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Matching-adjusted indirect comparison of eGFR in patients with IgAN treated with Nefecon (TRF budesonide) or sparsentan

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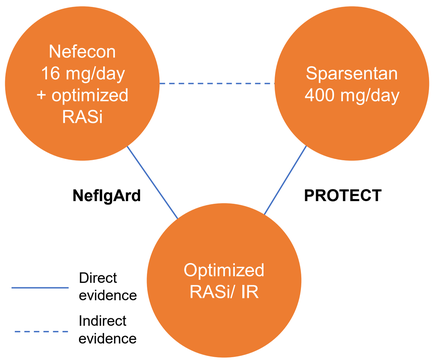
INTRODUCTION

- **In December 2023, the FDA granted full approval of Nefecon** (marketed as TARPEYO® by Calliditas Therapeutics), a TRF of budesonide, to reduce the loss of kidney function in adults with primary IgAN who are at risk for disease progression, **based on the Phase 3 NefIgArd trial**[1,2]
- **In February 2023, sparsentan** (marketed as FILSPARI™ by Travere Therapeutics) was granted **accelerated approval by the FDA** to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a UPCR ≥1.5 g/g, **based on the Phase 3 PROTECT study**[3,4]
- Change in eGFR is a well-established marker of declining kidney function[5]; MAIC is also a widely accepted and relevant methodology for comparing treatments across trials in the absence of head-to-head comparisons[6,7]

AIM

- In this analysis, we aimed to compare the effects of Nefecon + optimized RASi with sparsentan on kidney function deterioration in patients with IgAN, as assessed using eGFR

Figure 1: Network for anchored MAIC (all endpoints)



METHODS

- An **anchored MAIC using patient-level data from NefIgArd and trial-level data from PROTECT** was performed to estimate the relative effect of Nefecon + optimized RASi with sparsentan on the absolute eGFR change from baseline at 9, 12, and 24 months, with common comparators of optimized RASi for NefIgArd[2] and irbesartan (IR) for PROTECT[4]
- The following **baseline characteristics were used to determine the weights to obtain a patient population matching the PROTECT trial:** mean age (years), sex (% male), race (% White), mean eGFR (mL/min/1.73 m^2), mean UPCR (g/g), proportion of patients with UACR >1.1 g/g (%), and proportion of patients with urinary protein excretion >1.8 g/day (%)
- **Absolute change in eGFR in NefIgArd was analyzed using an MMRM method**, including 3-, 6-, 9-, 12-, 18-, and 24-month data, baseline eGFR, baseline eGFR-by-time interaction, treatment, and treatment-by-time interaction. The MAIC weights were incorporated into the MMRM
- A Bayesian fixed-effects network meta-analysis was performed on the relative effect from PROTECT and the weighted relative effect from NefIgArd, measured using the estimated absolute change in eGFR from baseline

RESULTS

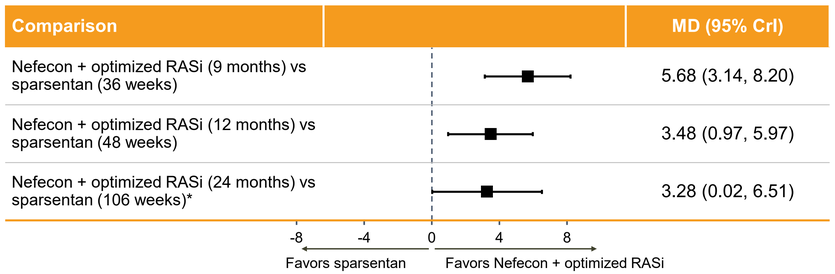
- The weighted NefIgArd population exhibited **very similar baseline characteristics** to the PROTECT population, with an effective sample size of the weighted NefIgArd population of 208 (Table 1)
- Results from the anchored MAIC showed **statistically significant favorable effects of Nefecon + optimized RASi vs sparsentan on eGFR** for all time points analyzed (Figure 2)
  - Mean differences in the absolute change in eGFR of 5.68 mL/min/1.73 m^2, 3.48 mL/min/1.73 m^2, and 3.28 mL/min/1.73 m^2 were observed when comparing Nefecon + optimized RASi with sparsentan at 9 months vs 36 weeks, 12 months vs 48 weeks, and 24 months vs 106 weeks, respectively
- In **an unanchored MAIC sensitivity analysis**, the results for eGFR showed favorable effects of Nefecon + optimized RASi vs sparsentan that were statistically significant for the time points at 9 months vs 36 weeks and 12 months vs 48 weeks

Table 1: Matching-adjustment of the NefIgArd and PROTECT trial populations

Study	N	Age (years)	Male (%)	White (%)	Mean eGFR (mL/min/1.73 m^2)	Mean UPCR (g/g)	UACR >1.1 g/g (%)	Urinary protein excretion >1.8 g/day (%)
NefIgArd	364	42.70	65.93	75.55	57.87	1.48	40.66	65.66
PROTECT	404	46.00	69.80	67.33	56.95	1.44	50.00	50.00
Weighted NefIgArd	**208***	**46.00**	**69.80**	**67.33**	**56.95**	**1.44**	**50.00**	**50.00**

**Number shown is the effective sample size after weighting.*

Figure 2: Mean difference in absolute eGFR change from baseline at 9, 12, and 24 months



**Week 106 in PROTECT was selected as a comparator because it was temporally closest to Month 24 in NefIgArd.*

LIMITATIONS

- The optimization strategy in NefIgArd (optimized RASi) differed from the optimization strategy in PROTECT (IR), and anchoring of the two trials at optimized RASi/IR might lead to biased results. However, we also evaluated an unanchored MAIC in a sensitivity analysis and found very similar results
- The MAIC method can only adjust the relative effect estimates for any observed effect modifier available in the data, but it cannot adjust for unobserved or unobservable effect modifiers. A significant number of potential treatment effect modifiers were included in the present analysis: age, sex, race, baseline eGFR, UPCR, UACR, and urinary protein excretion

CONCLUSIONS

- After accounting for differences in the patient populations from the NefIgArd and PROTECT trials, **the anchored MAIC showed that treatment with Nefecon 16 mg/day + optimized RASi for 9 months[2] was associated with greater eGFR benefit compared with continuous treatment with sparsentan 400 mg/day over 2 years.**[4] Significant differences were observed as early as 9 months after treatment initiation, which were sustained for up to 15 months of follow-up
- As with any indirect treatment comparison, our analysis includes an underlying assumption of exchangeability of patients between studies, which cannot be directly assessed. However, **these results suggest that Nefecon + optimized RASi may preserve kidney function to a greater extent than sparsentan and provide support for Nefecon as a disease-modifying therapy in IgAN**

DISCLOSURES

H. N. Reich received support to serve as a member of the steering committee of the present study and funding for its execution from Calliditas Therapeutics; has received grant support from the Canadian Institutes of Health Research and the Kidney Foundation of Canada (from John and Leslie Pearson); has received fellowship support from the Louise Fast Foundation; reports consulting fees, honoraria, or travel support from Calliditas Therapeutics, Chinook, Novartis, Omeros, Pfizer, and Travere Therapeutics; has served on advisory boards and steering committees for Chinook, Novartis, Omeros, Pfizer, and Travere Therapeutics; has been an investigator for Alnylam Pharmaceuticals, Calliditas Therapeutics, ChemoCentryx, Chinook, Omeros, and Pfizer; and is Director of the Glomerulonephritis Fellowship, funded by the Louise Fast Foundation. M. Patel is an employee of Calliditas Therapeutics. A. Kopiec, S. Fu, and N. Hummel are employees of Certara, which received funding from Calliditas Therapeutics for this research. R. Lafayette reports institutional grants from Calliditas Therapeutics, ChemoCentryx, Omeros, Otsuka, Pfizer, Roche, Travere Therapeutics, Vera Therapeutics, and Visterra; and has served on advisory boards for Cara Therapeutics.

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ABBREVIATIONS

CrI, credible interval; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; IgAN, immunoglobulin A nephropathy; IR, irbesartan; MAIC, matching-adjusted indirect comparison; MD, mean difference; MMRM, mixed model for repeated measures; RASi, renin–angiotensin system inhibition; TRF, targeted-release formulation; UACR, urine albumin–creatinine ratio; UPCR, urine protein–creatinine ratio.

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