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Nefecon treatment provides kidney benefits for patients with IgAN that extend to those with low levels of UPCR: A subanalysis of the Phase 3 NefIgArd trial

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INTRODUCTION

- **IgAN** is the most common form of primary glomerulonephritis and a major cause of chronic kidney disease and kidney failure worldwide[1]
- Recent data from the cohort of patients with IgAN in **RaDaR** (UK National Registry of Rare Kidney Diseases) showed that approximately **20% of patients with proteinuria <0.44 g/g** and **30% with proteinuria 0.44 to <0.88 g/g** progressed to **kidney failure within 10 years of diagnosis**. The study also concluded that even an **eGFR decline as low as 1 mL/min/1.73 m² per year** would result in approximately **40% of patients reaching kidney failure** and that an eGFR decline of **<1 mL/min/1.73 m² per year** should be the target for successful therapy[1]
- **Nefecon** is a novel, oral, targeted-release capsule formulation of budesonide, designed to treat IgAN by **reducing Gd-IgA1 production** at the Peyer's patch–rich distal ileum[2]
- Results from the global, double-blind, randomized, placebo-controlled Phase 3 **NefIgArd clinical trial** demonstrated that Nefecon treatment for 9 months led to a significant reduction in the average decline in eGFR over 2 years in patients with primary IgAN, which was **preserved during a 15-month off-drug observational period**[2]
- The benefit was **consistent across subgroups**, including patients with **baseline UPCR <1.5 g/g or ≥1.5 g/g**[2]
- In this analysis, we further explored the potential benefits of Nefecon treatment in patients with **baseline UPCR levels above and below 0.8 g/g**

METHODS

- Eligible patients were aged **≥18 years with primary IgAN**, with an **eGFR of 35-90 mL/min/1.73 m²** and **persistent proteinuria** with a high risk of kidney failure (defined as either **UPCR ≥0.8 g/g or proteinuria ≥1 g/24 h**), despite optimized RAS blockade[2]
- Patients received **Nefecon 16 mg/day or placebo**, in addition to optimized supportive care, for **9 months** (including optimized RAS inhibition), with a 2-week tapering period, followed by a **15-month blinded observational follow-up** with continued optimized supportive care[2]
- Here we report change in **eGFR**(calculated using CKD-EPI), measured at **multiple time points over 2 years** and compared with baseline, for those patients with **UPCR <0.8 g/g or ≥0.8 g/g**

RESULTS

Figure 1: Mean (±SE) absolute change in eGFR by baseline UPCR subgroup

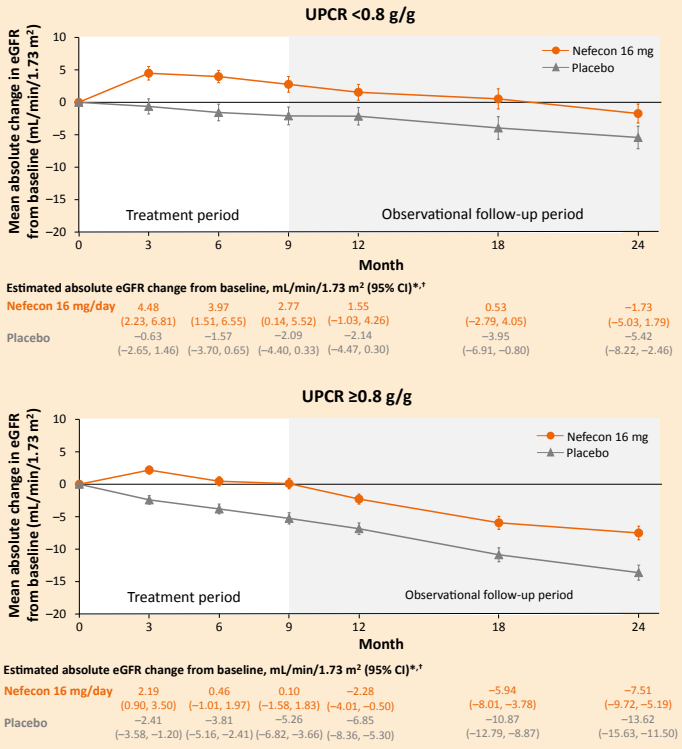

Table 1: Summary of eGFR (CKD-EPI) results by baseline UPCR subgroup

	UPCR <0.8 g/g (N=72)		UPCR ≥0.8 g/g (N=292)	
	Nefecon (n=36)	Placebo (n=36)	Nefecon (n=146)	Placebo (n=146)
Baseline characteristics				
Baseline eGFR, geometric mean, mL/min/1.73 m² (IQR)	54.1 (45.7, 62.6)	57.2 (44.1, 71.1)	56.5 (45.5, 72.0)	55.2 (46.0, 66.5)
Baseline UPCR geometric mean, g/g (IQR)	0.67 (0.62, 0.73)	0.63 (0.56, 0.72)	1.53 (1.11, 1.97)	1.50 (1.06, 1.85)
Baseline proteinuria geometric mean, g/24 h (IQR)	1.45 (1.21, 1.65)	1.46 (1.26, 1.69)	2.66 (1.91, 3.32)	2.60 (1.87, 3.62)
Absolute change from baseline in time-weighted eGFR over 2 years, using robust regression				
Absolute change in eGFR from baseline over 2 years, mL/min/1.73 m² (95% CI)†	1.2 (−1.0, 3.6)	−5.7 (−5.2, −1.1)	−3.6 (−5.2, −1.9)	−8.7 (−10.3, −7.1)
Treatment benefit vs placebo, mL/min/1.73 m²	4.4		5.1	
Ratio of time-weighted average eGFR over 2 years versus baseline, using robust regression				
Geometric LS mean (95% CI)	1.02 (0.98, 1.06)	0.94 (0.91, 0.98)	0.94 (0.91, 0.97)	0.84 (0.82, 0.87)
Ratio of geometric LS means, Nefecon:placebo (95% CI)	1.08 (1.02, 1.15) **p=0.0026** (one-sided)		1.11 (1.06, 1.16) **p<0.0001** (one-sided)	
Annualized 2-year eGFR total slope				
Annualized 2-year eGFR total slope, mL/min/1.73 m² per year (95% CI)‡	−0.25 (−1.81, 1.31)	−2.72 (−4.30, −1.13)	−3.17 (−4.30, −2.04)	−6.20 (−7.33, −5.06)
Treatment benefit vs placebo, mL/min/1.73 m² per year‡	2.47 (0.23, 4.70) **p=0.0156** (one-sided)		3.02 (1.43, 4.62) **p=0.0001** (one-sided)	

*Estimated absolute change from baseline = baseline geometric mean for total × (geometric LS mean of post-baseline value/baseline value for each treatment arm − 1). †Estimated absolute change from baseline = baseline geometric mean for total × (geometric LS mean of ratio of AUC over 2 years compared with baseline for each treatment arm − 1). ‡eGFR slopes are analyzed using a two-piece linear spline mixed-effect model with a knot at 3 months, within-subject variability modeled with a Power-of-Mean structure, between-subject variability modeled with a proportional treatment effect structure, allowing different estimates of variability between arms.

CONCLUSIONS

- Over the 2-year study period, mean **reductions in eGFR were lower in patients treated with Nefecon 16 mg/day** versus placebo **regardless of baseline UPCR**, and **eGFR benefit was maintained in the UPCR <0.8 g/g subgroup** for up to 24 months following treatment initiation, despite treatment cessation at Month 9
- There was a **significant difference between the Nefecon 16 mg/day and placebo treatment arms in the time-weighted average change in eGFR** over 2 years for patients with **UPCR <0.8 g/g (p=0.0026)** and **≥0.8 g/g (p<0.0001)**
- In this study, patients with UPCR <0.8 g/g who received Nefecon achieved an eGFR slope of –0.25 mL/min/1.73 m² per year; this suggests Nefecon treatment may support patients to achieve the **RaDaR treatment target** of an **eGFR decline of <1 mL/min/1.73 m² per year** with the objective to avoid kidney failure in their lifetime[1]

Scan to view Nefecon presentations, posters, and materials

REFERENCES

1. Pitcher D, *et al. Clin J Am Soc Nephrol* 2023;18:727-738. 2. Lafayette R, *et al. Lancet* 2023;402:859-870.

ABBREVIATIONS

AUC, area under the curve; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; Gd-IgA1, galactose-deficient immunoglobulin A1; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; LS, least squares; RaDaR, UK National Registry of Rare Kidney Diseases; RAS, renin–angiotensin system; SE, standard error; UPCR, urine protein-creatinine ratio.

DISCLOSURES

JB is a consultant to Calliditas and reports grants as well as consultancy and personal fees from Arzneimittel AG, Everest Medicines, Calliditas, and STADA. **JK** is a consultant for Calliditas. **AS** received support for the present study and reports consulting fees from AstraZeneca and Calliditas outside the submitted work. **JF** has received consultancy fees or honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Calliditas, Chinook, GSK, Novartis, Omeros, Otsuka, and Travere Therapeutics, and serves on data safety monitoring boards for Novo Nordisk and Visterra. **VT** has reported consultancy fees or honoraria from Calliditas, Novartis, Omeros, Otsuka, and Travere Therapeutics. **HT** has served on advisory boards for Calliditas and received grants, honoraria, consultancy fees, or travel support from Alexion, AstraZeneca, BioCryst, Calliditas, Chinook, George Clinical, Novartis, Omeros, Otsuka, Travere Therapeutics, and Vera Therapeutics. **HZ** has received consulting fees or honoraria from Calliditas, Chinook, Novartis, Omeros, and Otsuka. **NE** declares no competing interests. **AP** received honoraria and travel grants from Alexion, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Otsuka, STADA Arzneimittel AG, and Vifor Pharma. **HNR** received support to serve as a member of the steering committee and funding for the execution of the study from Calliditas, has received grant support from the Kidney Foundation of Canada, Canadian Institutes of Health Research, and John and Leslie Pearson; has received fellowship support from the Louise Fast Foundation; reports consulting fees, honoraria, or travel support from Calliditas, Chinook, Novartis, Omeros, Pfizer, and Travere Therapeutics; served in advisory boards and steering committees for Chinook, Novartis, Omeros, Pfizer, and Travere Therapeutics; has been an investigator for Alnylam Pharmaceuticals, Calliditas, ChemoCentryx, Chinook, Omeros, Pfizer; and is Director of the Glomerulonephritis Fellowship, funded by the Louise Fast Foundation. **BHR** received support for the present study from Calliditas; reports consulting fees from Alpine Immune Sciences, Alexion, Calliditas, Novartis, Omeros, Otsuka/Visterra, Q32 Bio, Travere Therapeutics, and Vera Therapeutics; and is Co-Chair of Glomerular Diseases Guidelines for KDIGO. **RL** received support for the present study from Calliditas; reports institutional grants from Calliditas, ChemoCentryx, Omeros, Otsuka, Pfizer, Roche, Travere Therapeutics, Vera Therapeutics, and Visterra; and has served on advisory boards for Cara Therapeutics.

Calliditas Therapeutics