Hematuria reduction in patients with IgAN following Nefecon treatment: A secondary analysis of the full 2-year NeflgArd Phase 3 trial results

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Nefecon has not been approved by the Japanese Pharmaceuticals and Medical Devices Agency.
I have the following relationships to disclose any COI for this research presentation within the period of 36 months.

* Employment/Leadership position/Advisory role: Calliditas Therapeutics
* Stock ownership or options:
* Patent royalties/licensing fees:
* Honoraria (e.g. lecture fees):
* Manuscript fees:
* Research funding: Calliditas Therapeutics
* Subsidies or donations:
* Endowed departments by commercial entities:
* Travel fees, gifts, and others:
Introduction

• Nefecon is a novel, oral, targeted-release budesonide formulation specifically designed to treat IgAN by inhibiting IgA formation in the Peyer’s-patch–rich distal ileum\(^1,2\)

• An interim analysis of the Phase 3 NefIgArd trial (N=199) demonstrated that Nefecon reduced proteinuria (27%, p=0.0003) and had an eGFR treatment benefit of 3.87 mL/min/1.73 m\(^2\) compared with placebo after 9 months\(^2\)
  – These findings led to FDA and EMA approval of Nefecon in patients with primary IgAN\(^3,4\)

• Changes in microhematuria can be measured to determine the efficacy of IgAN treatments\(^5\)

• Here, we present results from a secondary analysis of microhematuria data from the complete 2-year NefIgArd study (N=364)
**Methods**

**NefIgArd: A Phase 3, two-part, randomized, double-blind, placebo-controlled study**

**Aim of the analysis:** To assess the effect of Nefecon 16 mg/day on microhematuria in patients with IgAN over the 9-month treatment period and 15-month observational follow-up period of the Phase 3 NefIgArd trial

**Key inclusion criteria:**
- ≥18 years old with biopsy-confirmed primary IgAN
- UPCR ≥0.8 g/g or proteinuria ≥1 g/24h, despite optimized RAS inhibition
- eGFR 35-90 mL/min/1.73 m²

**Key exclusion criteria:**
- Secondary form of IgAN or non-IgAN glomerulonephritis
- Kidney transplant
- Systemic diseases that may cause mesangial IgA deposition
- Poorly controlled BP (≥140/90 mmHg)
- Poorly controlled T1D or T2D

**Primary efficacy endpoint:** Time-weighted average of eGFR over 2 years

**Secondary efficacy endpoint:** Proportion of patients without microhematuria* in at least 2 follow-up visits at 12, 18, and 24 months

*A patient was defined as without microhematuria if the urine dipstick returned a result of negative or trace. The proportion of patients without microhematuria was analyzed using a logistic regression model including treatment, log-baseline UPCR, log-baseline eGFR, and geographic region as covariates. Patients without at least two valid results from 12 months onwards were excluded from the analysis. BP, blood pressure; eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; RAS, renin–angiotensin system; T1D, type 1 diabetes; T2D, type 2 diabetes; UPCR, urine protein-creatinine ratio.
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Nefcon 16 mg (n=182)</th>
<th>Placebo (n=182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>43 (21-69)</td>
<td>42 (20-73)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>117 (64.3)</td>
<td>123 (67.6)</td>
</tr>
<tr>
<td>Race, White, n (%)</td>
<td>138 (75.8)</td>
<td>137 (75.3)</td>
</tr>
<tr>
<td>Race, Asian, n (%)</td>
<td>43 (23.6)</td>
<td>40 (22.0)</td>
</tr>
<tr>
<td>Systolic BP, median (IQR)</td>
<td>126 (121-132)</td>
<td>124 (117-130)</td>
</tr>
<tr>
<td>Diastolic BP, median (IQR)</td>
<td>79 (76-84)</td>
<td>79 (74-84)</td>
</tr>
<tr>
<td>UPCR, g/gram, median (IQR)</td>
<td>1.28 (0.90-1.76)</td>
<td>1.25 (0.88-1.74)</td>
</tr>
<tr>
<td>eGFR CKD-EPI, mL/min/1.73 m², median (IQR)</td>
<td>56.1 (45.5-71.0)</td>
<td>55.1 (46.0-67.7)</td>
</tr>
</tbody>
</table>

BP, blood pressure; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IQR, interquartile range; UPCR, urine protein-creatinine ratio.
Primary endpoint: Time-weighted eGFR change

Primary endpoint: Time-weighted average change from baseline in eGFR over the 2-year period

- **eGFR treatment benefit** of 5.05 (95% CI 3.24, 7.38) mL/min/1.73 m² with Nefecon 16 mg/day vs placebo (p<0.0001)
- eGFR benefit of Nefecon observed by 9 months of treatment was maintained over 15 months of observational follow-up

Error bars represent standard error.
CI, confidence interval; eGFR, estimated glomerular filtration rate.
Secondary endpoint: Change in UPCR

Mean percentage change in UPCR from baseline

Error bars represent standard error.
CI, confidence interval; UPCR, urine protein-creatinine ratio.

30% reduction in UPCR with Nefecon compared with placebo observed after the 9-month treatment period sustained up to 2 years
Secondary endpoint: eGFR benefit by baseline UPCR

Baseline UPCR subgroup: <1.5 g/gram

Baseline UPCR subgroup: ≥1.5 g/gram

Mean absolute change in eGFR from baseline (mL/min/1.73 m²)

Month

Treatment phase

Observational follow-up period

Nefecon 16 mg/day

Placebo

Nefecon 16 mg/day

Placebo

eGFR benefit with Nefecon vs placebo was consistent irrespective of baseline UPCR

Error bars represent standard error.

eGFR, estimated glomerular filtration rate; UPCR, urine protein-creatinine ratio.
Secondary endpoint: Proportion of patients without microhematuria

Proportion of patients without microhematuria at different time points during observational follow-up

Comparison of Nefecon 16 mg/day vs placebo:
OR (95% CI): 2.5 (1.6, 4.1); p=0.0001

Of the 364 patients in the full analysis set, 158/182 patients in the Nefecon group and 152/182 patients in the placebo group had at least two valid urine dipstick results during the observational follow-up period.

CI, confidence interval; OR, odds ratio.
Conclusions

• Patients receiving 9 months of Nefecon treatment were significantly less likely than those receiving placebo to have microhematuria up to 15 months after the end of treatment
  – The proportion of patients without microhematuria was 59.5% versus 38.8% (p=0.0001) during the observational follow-up for Nefecon and placebo, respectively

• These results may be due to a reduction in IgA immune complex-mediated inflammation in the glomeruli with Nefecon and provide further evidence for the disease-modifying effect of Nefecon

IgA, immunoglobulin A.