Durable proteinuria reduction over 2 years with Nefecon treatment: A secondary analysis of the full NefIgArd Phase 3 trial results

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BACKGROUND

- **Proteinuria** is a common clinical manifestation of IgAN, which can be **measured to determine the efficacy** of IgAN treatments[1,2]
- **Nefecon** is a novel, oral, targeted-release budesonide formulation specifically designed to treat IgAN by **acting locally in the distal ileum**[3]
- Previous findings from the **Phase 2b NEFIGAN trial** showed that patients treated with Nefecon 16 mg/day for 9 months, with a 3-month follow-up, showed a **reduction in UPCR** compared with placebo[4]
- In the **interim analysis** of the **Phase 3 NefIgArd trial**, treatment with Nefecon resulted in a **significant reduction in UPCR** (27%, p=0.0003) and **significant eGFR treatment benefit** of 3.87 mL/min/1.73 m^2 compared with placebo after 9 months[3]
  - These findings led to the **FDA and EMA approval** of Nefecon in patients with primary IgAN[5,6]
- Here, we present the **proteinuria data** from the **complete 2-year NefIgArd study**, comprising 9 months of treatment and 15 months of follow-up

AIM

- To assess the durability of effect of **Nefecon 16 mg/day** over 9 months of treatment and subsequent 15 months of follow-up on **proteinuria reduction** vs placebo in patients with IgAN in the full Phase 3 NefIgArd trial

METHODS

- **NefIgArd** was a 2-part randomized, double-blind, placebo-controlled study
- Patients received **Nefecon 16 mg/day or placebo**, in addition to optimized SoC, for **9 months** (including physician's choice of optimized RAS blockade), with a 2-week tapering period, followed by a **15-month blinded observational follow-up** with continued optimized SoC
- The NefIgArd study successfully **met its 2-year primary endpoint**, as presented in the NefIgArd full trial results poster
- **Pre-defined secondary efficacy endpoints:**
  - **Time-averaged UPCR and UACR** between 12 and 24 months following the first dose of the study drug and expressed as ratios vs baseline
- UPCR and UACR data were based on a 24-hour urine protein collection and were log-transformed prior to analysis using a MMRM including all timepoints from 3 months onwards
- UPCR and UACR values at 12, 18, and 24 months were given equal weight to obtain the geometric mean treatment effect during follow-up

Table 1: Eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Patients aged ≥18 years with biopsy-confirmed primary IgAN	• Other glomerulopathies and nephrotic syndrome
• Persistent proteinuria (≥1 g/24 h) despite optimized RAS blockade	• Kidney transplant
• eGFR of 35-90 mL/min/1.73 m^2	• Systemic diseases that may cause mesangial IgA deposition
	• Poorly controlled blood pressure (≥140/90 mmHg)

RESULTS

- **Baseline characteristics were well balanced** for the Nefecon 16 mg and placebo groups (Table 2)

Table 2: Patient demographics and baseline characteristics

	Nefecon 16 mg/day (n=182)	Placebo (n=182)
Age (years), median (range)	43 (21, 69)	42 (20, 73)
Sex (n, % male)	117 (64)	123 (68)
Race (n, % White)	138 (76)	137 (75)
Race (n, % Asian)	43 (24)	40 (22)
Systolic BP, median (range)	126 (121, 132)	124 (117, 130)
Diastolic BP, median (range)	79 (76, 84)	79 (74, 84)
UPCR (g/g), median (IQR)	1.28 (0.90, 1.76)	1.25 (0.88, 1.74)
UACR (g/g), median (IQR)	0.99 (0.68, 1.40)	0.98 (0.66, 1.42)
eGFR CKD-EPI (mL/min/1.73 m^2), median (IQR)	56.1 (45.5, 71.0)	55.1 (46.0, 67.8)

- At 24 months, **UPCR was reduced by 31%** from baseline in the **Nefecon group** compared with **1% in the placebo group** (comparative reductions at the end of the 9-month treatment period were 34% and 5%, respectively; Figure 1)
- The **predefined secondary analysis** of the durability of reduction in proteinuria showed:
  - A significant **41% reduction** from baseline in **time-averaged UPCR from 12 to 24 months** in the Nefecon group compared with placebo (95% CI 32, 49, p<0.0001; Table 3)
  - A significant **46% reduction** from baseline in **time-averaged UACR from 12 to 24 months** in the Nefecon group compared with placebo (95% CI 37, 55; p<0.0001; Table 3)

Figure 1: Percentage change in UPCR (g/gram) from baseline*

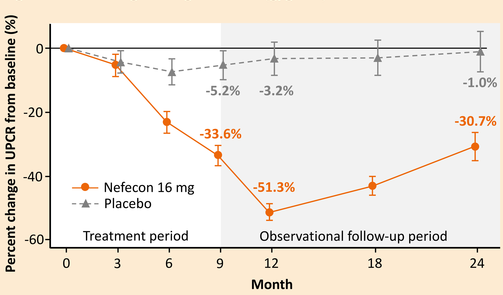

Table 3: Ratio of UPCR and UACR averaged over 12-24 months compared with baseline using MMRM

	% change vs placebo (95% CI) p-value†	% reduction from baseline (95% CI) Nefecon 16 mg/day (n=172)	% reduction from baseline (95% CI) Placebo (n=173)
UPCR	41% (32, 49) p<0.0001	40.3%	-1.0%
UACR	46% (37, 55) p<0.0001	48.2%	3.7%

CONCLUSIONS

- These secondary analyses show that after 9 months of Nefecon 16 mg/day treatment, a **clinically relevant reduction in proteinuria** (as measured by UPCR and UACR) was seen in patients with primary IgAN
- This effect was **durable** and was **maintained throughout the 15-month off-drug observation period** after the end of treatment, with a **maximum 50% reduction** in UPCR vs placebo observed at 12 months post baseline
- These results lend further support to the clinical benefit of Nefecon as well as provide further evidence of a **disease-modifying effect**

Scan to view Nefecon presentations, posters and materials

REFERENCES

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ABBREVIATIONS

BP, blood pressure; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, Food and Drug Administration; IgA, Immunoglobulin A; IgAN, Immunoglobulin A nephropathy; IQR, interquartile range; MMRM, mixed-effects model for repeated measures; RAS, renin-angiotensin system; SoC, standard of care; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

DISCLOSURES

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. **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. **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. **JB** is a consultant to Calliditas and reports grants as well as consultancy and personal fees from STADA Arzneimittel AG, Everest Medicines, and Calliditas. **NE** declares no competing interests.

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*Error bars represent standard error. †Corresponding percentage reduction and 95% CI is derived from (1–ratio of geometric least squares means) × 100.

Nefecon has not been approved by the Japanese Pharmaceuticals and Medical Devices Agency.

Calliditas Therapeutics