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

Dr Chee Kay Cheung

Consultant Nephrologist and Honorary Associate Professor John Walls Renal Unit, Leicester General Hospital

NATIONAL KIDNEY FOUNDATION
SCM24
SPRING CLINICAL MEETINGS

MA-SP-24-0061 06/2024

Disclosures

- Consulting fees from George Clinical and Vera Therapeutics; honoraria from Stada; research funding from GSK and Travere Therapeutics, Inc.; advisory boards for Calliditas, CSL Vifor, and Novartis; steering committee/DSMC for CSL Vifor, Alpine Immune Sciences, and Roche; and travel support from Otsuka and Chinook Therapeutics

Learning Objectives

At the conclusion of this CE* activity, participants should be better able to discuss PROTECT clinical trial results relative to delivery of standard of care (SoC) treatment for IgAN in other clinical settings.

*This oral presentation was not originally submitted as a CE activity, but assigned CE credit by NKF after abstract acceptance; no subsequent CE will be provided at this time (post-congress presentation).

Agenda

- Background
- Study Objective
- Methods
- Results
- Discussions & Conclusions

Background

Study Objective

Methods

Results

Discussions & Conclusions

1 2 3 4 5

Immunoglobulin A nephropathy (IgAN)

IgAN is an **immune complex-mediated glomerulonephritis** caused by the deposition of IgA in the glomerular mesangium and is often accompanied by persistent proteinuria, hypertension, and decreased kidney function[1,2]

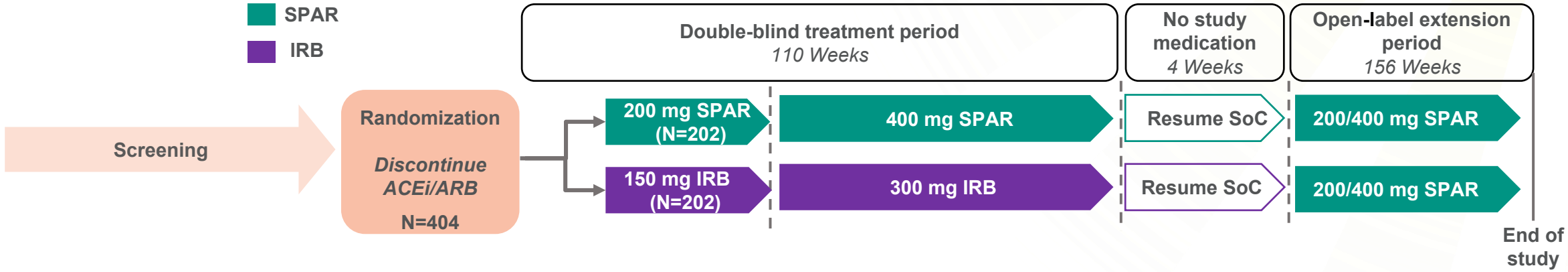
Health resource use and costs rise early as the proteinuria levels increase and kidney function worsens[3]

Kidney failure is still common in patients receiving supportive care, even with immunosuppression[4]

Kidney failure or **death** occurs in **50%** of adult and pediatric patients within 11 and 22 years, respectively[5]

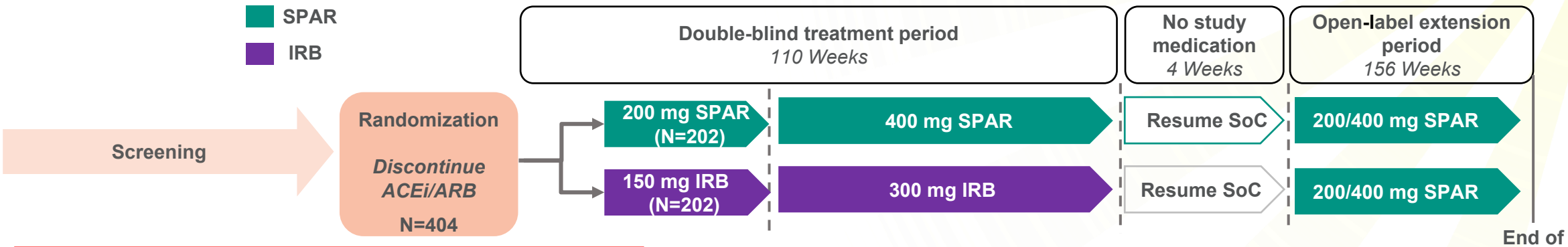
PROTECT

- PROTECT (NCT03762850) is a randomized, multicenter, double-blind, phase III trial comparing sparsentan (a dual endothelin and angiotensin receptor antagonist) against angiotensin receptor blocker (ARB), irbesartan, for the treatment of IgAN[6]



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

PROTECT



Key selection criteria

- Age ≥18 years
- Biopsy-proven IgAN
- eGFR ≥30 mL/min/1.73 m^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

- Almost two-thirds of patients in the irbesartan group (62%) were on stable ACEi and/or ARB therapy at the maximum labelled dose for at least 12 weeks before screening[6]
- The majority (97%) of patients in the irbesartan arm were titrated to the maximum labelled dose after randomization[6]
- Therefore, 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**)

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

Background

Study Objective

Methods

Results

Discussions & Conclusions

1 2 3 4 5

Study objective

- This study aimed to assess the effect of treatment with **sparsentan and irbesartan versus (vs) SoC** on the **two-year eGFR total slope**, which represents the annual rate of decline in eGFR over two years
- In the absence of head-to-head randomized trials, this assessment was conducted using **unanchored matching-adjusted indirect comparisons (MAICs)**[7]

Background

Study Objective

Methods

Results

Discussions & Conclusions

1 2 **3** 4 5

Data sources and comparisons

- Two published data sources for patients with IgAN who received SoC were utilized to compare sparsentan and irbesartan against SoC, respectively
  - The UK National Registry of Rare Kidney Diseases (RaDaR), reflecting SoC in the **real-world setting**[5]
  - The control arm from the NefIgArd trial, reflecting SoC in the **clinical trial setting**[8,9]
- The following comparisons were conducted in this study:
  - Sparsentan from PROTECT vs. RaDaR SoC
  - Irbesartan from PROTECT vs. RaDaR SoC
  - Sparsentan from PROTECT vs. NefIgArd SoC Control Arm
  - Irbesartan from PROTECT vs. NefIgArd SoC Control Arm

Published Data source (RaDaR)

- RaDaR, an initiative designed by the UK Kidney Association, amalgamates data on patients with select rare kidney diseases, including IgAN[5]
- It has enrolled patients from 106 adult and pediatric kidney units across the UK[5]
- Patients enrolled in RaDaR received SoC treatments reflective of real-world practices
- To ensure the alignment between the RaDaR cohort and the PROTECT trial population, data from a subset of the RaDaR population, chosen based on criteria mirroring those typically seen in a phase III randomized controlled trial (RCT) for IgAN, were utilized

Retrospective cohort study | **Full analysis population N=2439** | **Mean follow-up 8.0 years** | **Enrollment began in 2013**

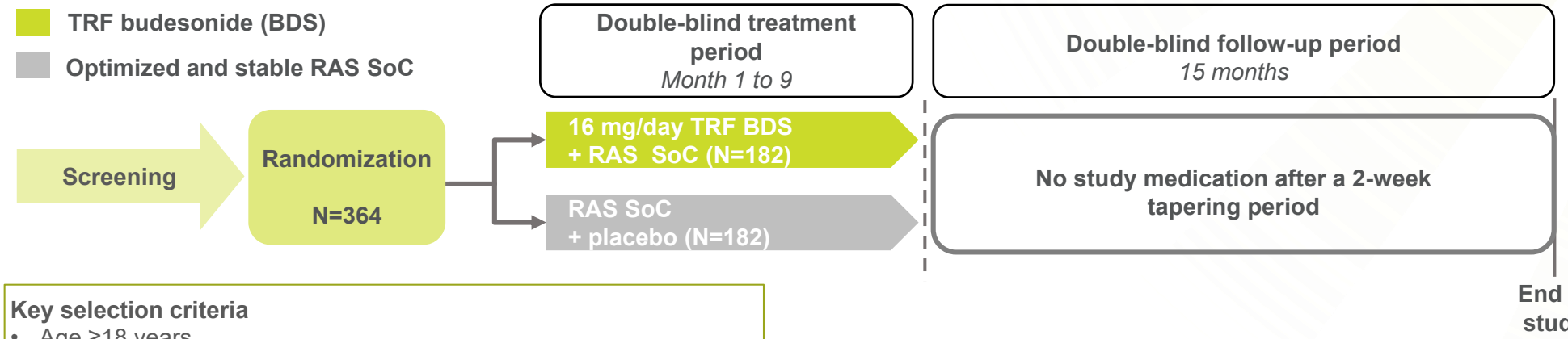
Phase III RCT-representative prevalent IgAN subpopulation (N=535)

- Age ≥18 years
- Biopsy-proven IgAN
- eGFR ≥30 mL/min/1.73 m^2
- UP/C ≥0.88 g/g at least 6 months from IgAN diagnosis to allow for RASB

Abbreviations: eGFR: estimated glomerular filtration rate; IgAN: Immunoglobulin A nephropathy; RCT: randomized controlled trial; UP/C: urine protein-creatinine ratio; RASB: Renin-angiotensin system blockade

Published Data source (NeflgArd)

- NeflgArd (NCT03643965) is a randomized, multicenter, double-blind phase III trial of targeted-release formulation (TRF) budesonide versus (vs) placebo with background optimized and stable renin-angiotensin system (RAS) inhibitor therapy (RAS SoC) for the treatment of IgAN[8,9]
- The key sample selection criteria of NeflgArd are sufficiently similar to those used in the PROTECT trial



Key selection criteria
- Age ≥18 years
- Biopsy-proven IgAN
- eGFR 35-90 mL/min/1.73 m^2
- Blood pressure <140/90 mmHg
- UP/C ≥0.8 g/g or urine protein ≥1 g/day
- Stable and optimized RAS inhibitor therapy with ACEi and/or ARB for ≥3 months

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BDS: budesonide; eGFR: estimated glomerular filtration rate; IgAN: Immunoglobulin A nephropathy; RAS SoC: standard of care with renin-angiotensin system inhibitor therapy; TRF: targeted-release formulation; UP/R: urine protein-creatinine ratio.

Review of SoC

Real-World Population (RaDaR)

- Assumed to be RASi, blood pressure control, and lifestyle management[5]

Clinical Trial Population (NeflgArd Placebo+)

- Stable and optimized RASi therapy with ACEi and/or ARB for at least 3 months before screening
  - Interim Safety Analysis Set (n=144)[8]
    - Use of RASi in 97% (n=140/144) of patients with 50% (n=70/140) achieving ≥80% of maximum allowable dose at baseline
  - Final Analysis Set (n=182)[9]
    - Use of RASi in 98% (n=179/182) of patients with 19% (n=34/179) on <50% and 81% (n=145/179) on ≥50% of the maximum allowable dose at baseline
- Maintenance of the optimized and stable RASi dosing throughout the study

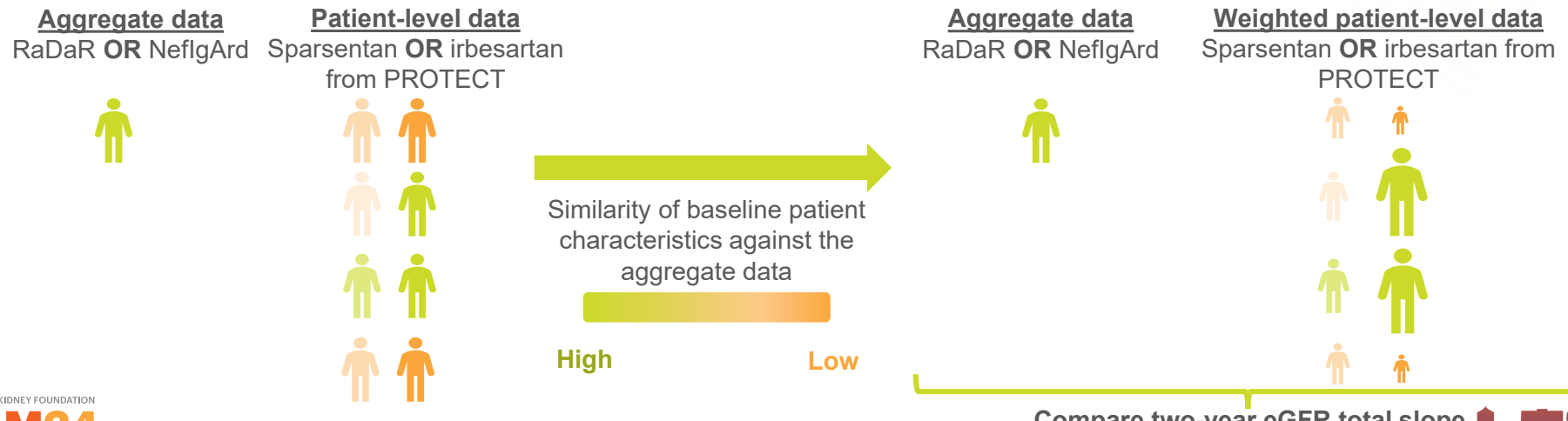
PROTECT (Irbesartan)

- Stable ACEi and/or ARB therapy at the patient's maximum tolerated dose and at least half of the maximum labelled dose for at least 12 weeks before screening[6]
  - Maximum labelled dose in 62% (n=125/202) of patients at screening;* and
- Blinded up-titration with the ARB irbesartan to maximized labelled dose after randomization[6]
  - Achieved by 97% (n=196/202)

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; RASi: renin-angiotensin system inhibition.
*Patients were required to remain on stable does of ACEi/ARB through the screening period to day-1.

Comparative method – unanchored MAIC

- MAIC is an indirect treatment comparison method to compare the effectiveness of two treatments when individual patient-level data are available for one treatment while only aggregate data are available for the other treatment[7]
- Specifically, in our study, patients from the sparsentan or irbesartan arms of the PROTECT trial were weighted to match key **treatment effect modifiers** and **prognostic factors** published for patients from RaDaR or patients from the control arm of the NefIgArd trial, respectively
  - Treatment effect modifiers are variables that influence the relative effectiveness of one treatment compared to another; the association between the treatment and the outcome is different across the levels of the effect modifiers
  - Prognostic factors are indicators used to predict the future health outcomes or progression of disease in patients
  - In an unanchored matching adjusted indirect comparison, it is essential to match both treatment effect modifiers and prognostic factors to ensure accurate comparisons
- Then, two-year eGFR 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



Background

Study Objective

Methods

Results

Discussions & Conclusions

1 2 3 **4** 5

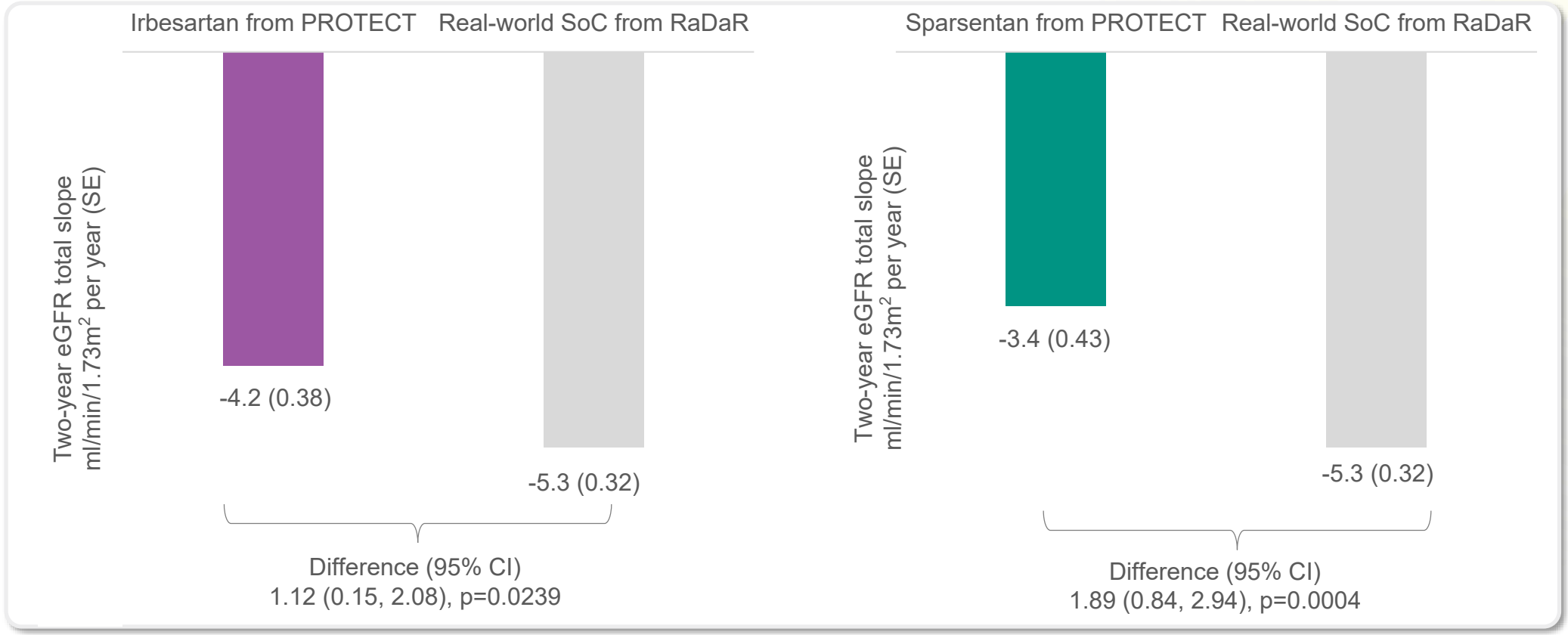
Sparsentan and irbesartan vs. RaDaR SoC

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

	RaDaR SoC	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 (standard deviation [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 body mass index (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 systolic blood pressure (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)

Sparsentan and irbesartan vs. RaDaR SoC (cont'd)

- After matching, 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/1.73m^2 per year (**p=0.0239**) for irbesartan and 1.89 ml/min/1.73m^2 per year (**p=0.0004**) for the sparsentan, respectively



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

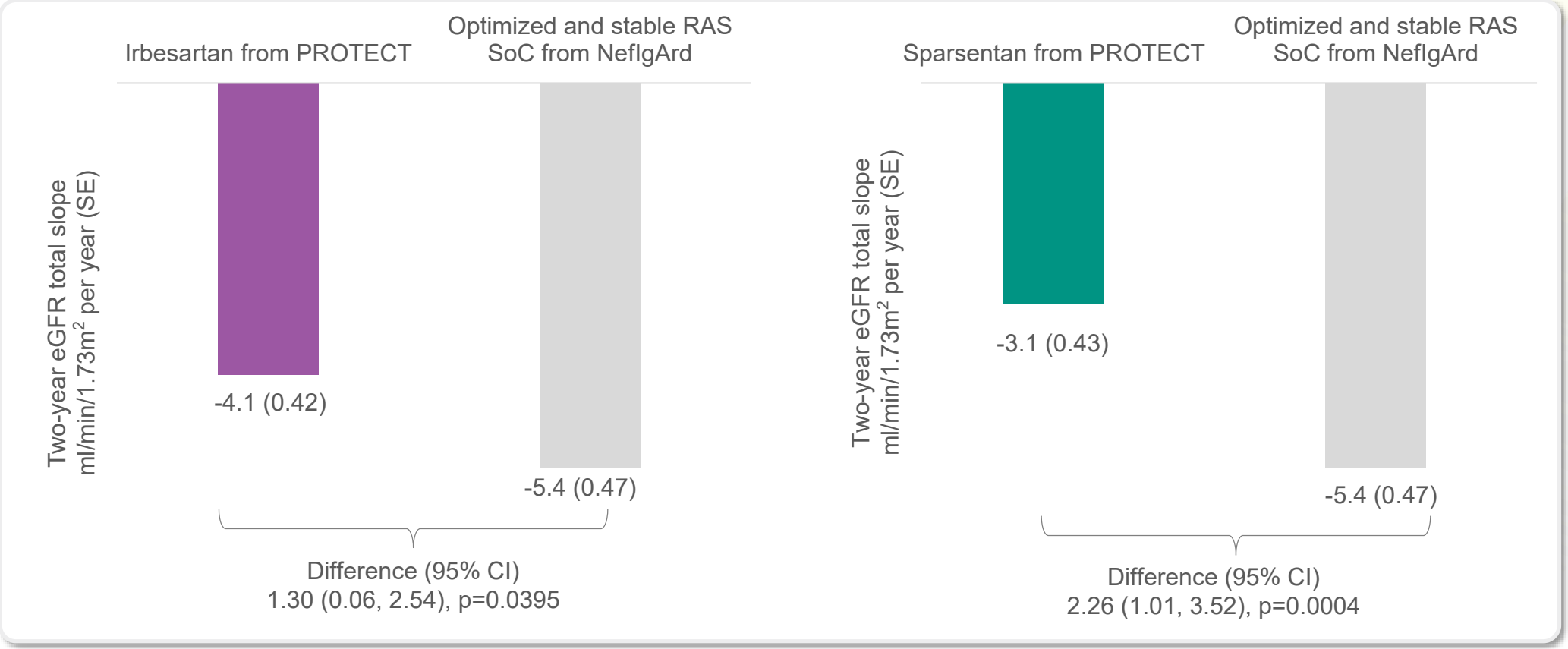
Sparsentan and irbesartan vs. NeflgArd SoC

- Compared with patients in the NeflgArd 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
- After weighting, the key effect modifiers and prognostic factors were balanced between the compared cohorts, while the ESSs decreased for the sparsentan cohort and the irbesartan cohort

	NeflgArd SoC	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 Asian	 0.75 0.22	 0.70 0.24	 -0.05 0.02	 0.75 0.22	 0.00 0.00	 0.64 0.33	 -0.11 0.11	 0.75 0.22	 0.00 0.00
Median systolic blood pressure, mmHg	124.00	128.00	4.00	124.00	0.00	128.00	4.00	124.00	0.00
Median diastolic blood pressure, 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 m^2, 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 m^2	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

Sparsentan and irbesartan vs. NeflgArd SoC (cont'd)

- Similar results were observed compared to SoC delivered in the clinical trial setting (NeflgArd), with a difference of 1.30 ml/min/1.73m^2 per year (**p=0.0395**) for irbesartan and 2.26 ml/min/1.73m^2 per year (**p=0.0004**) for the sparsentan, respectively



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

Background

Study Objective

Methods

Results

Discussions & Conclusions

1 2 3 4 **5**

Discussions

- 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
- Results from this study are subject to the following limitations
    - Only known baseline factors consistently 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

Conclusions

- 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 NeflgArd
- These results highlight the importance of considering the two-year eGFR total slope difference between arms of the PROTECT trial in the context of what is achieved in current clinical practice

References

1. Wyatt RJ, Julian BA. IgA nephropathy. New England Journal of Medicine. 2013 Jun 20;368(25):2402-14.
2. Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, Cook HT, Fervenza FC, Gibson KL, Glassock RJ, Jayne DR. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group.
3. Bensink M, Thakker KM, Lerma EV, Velez JC, Lieblich R, Bunke M, Wang K, Amari DT, Thanataveerat A, Oliveri D, Rava A. EE369 IgA Nephropathy (IGAN) in Adults: A Retrospective Analysis of US Prevalence and Impacts of Proteinuria and Kidney Function Decline on Healthcare Resource Utilization (HRU) and Costs. Value in Health. 2022 Jul 1;25(7):S407.
4. Rauen T, Wied S, Fitzner C, Eitner F, Sommerer C, Zeier M, Otte B, Panzer U, Budde K, Benck U, Mertens PR. After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy. Kidney international. 2020 Oct 1;98(4):1044-52.
5. Pitcher D, Braddon F, Hendry B, Mercer A, Osmaston K, Saleem MA, Steenkamp R, Wong K, Turner AN, Wang K, Gale DP. Long-term outcomes in IgA nephropathy. Clinical Journal of the American Society of Nephrology. 2023 Jun 1;18(6):727-38.
6. Rovin BH, Barratt J, Heerspink HJ, Alpers CE, Bieler S, Chae DW, Diva UA, Floege J, Gesualdo L, Inrig JK, Kohan DE. Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial. The Lancet. 2023 Dec 2;402(10417):2077-90.
7. Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS, Betts KA, Wu EQ. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value in Health. 2012 Sep 1;15(6):940-7.
8. European Medicines Agency. Kinpeygo (budesonide) - Public Assessment Report. 2022. https://www.ema.europa.eu/en/documents/assessment-report/kinpeygo-epar-public-assessment-report_en.pdf.
9. Lafayette R, Kristensen J, Stone A, Floege J, Tesař V, Trimarchi H, Zhang H, Eren N, Paliege A, Reich HN, Rovin BH. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial. The Lancet. 2023 Sep 9;402(10405):859-70.


NATIONAL KIDNEY FOUNDATION
SCM24
SPRING CLINICAL MEETINGS

Questions

MA-SP-24-0061 06/2024