Analysis of the NefIgArd Part A study population confirms Nefecon suppresses circulating levels of IgA-containing immune complexes in IgA nephropathy

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Introduction

- **Nefecon** is the first treatment approved by the FDA and EMA for adult patients with **primary IgAN at risk of rapid disease progression**[1-3]
- This targeted-release formulation of budesonide, designed to deliver treatment to the ileal gut-associated lymphoid tissue (GALT), **significantly reduced proteinuria and preserved estimated glomerular filtration rate at 9 months** compared with placebo, in both the Phase 2b NEFIGAN and the Phase 3 NefIgArd clinical trials[4,5]
- Central to the multi-hit hypothesis, which describes the pathogenic steps required for the development of IgAN, is the formation of **circulating immunoglobulin A-containing immune complexes (IgA-IC)**[6,7]
- These IgA-IC have a propensity to deposit within the glomerular mesangium, where they **can trigger glomerular inflammation and scarring**[6,7]
- A key contributor to IgA-IC formation in IgAN is an **excess of poorly *O*-galactosylated IgA1 (Gd-IgA1)** in the circulation, which is believed to be predominantly synthesized in the GALT[5-7]
- Results from the Phase 2b NEFIGAN trial (NCT01738035) and the interim (Part A) results from the Phase 3 NefIgArd trial (NCT03643965) showed that 9 months' treatment with **Nefecon 16 mg/day significantly reduced circulating levels of Gd-IgA1**[8,9]
- In the NEFIGAN trial, this reduction in Gd-IgA1 was also **associated with a significant reduction in circulating IgA-IC**[8]

Objectives

- This study investigated the effect of Nefecon on circulating levels of IgA-IC in participants of the interim (Part A) section of the NefIgArd clinical trial

Materials and methods

- The NefIgArd study was a randomized, double-blind, placebo-controlled, Phase 3 trial in patients with IgAN at high risk of progressive kidney disease despite optimized support care. It was comprised of two parts:
  - **Interim (Part A): 9-month treatment period with 3-month observational follow-up period off study drug**
  - **Full 2-year (Part B): 12-month additional observational follow-up period off study drug (Fig. 1)**
- IgA-IC levels in 160 participants of the NefIgArd trial (interim [Part A]) were measured in serum samples collected at baseline and at 3, 6, 9, and 12 months post randomization using an in-house sandwich enzyme-linked immunosorbent assay designed to detect IgG-containing IgA-IC
- 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**

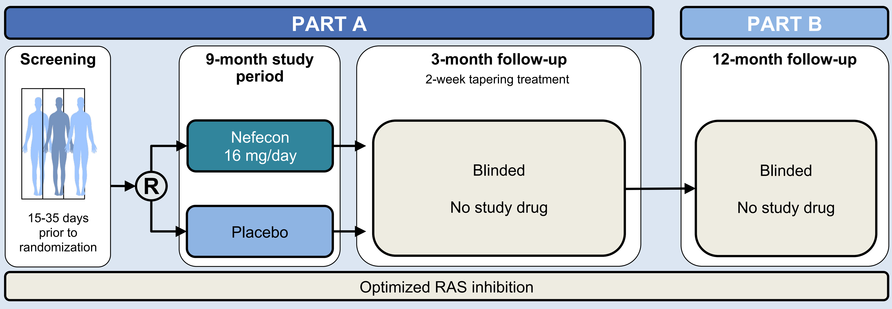

Fig. 1. NefIgArd study design

Results

- Levels of IgA-IC were **not significantly different** in the Nefecon 16 mg/day and placebo groups at baseline **(Fig. 2A)**
- Treatment with **Nefecon 16 mg/day significantly reduced levels of circulating IgA-IC** compared with baseline at 3 months (p=0.0055; **Fig. 2B**), 6 months (p=0.047; **Fig. 2C**), and 9 months (p=0.0169; **Fig. 2D**) vs placebo
- Levels of IgA-IC in the Nefecon 16 mg/day group **returned to levels seen in the placebo group** at the 3-month follow-up **(Fig. 2E)**

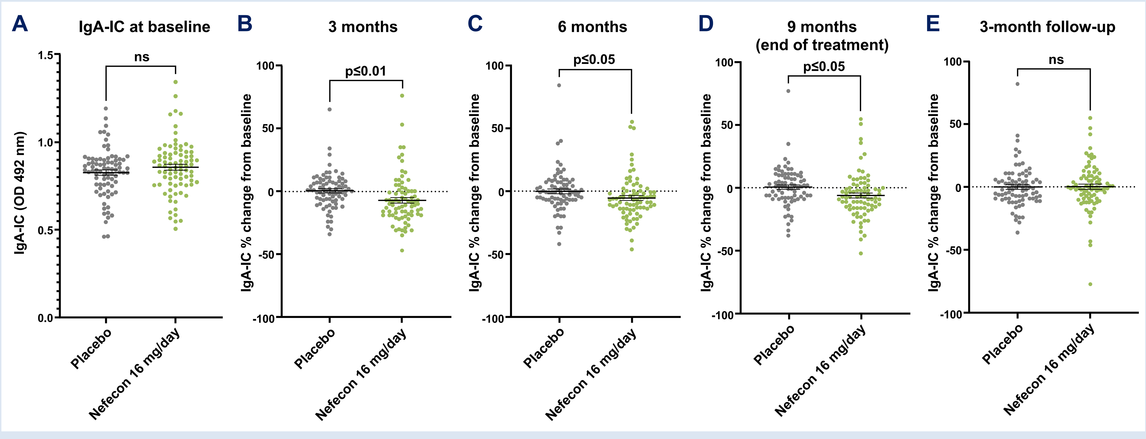

Fig. 2. Levels of IgA-ICs in serum of patients in the NefIgArd trial. Levels of IgA-IC in the placebo and Nefecon 16 mg/day groups at baseline **(A)**. Percentage change in the levels of IgA-IC in the placebo and Nefecon 16 mg/day treatment groups at 3 months **(B)**, 6 months **(C)**, 9 months (end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

Discussion

- These data **validate the results seen in the NEFIGAN study** and confirm the disease-modifying action of Nefecon in patients with IgAN
- By supressing both Gd-IgA1 and IgA-IC, the two key foundation stones of the multi-hit hypothesis, treatment with **Nefecon offers an unprecedented opportunity** to target the fundamental immune abnormalities that drive mesangial IgA deposition and the development of IgAN

EMA, European Medicines Agency; FDA, Food and Drug Administration; GALT, gut-associated lymphoid tissue; Gd-IgA1, poorly *O*-galactosylated immunoglobulin A type 1; IgA, immunoglobulin A; IgA-IC, immunoglobulin A-containing immune complexes; IgAN, immunoglobulin A nephropathy; IgG, immunoglobulin G; ns, not significant; OD, optical density; RAS, renin–angiotensin system.

1. Calliditas Therapeutics AB. Press Release March 12, 2023. Available at: https://www.calliditas.se/en/calliditas-announces-primary-endpoint-successfully-met-in-phase-3-nefigard-trial-evaluating-nefecon-in-iga-nephropathy/ (accessed August 8, 2023). 2. Calliditas Therapeutics AB. Kinpeygo (budesonide) EU SmPC. 2023. 3. Calliditas Therapeutics AB. TARPEYO (budesonide) US PI. 2021. 4. Barratt J, *et al. Kidney Int* 2022;103:391-402. 5. Barratt J, *et al. Kidney Int Rep* 2020;5:1620-1624. 6. Barratt, J. *et al. Semin Immunopathol* 2007;29:427-443. 7. Lai KN, *et al. Nat Rev Dis Primers* 2016;11:160001. doi: 10.1038/nrdp.2016.1. 8. Bhachu, JS, *et al*. Poster presentation at IIgANN, 27-29 September 2018, Buenos Aires, Argentina. 9. Molyneux K, *et al*. Poster presentation at ASN Kidney Week, 3-6 November 2022, Orlando, FL, USA.

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