61ST ERA CONGRESS
STOCKHOLM & VIRTUAL
MAY 23-26, 2024

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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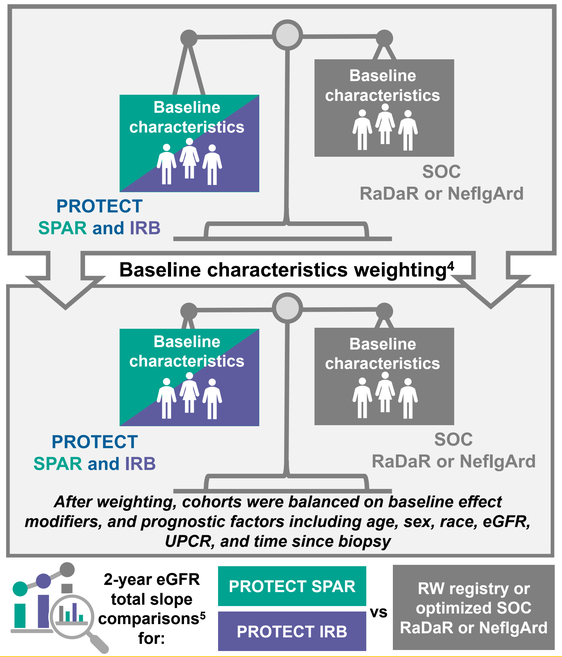
INTRODUCTION

PROTECT is a phase 3 RCT comparing sparsentan (SPAR) with irbesartan (IRB) titrated to the maximum labeled dose[1]; this active control design warrants an understanding of PROTECT results relative to delivery of SOC treatment for IgAN in other clinical settings

AIM

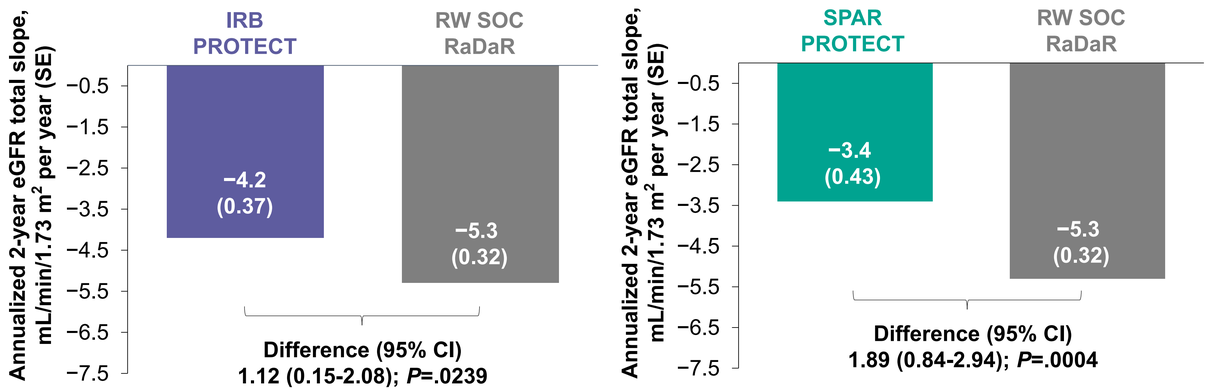
To compare 2-year eGFR total slope outcomes between the 2 arms of PROTECT[1] and delivery of SOC in 2 populations,[2,3] applying similar eligibility criteria using matching-adjusted indirect comparisons (MAICs)

METHODS

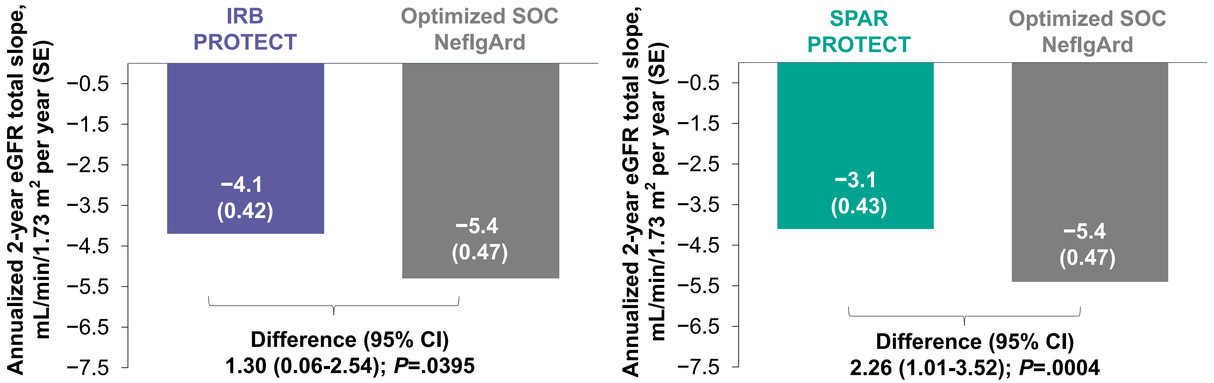


RESULTS

Comparisons of 2-Year Annualized eGFR Total Slopes in PROTECT and SOC in RaDaR



Comparisons of 2-Year Annualized eGFR Total Slopes in PROTECT and SOC in NefIgArd



Patients treated with SPAR or maximum labeled dose IRB in PROTECT had slower kidney function decline than those receiving SOC in a RW registry (RaDaR) or clinical (NefIgArd) setting

CONCLUSIONS

- In PROTECT, maximally tolerated IRB was associated with a slower rate of kidney function decline than RW SOC treatment in RaDaR and physician-defined, optimized SOC in NefIgArd
- In PROTECT, SPAR was associated with a slower rate of kidney function decline than maximally tolerated IRB, despite maximally tolerated IRB outperforming RW optimized SOC in this MAIC
- The significantly slower decline in kidney function with maximum labeled dose IRB compared with SOC in both RW and optimized clinical trial settings highlights the need to improve the clinical care of patients with IgAN receiving SOC

ACKNOWLEDGEMENTS

This study was sponsored by Travere Therapeutics, Inc. Medical writing support was provided by Ari Simenauer, PhD, of Nucleus Global, an Inizio Company, London, UK. Author disclosures are available via the QR code.

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eGFR; estimated glomerular filtration rate; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IRB, irbesartan; MAIC, matching-adjusted indirect comparison; RaDaR; National Registry of Rare Kidney Diseases; RCT, randomized controlled trial; RW, real-world; SOC, standard of care; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.

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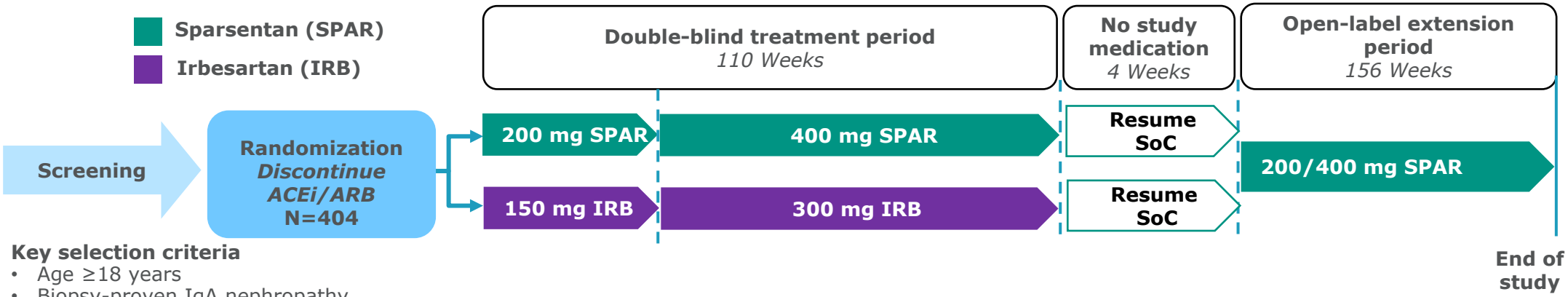
Presented at the 61st European Renal Association (ERA) Congress 2024 in Stockholm, Sweden from May 23-26

MA-SP-24-0065 05/2024

Background

- Immunoglobulin A (IgA) nephropathy is an immune complex-mediated glomerulonephritis, attributed to IgA deposition in the glomerular mesangium, leading to progressive loss of renal function and increased risk of kidney failure[1]
- PROTECT (NCT03762850) is a randomized, multicenter, double-blind, phase III trial comparing sparsentan, a dual endothelin and angiotensin receptor antagonist, against irbesartan, a renin-angiotensin system inhibitor (RASi), for the treatment of IgA nephropathy[2]
    - Consistent with the KDIGO guideline for the management of glomerular diseases,[3] the majority (97%) of patients in the irbesartan arm were titrated to the maximum labelled dose after randomization

Figure 1. The PROTECT trial



Key selection criteria

- Age ≥18 years
- Biopsy-proven IgA nephropathy
- Estimated eGFR ≥30 mL/min/1.73m^2
- 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

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

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INTRODUCTION

- The active control design of PROTECT warrants an understanding of PROTECT results relative to delivery of SOC treatment for IgAN in other clinical settings
- In the absence of head-to-head randomized trials, this study aimed to compare 2-year eGFR total slope outcomes between the 2 arms of PROTECT1 and delivery of SOC in 2 populations applying similar eligibility criteria using matching-adjusted indirect comparisons (MAICs)

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METHOD

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 PROTECT trial (NCT03762850) in patients with IgA nephropathy[2]
  - Published aggregate data of a subset of patients with IgA nephropathy in the UK National Registry of Rare Kidney Diseases (RaDaR) who received real-world SoC and met a similar set of inclusion/exclusion criteria as the PROTECT trial (N=535)[4]
  - Published aggregated data from the control arm (i.e., placebo + optimized and stable RASi standard of care [RASi SoC], N=182) of the phase III, randomized, double-blind NefIgArd trial (NCT03643965) in patients with IgA nephropathy[5]

Study outcome

- Annualized 2-year eGFR total slope: the annualized rate of decline in eGFR over the 2-year period following randomization in the PROTECT and NefIgArd trials or following the beginning of follow-up in RaDaR

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METHOD

Statistical analysis

- Patients in the sparsentan or irbesartan arms of the PROTECT trial were weighted to match key baseline effect modifiers and prognostic factors of patients from RaDaR or patients from the control arm of the NefIgArd trial, respectively
    - Matching weights were estimated using the method of moments[6]
- Annualized 2-year eGFR total slopes estimated from the weighted sparsentan or irbesartan cohorts were compared against that reported in RaDaR or in 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[7]
- P-values were calculated using the two-tailed z-test with a pooled standard error

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RESULTS

Sparsentan and irbesartan vs SoC in RaDaR

Patient characteristics

- In contrast to patients in RaDaR, participants in the PROTECT trial had older age, a lower percentage of White patients, a higher percentage of Asian patients, lower systolic blood pressure (SBP), lower eGFR, lower urine protein–creatinine ratio (UPCR), and a longer duration of time since biopsy (**Table 1**)
- After weighting, all matched baseline effect modifiers and prognostic factors were balanced between the compared cohorts, although the effective sample sizes decreased for the sparsentan cohort and the irbesartan cohort

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RESULTS

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)
UPCR >2.64 g/g, proportion	0.19	0.08	-0.10	0.19	0.00	0.09	-0.10	0.19	0.00
Median UPCR, 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)

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

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RESULTS

Sparsentan and irbesartan vs SoC in RaDaR

Two-year eGFR total slope

- After matching, patients treated with maximally titrated irbesartan in the PROTECT trial demonstrated a significantly reduced annual rate of kidney function decline (-4.2 ml/min/1.73m^2) compared to those receiving SoC in a real-world setting (RaDaR, -5.3 ml/min/1.73m^2), showing a difference of 1.12 ml/min/1.73m^2 per year (p=0.02; **Figure 2**)
- For sparsentan the difference was even greater at 1.89 ml/min/1.73m^2 per year (p<0.001)

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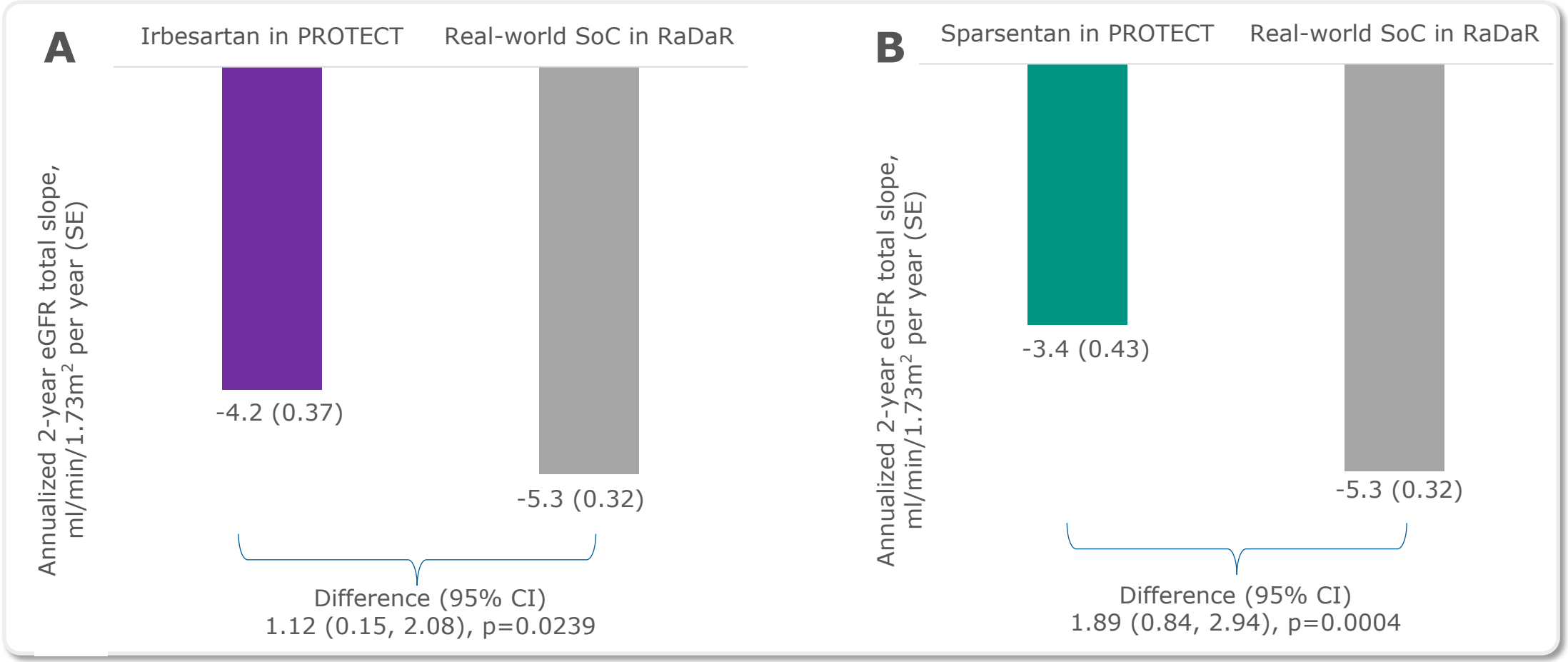
RESULTS

Figure 2. Comparisons of 2-year eGFR total slope in PROTECT and RaDaR



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

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RESULTS

Sparsentan and irbesartan vs SoC in NefIgArd

Patient characteristics

- In contrast to patients in NefIgArd, participants in the PROTECT trial had older age, higher blood pressures, lower eGFR, lower urine protein, a higher percentage of baseline diabetes, and a longer duration of time 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

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RESULTS

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 UPCR (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

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

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RESULTS

Sparsentan and irbesartan vs SoC in NefIgArd

Two-year eGFR total slope

- After matching, similar results were observed when compared to SoC delivered in the clinical trial setting (NefIgArd)
  - Patients treated with maximally titrated irbesartan in the PROTECT trial demonstrated a significantly reduced annual rate of kidney function decline (-4.1 ml/min/1.73m^2) compared to those receiving optimized and stable RASi SoC in the NefIgArd trial (-5.4 ml/min/1.73m^2), showing a difference of 1.30 ml/min/1.73m^2 per year (p=0.04; **Figure 3**)
  - For sparsentan the difference was even greater at 2.26 ml/min/1.73m^2 per year (p<0.001)

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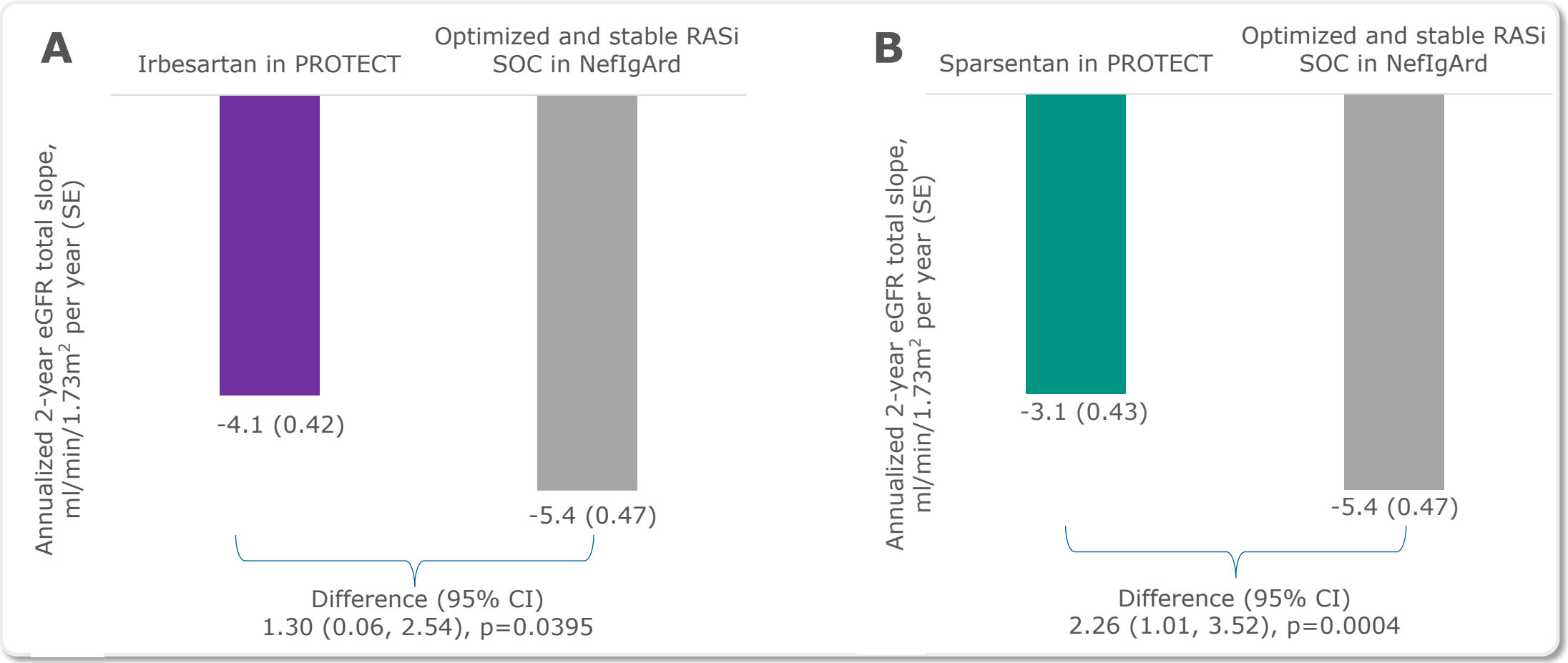
RESULTS

Figure 3. Comparisons of 2-year eGFR total slope in PROTECT and NefIgArd control arm



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

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LIMITATIONS

- Similar to other indirect treatment comparisons, MAICs operate under the exchangeability of patients assumption, a premise that is difficult to definitively verify
- Only baseline factors consistently reported across datasets could be aligned; results may be impacted by unreported or unmeasured variable
- Given that this analysis was based on specific source populations, its findings might not apply universally beyond the study sample

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CONCLUSIONS

- In PROTECT, maximally tolerated IRB was associated with a slower rate of kidney function decline than real-world SOC treatment in RaDaR and physician-defined, optimized SOC in NefIgArd
- In PROTECT, SPAR was associated with a slower rate of kidney function decline than maximally tolerated IRB, despite maximally tolerated IRB outperforming real-world optimized SOC in this MAIC
- The significantly slower decline in kidney function with maximum labeled dose IRB compared with SOC in both real-world and optimized clinical trial settings highlights the need to improve the clinical care of patients with IgAN receiving SOC

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