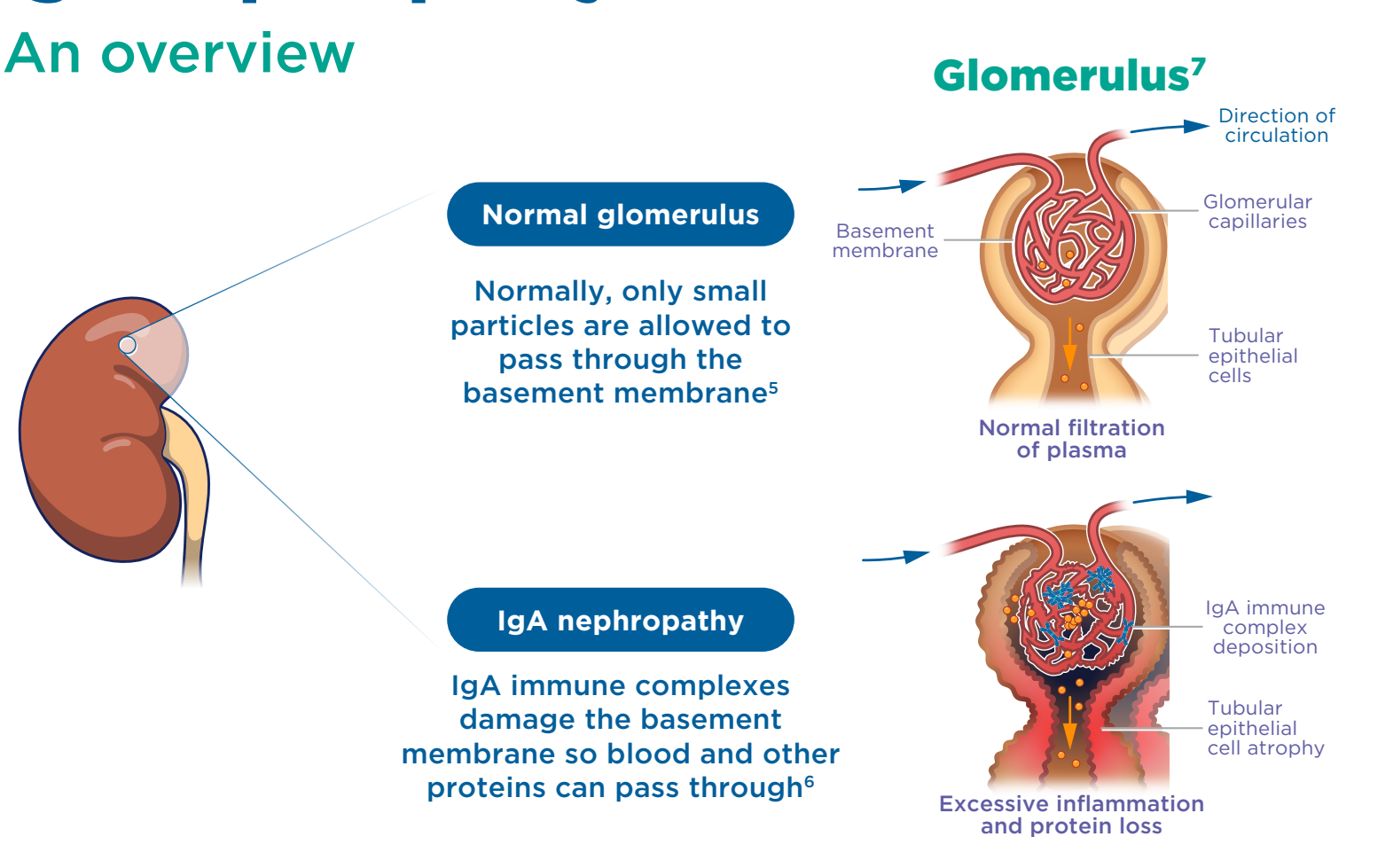
IgA nephropathy:
An overview

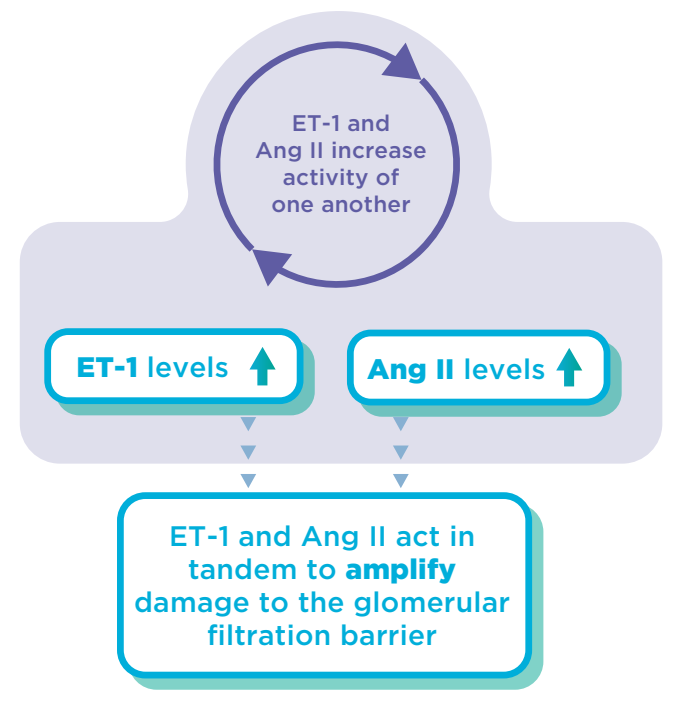


Glomerulus[7]
Normal glomerulus
Normally, only small particles are allowed to pass through the basement membrane[5]
IgA nephropathy
IgA immune complexes damage the basement membrane so blood and other proteins can pass through[6]
Direction of circulation
Basement membrane
Glomerular capillaries
Tubular epithelial cells
Normal filtration of plasma
IgA immune complex deposition
Tubular epithelial cell atrophy
Excessive inflammation and protein loss

IgA nephropathy, a rare kidney disease, is an **immune complex-mediated glomerulonephritis**[1,8,9]

It is characterized by the **deposition of IgA-containing immune complexes** in the glomerular mesangium of the kidney, resulting in activated mesangial cells and kidney injury[8,9]

Endothelin-1 (ET-1) and angiotensin II (Ang II) are two critical peptides that work in tandem to exacerbate mesangial cell proliferation, inflammation, vascular dysfunction, and tubulointerstitial injury[10,11]



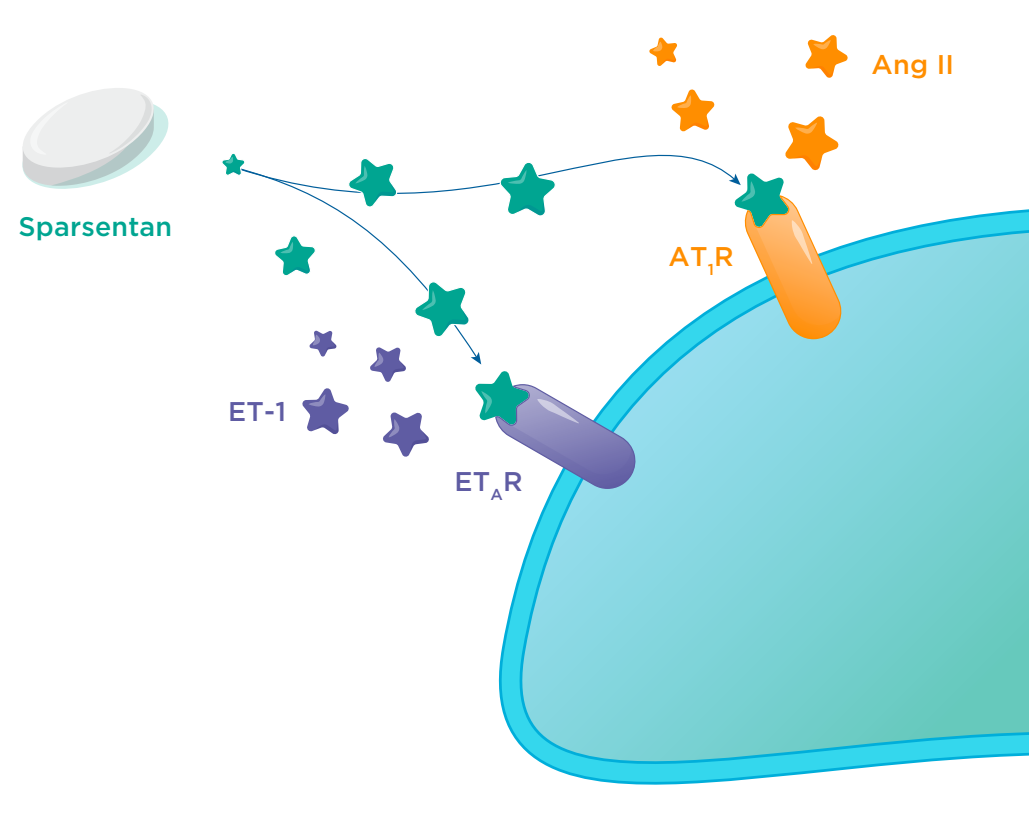
They underlie the progression of IgA nephropathy, which often leads to progressive kidney function decline and kidney failure within 10 to 20 years of diagnosis[1,2,10,11]

Current clinical outcomes reflect the need for new targeted treatments to slow the rate of disease progression and prevent kidney failure[4]

Sparsentan:
A treatment for IgA nephropathy

Sparsentan is a non-immunosuppressive, single-molecule, Dual Endothelin Angiotensin Receptor Antagonist (DEARA)[4]

Sparsentan was approved by the US FDA to slow kidney function decline in adults with primary IgA nephropathy who are at risk for disease progression[3]

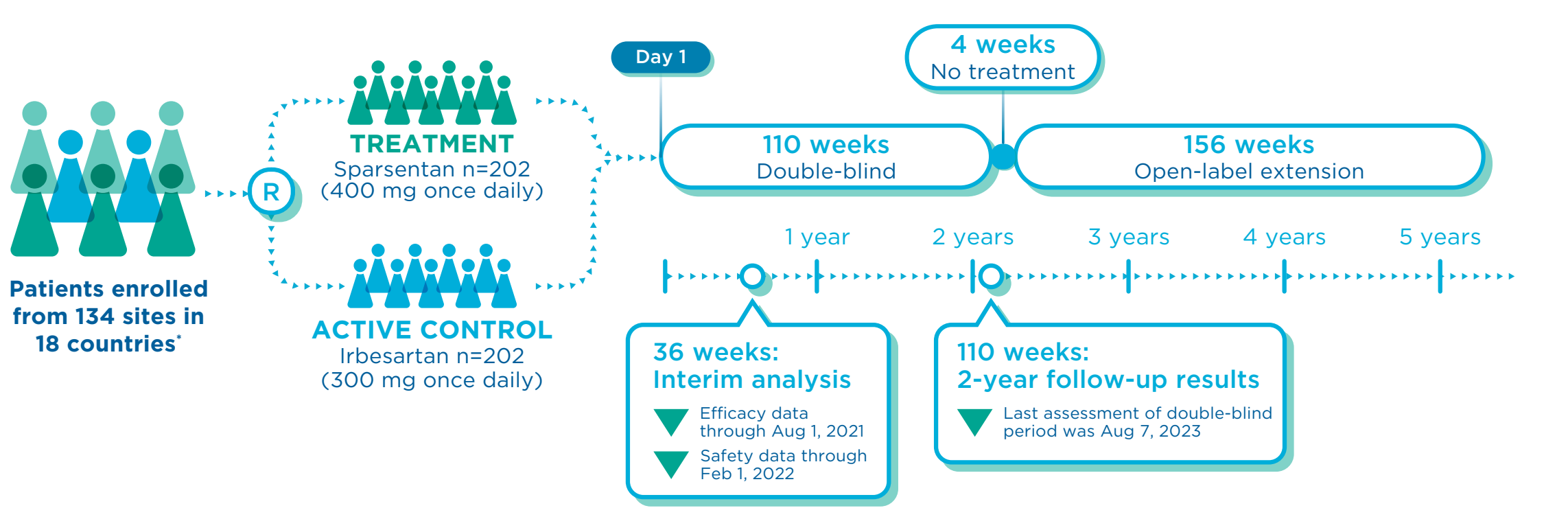


PROTECT:
Study design

PROTECT is a large, international, randomized, double-blind, active-controlled Phase 3 trial to assess the efficacy and safety of sparsentan vs. irbesartan[4,12]

Key eligibility criteria[4]:

- Biopsy-proven primary IgA nephropathy
- Proteinuria ≥1 g/day
- eGFR ≥30 mL/min/1.73 m²
- SBP ≤150 mmHg
- DBP ≤100 mmHg
- Maximum tolerated (stable) dose of ACEi and/or ARB therapy for ≥12 weeks



Patients enrolled from 134 sites in 18 countries*
R
TREATMENT
Sparsentan n=202
(400 mg once daily)
ACTIVE CONTROL
Irbesartan n=202
(300 mg once daily)
Day 1
4 weeks
No treatment
110 weeks
Double-blind
156 weeks
Open-label extension
1 year
2 years
3 years
4 years
5 years
36 weeks:
Interim analysis
Efficacy data through Aug 1, 2021
Safety data through Feb 1, 2022
110 weeks:
2-year follow-up results
Last assessment of double-blind period was Aug 7, 2023

Primary endpoint[4]:
- Change in proteinuria

Secondary and exploratory endpoints[4]:
- Absolute change in eGFR
- Chronic and total eGFR slope, UPCR, UACR, urine protein and albumin excretion
- Proportion of patients that achieved the composite kidney endpoint,† reached complete and partial proteinuria, and used IST

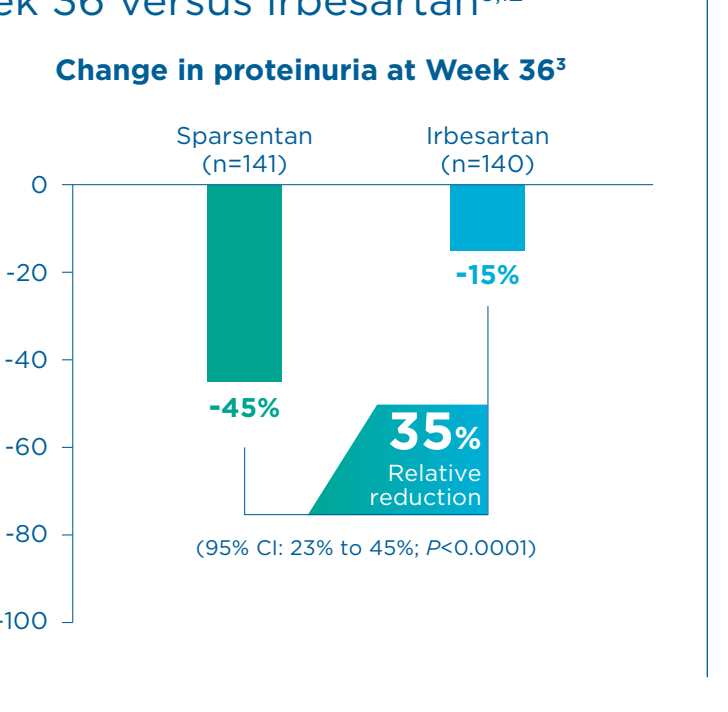
Safety outcomes[4]:
- Treatment-emergent adverse events (TEAEs)
- Serious TEAEs
- TEAEs that led to treatment discontinuation

Primary endpoint:
Proteinuria

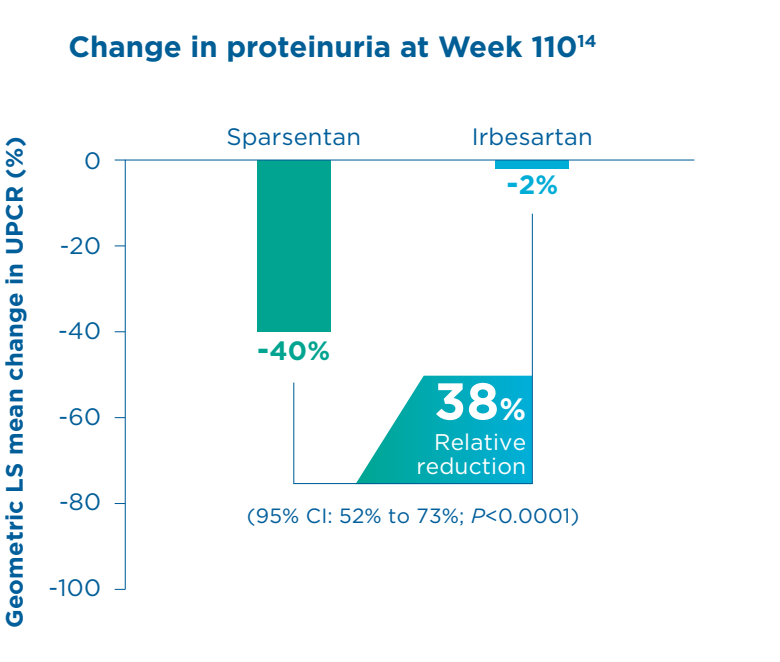
Sparsentan met its primary endpoint showing **superior reduction in proteinuria** from baseline to Week 36 versus irbesartan[3,12]

The beneficial treatment effect was consistent across predefined patient subgroups by demographics and baseline characteristics (age, gender, race, region, BMI), including proteinuria and eGFR[12,13]

Significant reductions were observed at the first follow-up visit (Week 4)[12,14]



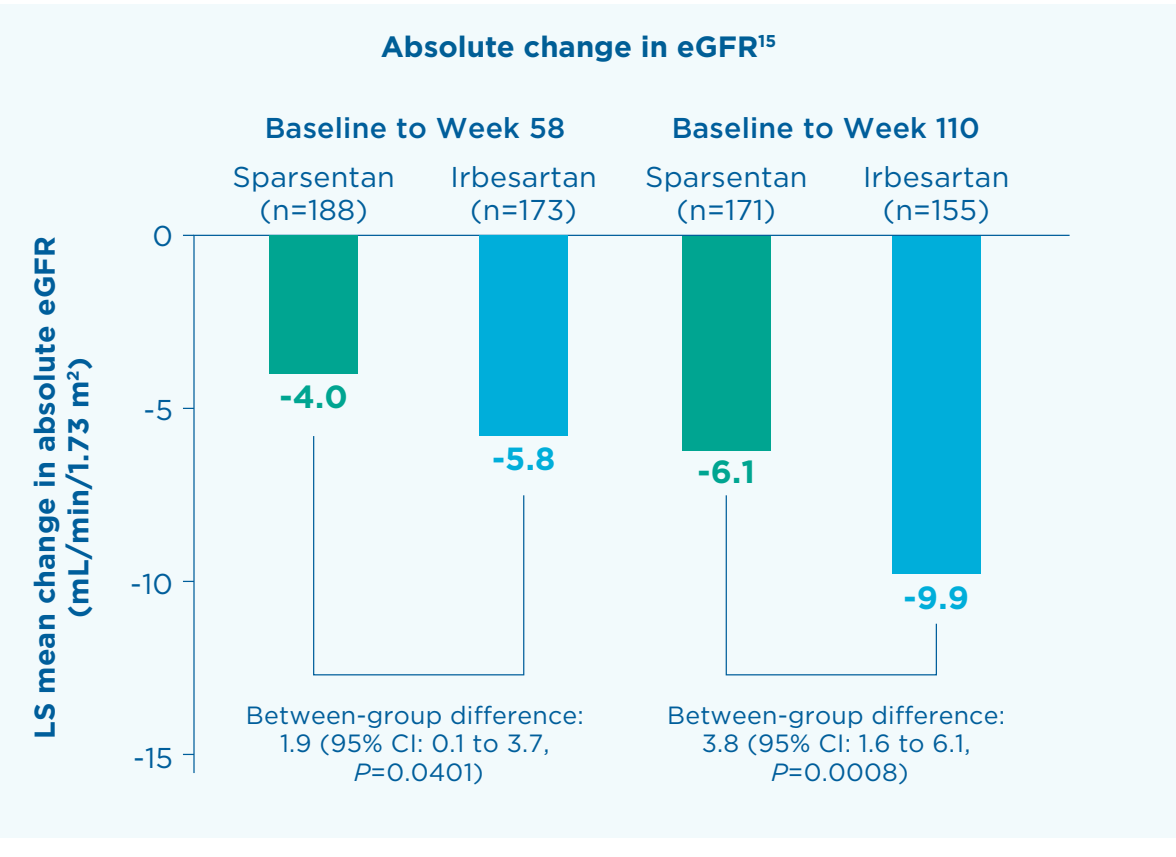
Reduction in proteinuria was sustained over 2 years[3,4,14]



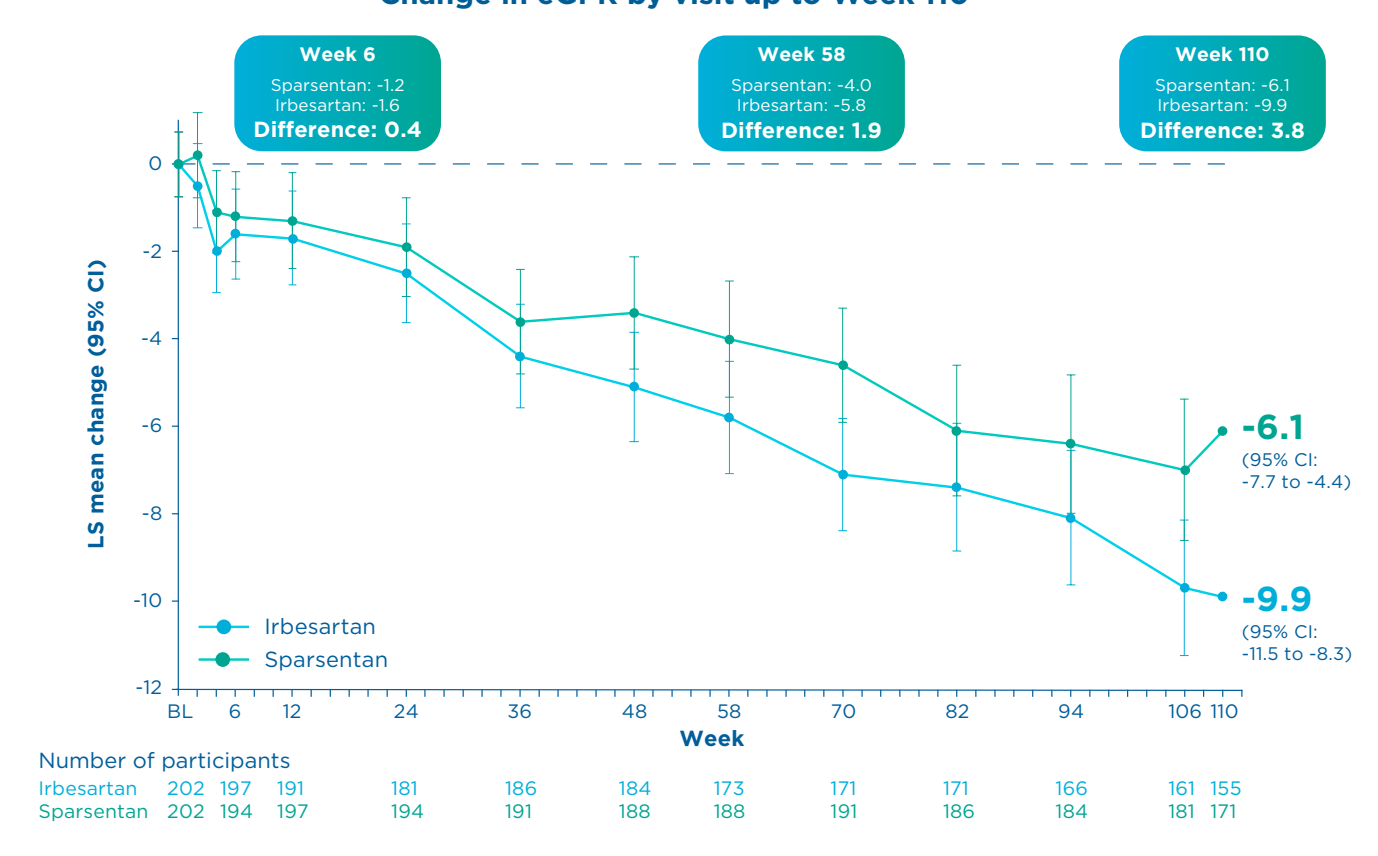
Select secondary and exploratory endpoints:
Kidney function

Absolute eGFR

- The absolute LS mean change in eGFR from baseline to Week 110 was smaller with sparsentan versus irbesartan, demonstrating a greater preservation of kidney function with sparsentan[4,15]
- The absolute change from baseline in eGFR showed a difference between sparsentan and irbesartan that was larger at year 2 compared to year 1, suggesting that the benefits of sparsentan accrue year on year[15,16]



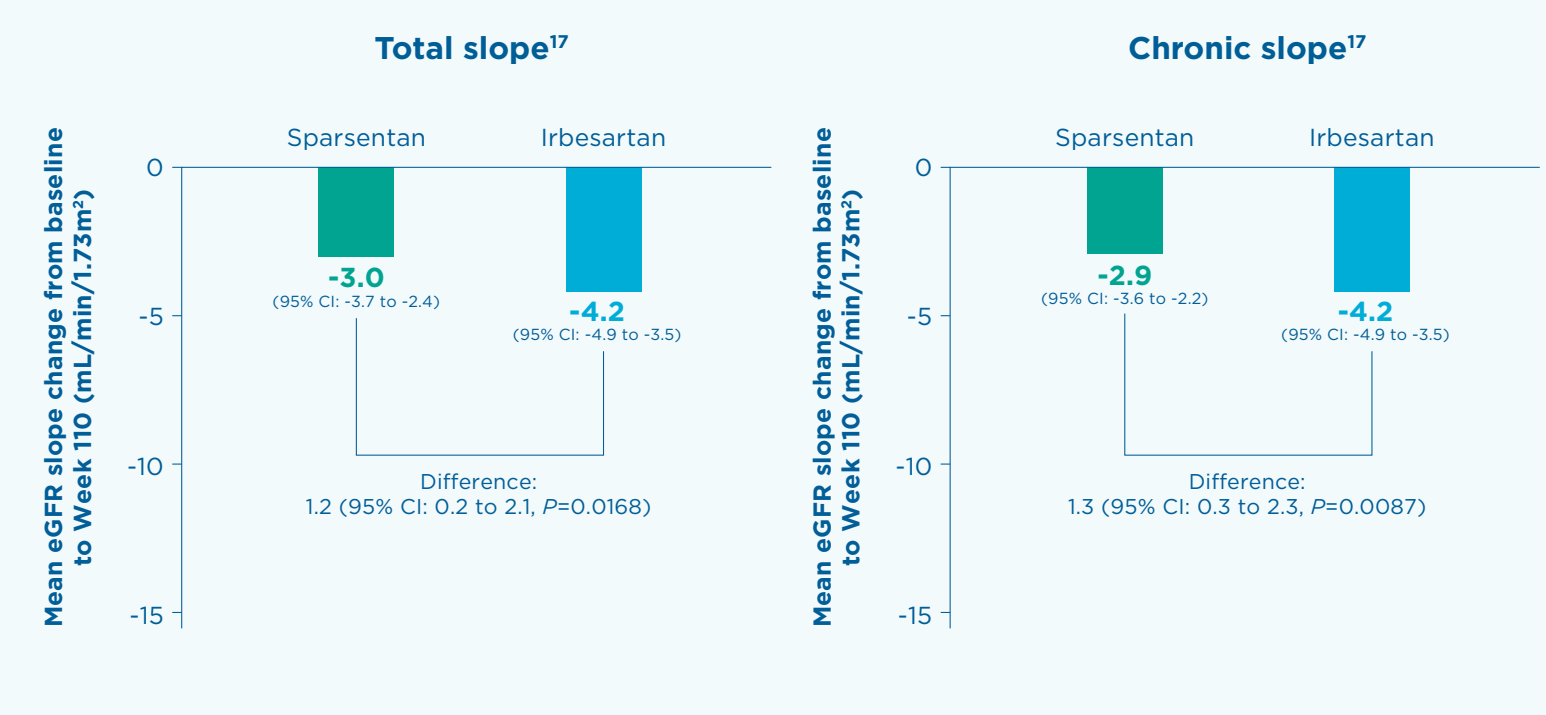
Absolute change in eGFR[15]
Baseline to Week 58
Baseline to Week 110
Sparsentan (n=188)
Irbesartan (n=173)
Sparsentan (n=171)
Irbesartan (n=155)
LS mean change in absolute eGFR (mL/min/1.73 m²)
0
-5
-10
-15
-4.0
-5.8
-6.1
-9.9
Between-group difference: 1.9 (95% CI: 0.1 to 3.7, P=0.0401)
Between-group difference: 3.8 (95% CI: 1.6 to 6.1, P=0.0008)



Change in eGFR by visit up to Week 110[3,15]
Week 6
Sparsentan: -1.2
Irbesartan: -1.6
Difference: 0.4
Week 58
Sparsentan: -4.0
Irbesartan: -5.8
Difference: 1.9
Week 110
Sparsentan: -6.1
Irbesartan: -9.9
Difference: 3.8
LS mean change (95% CI)
-6.1
(95% CI: -7.7 to -4.4)
-9.9
(95% CI: -11.5 to -8.3)
Irbesartan
Sparsentan
BL 6 12 24 36 48 58 70 82 94 106 110
Week
Number of participants
Irbesartan 202 197 191 181 186 184 173 171 171 166 161 155
Sparsentan 202 194 197 194 191 188 188 191 186 184 181 171

Change in eGFR slope

- Sparsentan slowed the rate of kidney function decline[3,4,15]
- The treatment effect was generally consistent across key subgroups, including key demographic and baseline disease characteristics[3]:
  - Key demographics include age, sex, race, ethnicity, and region
  - Baseline disease characteristics include baseline BMI and baseline proteinuria



Total slope[17]
Sparsentan
Irbesartan
Mean eGFR slope change from baseline to Week 110 (mL/min/1.73m²)
0
-5
-10
-15
-3.0
(95% CI: -3.7 to -2.4)
-4.2
(95% CI: -4.9 to -3.5)
Difference: 1.2 (95% CI: 0.2 to 2.1, P=0.0168)
Chronic slope[17]
Sparsentan
Irbesartan
-2.9
(95% CI: -3.6 to -2.2)
-4.2
(95% CI: -4.9 to -3.5)
Difference: 1.3 (95% CI: 0.3 to 2.3, P=0.0087)

Total and chronic slope

- Over two years, the differences in total and chronic slope were significantly lower with sparsentan versus irbesartan[3,17]
- Chronic slope is thought to most accurately reflect nephroprotective effects[4]

Key safety outcomes:
Adverse events

The most common AEs were[3]:

AE	Sparsentan	Irbesartan
Hyperkalemia	34 (17%)	27 (13%)
Hypotension	33 (16%)	13 (6%)
Peripheral edema	33 (16%)	29 (14%)
Dizziness	32 (16%)	14 (7%)
Anemia	16 (8%)	9 (4%)
Acute kidney injury	12 (6%)	5 (2%)
Transaminase elevations	7 (3.5%)	8 (4%)

The incidence of AEs was similar for sparsentan versus irbesartan, except for dizziness and hypotension[3,4]

There were **NO cases** of[4]:
- Serious hepatic TEAEs or drug-induced liver injury
- Serious TEAEs of drug-related edema or discontinuations due to edema
- Discontinuations due to heart failure

Key takeaways:

- Over two years sparsentan demonstrated superior reductions in proteinuria, better preservation of kidney function that accrued over time, and a comparable safety profile with irbesartan[3,4,16]
- Projected eGFR data of sparsentan and irbesartan suggested prolonged kidney survival with sparsentan[4]
- Overall, findings suggest that sparsentan could be used as a long-term therapy for IgA nephropathy[4]
- Sparsentan is being further evaluated in the PROTECT OLE[4]

The data presented here is from the modified intention-to-treat (mITT) analysis.

*Participants were enrolled between December 2018 and May 2021.[4]

†Composite kidney failure endpoint defined as confirmed 40% eGFR reduction, end-stage kidney disease (defined as initiation of renal replacement therapy or sustained eGFR <15 mL/min per 1.73 m²), or all-cause mortality.[4]

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; Ang II, angiotensin II; ARB, angiotensin receptor blocker; AT_1R, angiotensin II subtype 1 receptor; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; DEARA, Dual Endothelin Angiotensin Receptor Antagonist; eGFR, estimated glomerular filtration rate; ET-1, endothelin-1; ET_AR, endothelin type A receptor; FDA, Food and Drug Administration; IgA, immunoglobulin A; IST, immunosuppressive therapy; LS, least square; mITT, modified intention-to-treat; OLE, open-label extension; SBP, systolic blood pressure; TEAE, treatment-emergent adverse event; UACR, urine albumin-creatinine ratio; UPCR, urine protein-creatinine ratio.

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TRAVERE THERAPEUTICS
GLOBAL MEDICAL AFFAIRS