60TH ERA CONGRESS
MILAN & VIRTUAL
JUNE 15-18, 2023

Matching-adjusted indirect comparison of sparsentan vs. delayed-release formulation budesonide for proteinuria reduction in adults with IgA nephropathy

Mark Bensink[1], **Wu Gong** [1], **Xinglei Chai**[2], **Sophie Gao**[3], **Ulysses Diva**[1], **Bruce Hendry**[1], **Alex Mercer**[4], **Zheng-Yi Zhou**[5]

[1]Travere Therapeutics, Inc., San Diego, USA; [2]Analysis Group, Boston, USA; [3]Analysis Group, Los Angeles, USA; [4]JAMCO Pharma Consulting, Sweden; [5]Analysis Group, London, UK

ANALYSIS GROUP

TRAVERE THERAPEUTICS

INTRODUCTION

- Immunoglobulin A (IgA) nephropathy is a rare kidney disorder characterized by deposition of IgA in the glomeruli and associated with a reduction in renal function and increased risk of kidney failure.[1,2]
- Under accelerated approval based on reduction in proteinuria at 9 months, two treatment options for IgA nephropathy now include sparsentan (US),[3] an endothelin and angiotensin II receptor antagonist, and delayed-release formulation budesonide (US and Europe).[4,5]
- With the availability of proteinuria (urine protein-creatinine ratio [UPCR]) efficacy outcomes for both options, but the absence of head-to-head trials, information on the relative efficacy of these two treatment options is needed.
- The objective of this analysis was to compare 9-month proteinuria efficacy outcomes for sparsentan and delayed-release formulation budesonide.

METHODS

- We completed a feasibility assessment to evaluate key points of similarity and heterogeneity between the PROTECT clinical trial for sparsentan[6] and clinical trials for delayed-release formulation budesonide[7,8] along with different methods for indirect comparison.[9,10]
- Assessment of cross-trial heterogeneities suggested that the PROTECT[11] and NefIgArd[12] studies were sufficiently similar in terms of key inclusion and exclusion criteria and outcome definitions to make an indirect comparison feasible. However, the PROTECT study compared sparsentan to an active control arm, optimized renin-angiotensin-aldosterone system (RAAS) inhibition with maximum tolerable dose of irbesartan within the trial, while the NefIgArd study compared delayed-release formulation budesonide to placebo in addition to real-world optimized and stable renin-angiotensin system (RAS) blockade.
- Based on these observations, we deemed matching-adjusted indirect comparison to be an appropriate approach to compare sparsentan and delayed-release formulation budesonide. With PROTECT data, geometric mean ratio (GMR) results were derived using a mixed model repeated measures (MMRM) approach including treatment, stratification at randomization, log (baseline) UPCR, visit, and treatment-by-visit interaction to provide a GMR at week 36 (Month 9) relative to baseline with 95% CIs.
- Before MMRM modeling, patients in the sparsentan arm of PROTECT were weighted to match key baseline characteristics of patients in the delayed-release formulation budesonide arm of NefIgArd and patients in the active control arm of PROTECT were also weighted to match key baseline characteristics of patients in the placebo arm of NefIgArd.

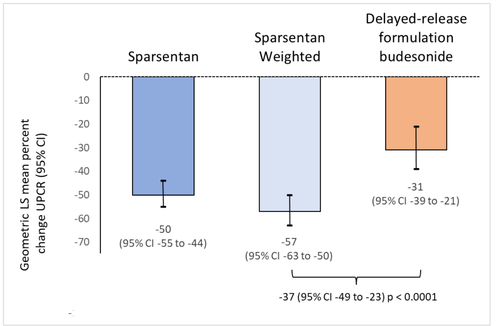
RESULTS

- Based on pre-weighting results, sparsentan had a greater relative reduction from baseline in UPCR at Month 9 (**Table 1**).
- Post-weighting, sparsentan was associated with a greater reduction from baseline in UPCR at Month 9 than delayed-release formulation budesonide; ratio of GMRs (95% CI) **(Table 1**) and associated relative percentage difference in GMRs (95% CI) (**Figure 1**).
- Prior to weighting, patients in the sparsentan arm of PROTECT (N=202) had differences compared with patients in the delayed-release formulation budesonide arm of NefIgArd (N=97) including higher mean (SD) age, differences in racial distribution and a lower proportion of patients with proteinuria >2 g/day (**Table 2**).

Table 1. Summary of outcomes pre- and post-weighting

	Delayed-release formulation budesonide	Sparsentan
Pre-weighting MMRM estimated GMR (95% CI)	0.69 (0.61, 0.79)	0.50 (0.45, 0.56)
Post-weighting MMRM estimated GMR (SE)	0.69 (0.06)	0.43 (0.08)
Comparison Ratio of GMRs (95% CI)	0.63 (0.51, 0.77)	

MMRM, mixed model repeated measures; GMR, geometric mean ratio; SE, standard error; CI, confidence interval.



Associated relative reduction in UPCR is calculated as 1-GMR. Relative percentage difference is calculated as 1-Ratio of GMRs (sparsentan/budesonide).

- Similarly, prior to weighting, patients in the active control arm of PROTECT (irbesartan: N=202) had differences compared with patients in the placebo arm of NefIgArd (N=102) including higher mean [SD] age, differences in racial distribution and a lower proportion of patients with proteinuria >2 g/day (**Table 3**).
- Post-weighting, the effective sample size (ESS) for the sparsentan and irbesartan arms of PROTECT were 52.7 and 35.9, respectively indicative of small overlap in the patient population between the two studies; all weighted absolute differences approached zero (**Table 2** and **Table 3**).

Table 2. Baseline characteristics of the treatment arms (sparsentan [PROTECT] vs delayed-release formulation budesonide [NefIgArd]), before and after weighting

	Delayed-release formulation budesonide Aggregated	Sparsentan Unweighted	Difference Unweighted	Sparsentan Weighted	Difference Weighted
Mean age (SD), years	43.80 (10.80)	46.56 (12.76)	2.7594 (1.9552)	43.80 (10.83)	–0.0001 (0.0267)
Male, %	70.10	68.81	–1.2912	70.10	–0.0001
Race, %					
White	87.63	64.36	–23.2724	87.63	–0.0001
Asian	11.34	33.17	21.8281	11.34	0.0002
Mean SBP (SD), mmHg	128.00 (10.50)	128.00 (14.41)	–0.0050 (3.9113)	128.00 (10.53)	–0.0001 (0.0263)
Mean eGFR (SD), ml/min/1.73 m²	57.00 (15.60)	56.86 (24.38)	–0.1436 (8.7791)	57.00 (15.64)	0.0001 (0.0385)
eGFR <60 ml/min/1.73 m², %	64.95	62.87	–2.0772	64.95	–0.0004
Mean UPCR (SD), g/g	1.5 (0.9)	1.43 (0.90)	–0.0732 (–0.0000)	1.50 (0.90)	0.0000 (0.0022)
Proteinuria, %					
>2 to ≤3.5 g/day	37.11	32.18	–4.9352	37.11	0.0003
>3.5 g/day	22.68	12.38	–10.3042	22.68	0.0002
Diabetes, %	9.28	8.42	–0.8625	9.28	–0.0002
Mean time since kidney biopsy (SD), years	3.60 (3.70)	6.41 (6.48)	2.8109 (2.7795)	3.60 (3.71)	0.0001 (0.0092)

Table 3. Baseline characteristics of the control arms (irbesartan [PROTECT] vs placebo [NefIgArd]), before and after weighting

	Placebo Aggregated	Irbesartan Unweighted	Difference Unweighted	Irbesartan Weighted	Difference Weighted
Mean age (SD), years	42.90 (10.60)	45.43 (12.12)	2.53074 (1.5187)	42.90 (10.63)	–0.0004 (0.0263)
Male, %	65.69	70.79	5.1058	65.69	0.0003
Race, %					
White	84.31	70.30	–14.0167	84.31	0.0003
Asian	12.75	23.76	11.0173	12.74	–0.0006
Mean SBP (SD), mmHg	124.00 (10.30)	129.94 (12.39)	5.9406 (2.0891)	124.00 (10.33)	0.0004 (0.0260)
Mean eGFR (SD), ml/min/1.73 m²	58.60 (16.30)	57.08 (23.58)	–1.5208 (7.2772)	58.60 (16.34)	–0.0000 (0.0403)
eGFR <60 ml/min/1.73 m², %	59.80	63.86	4.0575	59.80	0.0002
Mean UPCR (SD), g/g	1.60 (1.40)	1.44 (0.89)	–0.1593 (–0.5063)	1.60 (1.40)	0.0000 (0.0035)
Proteinuria, %					
>2 to ≤3.5 g/day	30.39	30.69	0.3009	30.39	–0.0008
>3.5 g/day	27.45	11.88	–15.5698	27.45	0.0009
Diabetes, %	0.98	6.93	5.9503	0.98	–0.0000
Mean time since kidney biopsy (SD), years	4.30 (4.80)	6.37 (7.10)	2.0663 (2.3037)	4.30 (4.81)	–0.0001 (0.0117)

DISCUSSION

- To support to our comparison of efficacy outcomes, we completed population weighting to account for underlying differences in PROTECT (sparsentan) and NefIgArd (delayed-release formulation budesonide) patient population characteristics, the most notably being the distribution of patients with proteinuria >2 g/day at baseline and the proportion of White vs. Asian patients.
- Accounting for these and other differences resulted in a numerically greater relative reduction in UPCR (50% pre-weighting to 57% post-weighting) with post-weighting relative reduction of 57% being significantly greater than the 31% reported for delayed-release formulation budesonide.

LIMITATIONS

- Like any indirect treatment comparison, our analysis includes an underlying assumption of exchangeability of patients between studies which cannot be directly addressed.
- While our analysis is aligned to a matching-adjusted indirect treatment comparison focusing on treatment arms due to differences in control arms between PROTECT and NefIgArd trials, the inclusion of treatment group and visit-by-treatment group interaction in the MMRM analysis for both trials inherently includes information from the control arms of each study. This approach has been included in covariate adjusted modelling within the context of a matching-adjusted indirect treatment comparison previously;[13] however, while matching of PROTECT and NefIgArd control arm patient populations was completed prior to conducting the matched PROTECT MMRM analysis, there may be a residual impact on the relative difference reported here.
- Only known baseline factors consistently reported in the trials were able to be matched on; it was obviously not possible to adjust for variables that were neither reported nor measured.
- This analysis was based on trial populations and thus results may not be generalizable beyond the study samples included.

CONCLUSIONS

➢ **Sparsentan was associated with a significantly larger percentage reduction in UPCR from baseline at 9 months, a recognized surrogate of long-term kidney outcomes, as compared with delayed-release formulation of budesonide in addition to optimized and stable RAS blockade.**

DISCLOSURES

This study was sponsored by Travere Therapeutics, Inc.

Wu Gong, Ulysses Diva and **Bruce Hendry** are employees of Travere Therapeutics, Inc. and have equity or other financial interest in Travere Therapeutics, Inc. **Mark Bensink** is the managing director of Benofit Consulting, which received consulting fees from Travere Therapeutics, Inc. **Alex Mercer** is an employee of JAMCO Pharma Consulting, which received consulting fees from Travere Therapeutics, Inc. **Xinglei Chai, Sophie Gao** and **Zheng-Yi Zhou** are employees of Analysis Group, which received consulting fees from Travere Therapeutics, Inc.

REFERENCES

1. Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med*. 2013;368(25):2402-2414.
2. Barratt J, Saleem MA, Braddon F, Carroll KJ, Ping H, Hendry B, et al. Natural history of IgA nephropathy: Analysis of a UK National RaDaR IgA nephropathy cohort. *J Am Soc Nephrol*. 2021;32:S494.
3. U.S Food and Drug Administration. Novel Drug Approvals for 2023. Available at: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2023
4. U.S. Food and Drug Administration. FDA approves first drug to decrease urine protein in IgA nephropathy, a rare kidney disease. 2021. Available at: https://www.fda.gov/drugs/fda-approves-first-drug-decrease-urine-protein-iga-nephropathy-rare-kidney-disease
5. European Medicines Agency. Kinpeygo (budesonide). 2022. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/kinpeygo
6. A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy (PROTECT). 2023. Available at: https://clinicaltrials.gov/ct2/show/NCT03762850
7. The Effect of Nefecon® in Patients With Primary IgA Nephropathy at Risk of Developing End-stage Renal Disease (NEFIGAN). 2015. Available at: https://clinicaltrials.gov/ct2/show/NCT01738035
8. Efficacy and Safety of Nefecon in Patients With Primary IgA (Immunoglobulin A) Nephropathy (Nefigard). 2023. Available at: https://clinicaltrials.gov/ct2/show/NCT03643965
9. Signorovitch JE, Sikirica V, Erder MH, Jipan Xie J, Lu M, Hodgkins PS. Matching-Adjusted Indirect Comparisons: A New Tool for Timely Comparative Effectiveness Research. Value in Health. 2012; 15:940-947.
10. Lumley T. Network meta-analysis for indirect treatment comparisons. Statistics in medicine. 2002;21(16):2313-2324.
11. Heerspink HJL, Radhakrishan J, Alpers CS, et al. Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial. The Lancet. April 01, 2023 DOI:https://doi.org/10.1016/S0140-6736(23)00569-X.
12. Barratt J, Lafayette R, Kristensen J, et al. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary IgAN. Kidney Int. 2023;103(2):391–402.
13. White D, Hendrix LH, Sun L, Tam I, Macsai M, Gibson AA. Matching-adjusted indirect comparison of phase 3 clinical trial outcomes of OC-01 (varenicline solution) nasal spray and liftegrast 5% ophthalmic solution for the treatment of dry eye disease. J Manag Care Spec Pharm. 2023; 29(1):69-79.

CONTACT INFORMATION
Mark.Bensink@travere.com