Matching-Adjusted Indirect Comparisons of eGFR slopes in the PROTECT study with UK RaDaR IgA Nephropathy population and the control arm of NefIgArd

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RESULTS

Sparsentan and irbesartan vs SoC in RaDaR

Patient characteristics

- Compared with patients in RaDaR, those in the PROTECT trial exhibited older age, a lower proportion of White patients, a higher proportion of Asian patients, lower systolic blood pressure (SBP), lower eGFR levels, lower urine protein–creatinine ratio (UP/C) ratios, and a longer duration since biopsy (**Table 1**)
- After weighting, all matched effect modifiers and prognostic factors were balanced between the compared cohorts, while the effective sample sizes decreased for the sparsentan cohort and the irbesartan cohort

Two-year eGFR total slope

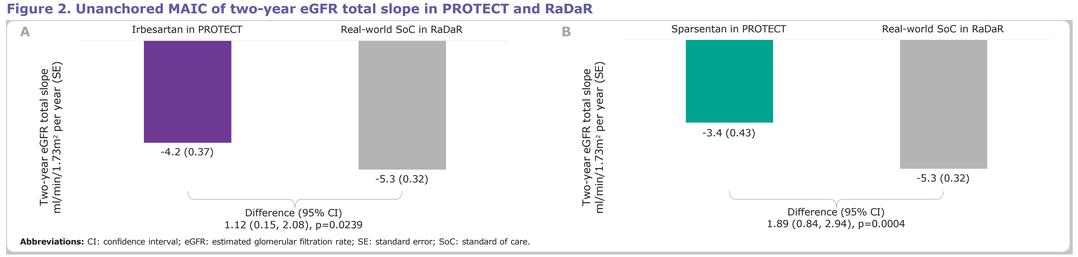
- Patients treated with maximally titrated irbesartan or sparsentan in the PROTECT trial exhibit a slower decline in kidney function compared to SoC delivered in a real-world setting (RaDaR), with a difference of 1.12 ml/min/1.73m² per year (p=0.0239) for irbesartan and 1.89 ml/min/1.73m² per year (p=0.0004) for the sparsentan, respectively (**Figure 2**)

Table 1. Baseline patient characteristics of sparsentan and irbesartan arms from the PROTECT trial vs. the SoC cohort from RaDaR

	SoC from RaDaR	Irbesartan				Sparsentan			
		Before matching		After matching		Before matching		After matching	
		Summary statistic (N=202)	Difference against SoC	Summary statistic (ESS=79.6)	Difference against SoC	Summary statistic (N=202)	Difference against SoC	Summary statistic (ESS=33.0)	Difference against SoC
Mean age (SD), years	43.00 (13.00)	45.43 (12.12)	2.43 (-0.88)	43.00 (13.03)	0.00 (0.03)	46.56 (12.76)	3.56 (-0.24)	43.00 (13.03)	0.00 (0.03)
Male, proportion	0.66	0.71	0.05	0.66	0.00	0.69	0.03	0.66	0.00
Race, proportion									
White	0.73	0.70	-0.03	0.73	0.00	0.64	-0.09	0.73	0.00
Asian	0.12	0.24	0.12	0.12	0.00	0.33	0.22	0.12	0.00
Mean BMI (SD), kg/m²	29.00 (5.80)	28.32 (5.65)	-0.68 (-0.15)	29.00 (5.81)	0.00 (0.01)	28.54 (5.21)	-0.46 (-0.59)	29.00 (5.81)	0.00 (0.01)
Mean SBP (SD), mmHg	136.00 (15.00)	129.94 (12.39)	-6.06 (-2.61)	136.00 (15.04)	0.00 (0.04)	128.00 (14.41)	-8.01 (-0.59)	136.00 (15.04)	0.00(0.04)
Mean eGFR (SD), ml/min/1.73 m²	61.00 (26.00)	57.07 (23.58)	-3.93 (-2.42)	61.00 (26.06)	0.00 (0.06)	56.78 (24.33)	-4.22 (-1.67)	61.00 (26.06)	0.00 (0.06)
UP/C >2.64 g/g, proportion	0.19	0.08	-0.10	0.19	0.00	0.09	-0.10	0.19	0.00
Median UP/C, g/g	1.49	1.23	-0.26	1.49	0.00	1.25	-0.24	1.48	-0.01
Mean time since biopsy (SD), years	4.70 (6.50)	6.37 (7.07)	1.67 (0.57)	4.70 (6.52)	0.00 (0.02)	6.41 (6.45)	1.71 (-0.05)	4.70 (6.52)	0.00 (0.02)

Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate; ESS: effective sample size; UP/C: urine protein–creatinine ratio; SBP: systolic blood pressure; SD: standard deviation; SoC: standard of care.

Figure 2. Unanchored MAIC of two-year eGFR total slope in PROTECT and RaDaR



Abbreviations: CI: confidence interval; eGFR: estimated glomerular filtration rate; SE: standard error; SoC: standard of care.

Sparsentan and irbesartan vs SoC in NefIgArd

Patient characteristics

- Compared with patients in the NefIgArd trial, those in the PROTECT trial exhibited older age, higher blood pressures, lower eGFR levels, lower urine protein levels, a higher proportion of baseline diabetes, and a longer duration since biopsy (**Table 2**)
- After weighting, all matched effect modifiers and prognostic factors were balanced between the compared cohorts, while the effective sample sizes decreased

Two-year eGFR total slope

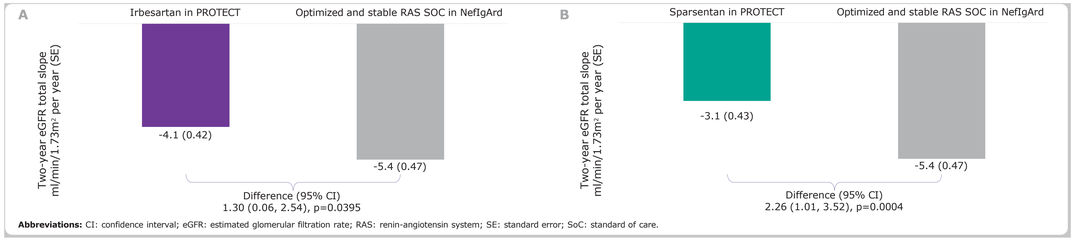
- Similar results were observed compared to SoC delivered in the clinical trial setting (NefIgArd), with a difference of 1.30 ml/min/1.73m² per year (p=0.0395) for irbesartan and 2.26 ml/min/1.73m² per year (p=0.0004) for the sparsentan, respectively (**Figure 3**)

Table 2. Baseline patient characteristics of sparsentan and irbesartan arms from the PROTECT trial vs. the SoC arm from the NefIgArd Trial

	SoC from NefIgArd	Irbesartan				Sparsentan			
		Before matching		After matching		Before matching		After matching	
		Summary statistic (N=202)	Difference against SoC	Summary statistic (ESS=50.6)	Difference against SoC	Summary statistic (N=202)	Difference against SoC	Summary statistic (ESS=59.4)	Difference against SoC
Median age, years	42.00	46.00	4.00	42.00	0.00	47.00	5.00	41.00	-1.00
Male, proportion	0.68	0.71	0.03	0.68	0.00	0.69	0.01	0.68	0.00
Race, proportion									
White	0.75	0.70	-0.05	0.75	0.00	0.64	-0.11	0.75	0.00
Asian	0.22	0.24	0.02	0.22	0.00	0.33	0.11	0.22	0.00
Median SBP, mmHg	124.00	128.00	4.00	124.00	0.00	128.00	4.00	124.00	0.00
Median DBP, mmHg	79.00	83.00	4.00	79.00	0.00	81.00	2.00	79.00	0.00
eGFR <60 ml/min/1.73 m², proportion	0.60	0.64	0.04	0.60	0.00	0.63	0.03	0.60	0.00
Median eGFR, ml/min/1.73 m²	55.11	50.00	-5.11	55.00	-0.11	50.00	-5.11	55.00	-0.11
Mean UP/C (SD), g/g	1.48 (1.15)	1.44 (0.89)	-0.04 (-0.26)	1.48 (1.15)	0.00 (0.00)	1.43 (0.90)	-0.05 (-0.25)	1.48 (1.15)	0.00 (0.00)
Urine protein <2 g/day, proportion	0.43	0.57	0.14	0.43	0.00	0.55	0.12	0.43	0.00
Median urine protein, g/day	2.17	1.82	-0.35	2.18	0.01	1.76	-0.41	2.16	-0.01
Diabetes, proportion	0.04	0.07	0.03	0.04	0.00	0.09	0.05	0.04	0.00
Median time since biopsy, years	2.60	3.51	0.91	2.58	-0.02	4.13	1.53	2.7	0.10

Abbreviations: DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; ESS: effective sample size; UP/C: urine protein–creatinine ratio; SBP: systolic blood pressure; SD: standard deviation; SoC: standard of care.

Figure 3. Unanchored MAIC of two-year eGFR total slope in PROTECT and NefIgArd control arm

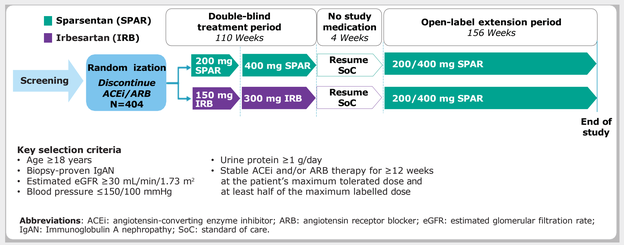


Abbreviations: CI: confidence interval; eGFR: estimated glomerular filtration rate; RAS: renin-angiotensin system; SE: standard error; SoC: standard of care.

BACKGROUND

- Immunoglobulin A nephropathy (IgAN) is an immune complex-mediated glomerulonephritis caused by the deposition of IgA in the glomerular mesangium, leading to an increased risk of kidney failure[1]
- The PROTECT (NCT03762850) trial examined the long-term nephroprotective potential of sparsentan versus (vs) the active control angiotensin receptor blocker (ARB), irbesartan, in patients with IgAN (**Figure 1**)[2]
  - The majority (97%) of patients in the irbesartan arm were titrated to the maximum labelled dose after randomization[2]
- To better quantify the clinical value of sparsentan, it is important to understand how sparsentan and its active control arm, irbesartan, performed relative to contemporaneous standard of care (SoC) treatment for IgAN
- In the absence of head-to-head randomized trials, matching-adjusted indirect comparisons (MAIC) can be used to compare sparsentan and irbesartan against SoC

Figure 1. The PROTECT trial



Key selection criteria

- Age ≥18 years
- Biopsy-proven IgAN
- Estimated eGFR ≥30 mL/min/1.73 m²
- Blood pressure ≤150/100 mmHg
- Urine protein ≥1 g/day
- Stable ACEi and/or ARB therapy for ≥12 weeks at the patient's maximum tolerated dose and at least half of the maximum labelled dose

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; IgAN: Immunoglobulin A nephropathy; SoC: standard of care.

OBJECTIVE

- To evaluate the impact of treatment with sparsentan and irbesartan vs SoC on annualized estimated glomerular filtration rate (eGFR) total slope at two years using unanchored matching-adjusted indirect comparisons (MAICs)

METHODS

Data Source

- The following data were utilized in this study:
  - Individual patient-level data from the sparsentan (N=202) and irbesartan (N=202) arms of the phase III, randomized, double-blind PROTECT trial (NCT03762850) in patients with IgAN[2]
  - The published aggregate data of a subset of patients with IgAN in the UK National Registry of Rare Kidney Diseases (RaDaR) who received SoC and met a similar set of inclusion/exclusion criteria as the PROTECT trial (N=535)[3]
  - The published aggregated data from the control arm (i.e., placebo + optimized and stable renin-angiotensin system [RAS] inhibitor therapy [RAS SoC], N=182) of the phase III, randomized, double-blind NefIgArd trial (NCT03643965) in patients with IgAN[4]

Outcome

- Annualized two-year eGFR total slope: the annualized rate of decline in eGFR over the two-year period following randomization in the PROTECT and NefIgArd trials or following the beginning of follow-up in RaDaR

Statistical Analysis

- Patients in the sparsentan or irbesartan arms of the PROTECT trial were weighted to match key baseline characteristics of patients from RaDaR or patients from the control arm of the NefIgArd trial, respectively
  - Matching weights were estimated using the method of moments
- Annualized two-year eGFR total slopes estimated from the weighted sparsentan or irbesartan cohorts were compared against the published two-year eGFR slopes in RaDaR or the control arm of the NefIgArd trial, respectively
- Matching-adjusted eGFR slopes and their corresponding standard errors were estimated using a weighted random intercept and random slope model[6]
- P-values were estimated using the two-tailed z-test with pooled standard error

CONCLUSIONS

- In the absence of head-to-head trials comparing sparsentan vs SoC, MAIC is an appropriate approach that can be utilized to generate relevant comparative evidence using sufficiently aligned data sources
- Results from this study provide important context for the performance of treatments evaluated in the PROTECT trial
- Both maximally tolerated irbesartan and sparsentan were associated with significantly slower decline in kidney function compared to real-world SoC treatment in RaDaR and physician defined, optimized SoC in NefIgArd
- These results highlight the importance of considering the 2-year eGFR total slope difference between arms of the PROTECT trial in the context of what is achieved in current clinical practice

LIMITATIONS

- Like any indirect treatment comparisons, MAICs assume exchangeability of patients between studies, the validity of which is always challenging to be conclusively addressed
- Only known baseline factors consistentlyy reported across data sources were able to be matched on; it was not feasible to adjust for unreported or unmeasured variables
- This analysis was based on source populations, so the results may not be generalizable beyond the study samples

DISCLOSURES

WG and **BH**: Employees with equity or other financial interest in Travere Therapeutics, Inc. **UD**: Former employee with equity or other financial interest in Travere Therapeutics, Inc. **MB** and **AM**: Received consultancy fees from Travere Therapeutics, Inc. **XC, SG** and **ZZ**: Employees of Analysis Group, which received consultancy fees from Travere Therapeutics, Inc. **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.

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