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Analysis of the NefIgArd Part A study population confirms Nefecon reduces levels of dietary antigen-specific IgA in patients with IgA nephropathy

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1. Introduction

- **Nefecon**, the targeted-release formulation of budesonide, is delivered to the GALT of the terminal ileum, **a major site of IgA production**[1]
- The Phase 3 clinical trial, NefIgArd (NCT03643965), tested the efficacy of Nefecon in patients with **IgAN at high risk of progressive kidney disease despite optimized supportive care**[2]
- Treatment with Nefecon 16 mg/day **significantly reduced proteinuria after 9 months of treatment** compared with placebo (p=0.0003), and this effect was maintained, along with the **preservation of eGFR** (p<0.0001), over the 15-month off-drug observational follow-up period[2,3]

2. Objective

- This study investigated the effect of Nefecon treatment on circulating levels of dietary antigen-specific IgA, **secretory IgA**, and a marker of gut permeability, **FABP2**, in participants from Part A of the NefIgArd clinical trial

3. Methods

- The NefIgArd study was a randomized, double-blind, placebo-controlled, Phase 3 trial, comprised of two parts:
  1. **Part A: 9-month treatment period with 3-month off-drug observational follow-up**
  2. **Part B: 12-month additional observational follow-up period off study drug (Figure 1)**
- Circulating levels of secretory IgA, anti-gliadin IgA, anti-casein IgA, and FABP2 were measured in baseline serum samples and 3, 6, 9 and 12 months after randomization during Part A of the NefIgArd trial using enzyme-based immunosorbent assays
- Comparisons between placebo- and Nefecon-treated groups were made at each study time point using unpaired t-tests, **with a significance level of p<0.05**

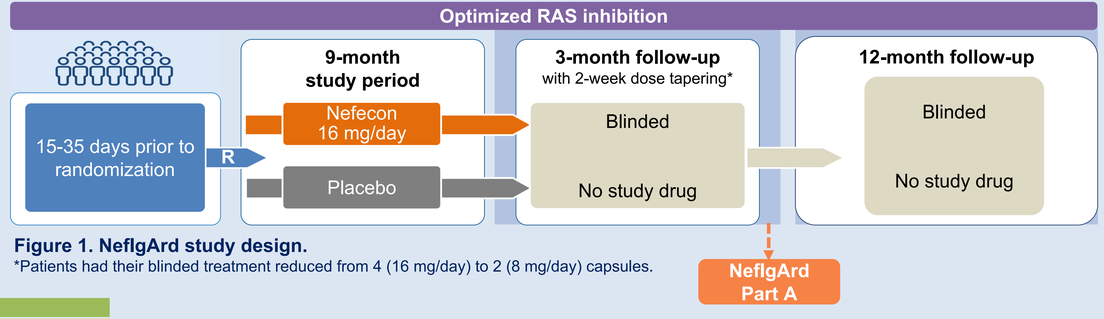

Figure 1. NefIgArd study design.
*Patients had their blinded treatment reduced from 4 (16 mg/day) to 2 (8 mg/day) capsules.

4. Results

- Treatment with **Nefecon 16 mg/day significantly reduced the levels of anti-gliadin IgA from baseline** at 3 months (**p=0.044**), 6 months (**p=0.029**), and 9 months (**p=0.027**; **Figure 2B**), **and the levels of anti-casein IgA** at 9 months (**p=0.023; Figure 2C**) compared to the placebo. These data are consistent with the Nefecon 16 mg/day results obtained in the Phase 2b NEFIGAN clinical trial (NCT01738035)
- No significant changes were seen in levels of secretory IgA (**Figure 2A**) or FABP2 (**Figure 2D**) from baseline between Nefecon 16 mg/day and placebo groups

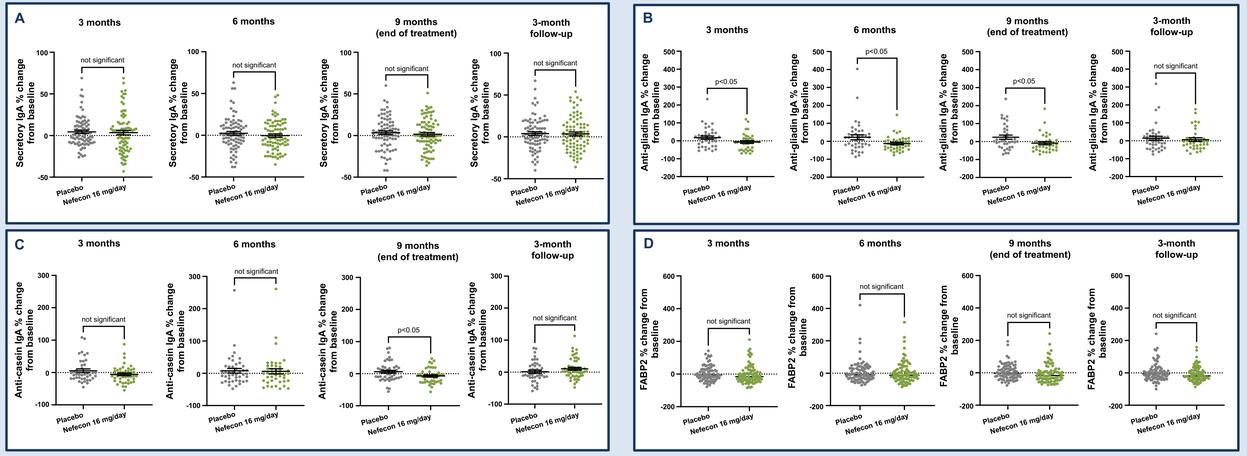

Figure 2. Levels of biomarkers in the serum of patients in the NefIgArd trial. Percentage change in the levels of secretory IgA **(A)**, anti-gliadin IgA **(B)**, anti-casein IgA **(C)**, and FABP2 **(D)** in the placebo and Nefecon 16 mg/day treatment groups at 3, 6, and 9 (end of treatment) months, and at the end of the 3-month follow-up, compared with baseline.

5. Discussion

- Reductions in IgA antibodies against mucosally encountered antibodies confirm a local mucosal effect of Nefecon in IgAN
- This effect is likely mediated by a direct action on GALT B-cell IgA production rather than an effect on gut permeability and increased antigen exclusion
- Additional cohort data are expected in the future

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eGFR, estimated glomerular filtration rate; FABP2, fatty acid–binding protein 2; GALT, gut-associated lymphoid tissue; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; R, randomization; RAS, renin–angiotensin system.

1. Barratt J, *et al. Kidney Int Rep* 2020;5:1620-1624. 2. Barratt J, *et al. Kidney Int* 2023;103:391-402. 3. Lafayette R, *et al. Lancet* 2023;402:859-870.

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