Analysis of the NefIgArd Part A study population confirms that Nefecon modulates circulating levels of the chemokines CXCL5, CCL11, and CCL13 in IgA nephropathy

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Background

- **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]
  - Approval was based on the interim (Part A) results of the Phase 3, double-blinded, randomized controlled NefIgArd trial, which included a 9-month treatment course with Nefecon 16 mg/day or placebo, plus a 3-month follow-up period[1-3]
  - The full results from the **complete 2-year study**, comprising 9 months of treatment and 15 months of follow-up, have been presented[4]
- This targeted-release formulation of budesonide, designed to deliver treatment to the ileal GALT, **significantly reduced proteinuria and preserved eGFR at 9 months** compared with placebo in both the Phase 2b NEFIGAN and the Phase 3 NefIgArd clinical trials[4-6]
  - Nine months of treatment with Nefecon 16 mg/day also resulted in **significant reductions in circulating levels of the key pathogenic biomarkers Gd-IgA1 and IgA/IgG immune complexes** in the NEFIGAN trial[7]
  - These reductions were associated with a pattern of changes in serum chemokine and cytokine levels that, following pathway analysis, congregated within the intestinal immune network for IgA production[7-9]

Objectives

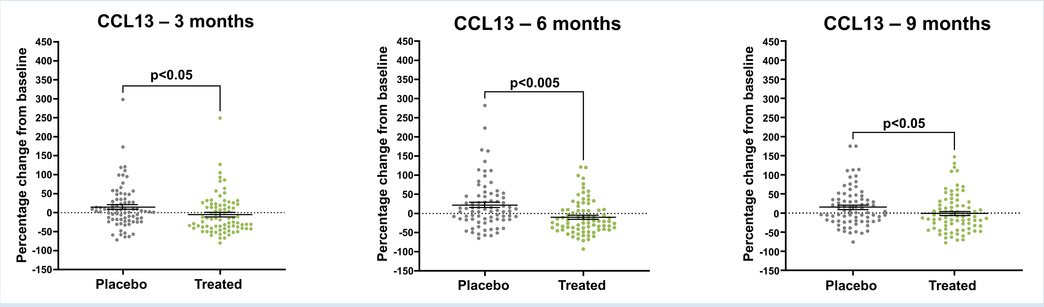
- To investigate the effect of Nefecon 16 mg/day on circulating levels of three chemokines, **CXCL5, CCL11, and CCL13**, in the NefIgArd interim (Part A) study population

Materials and methods

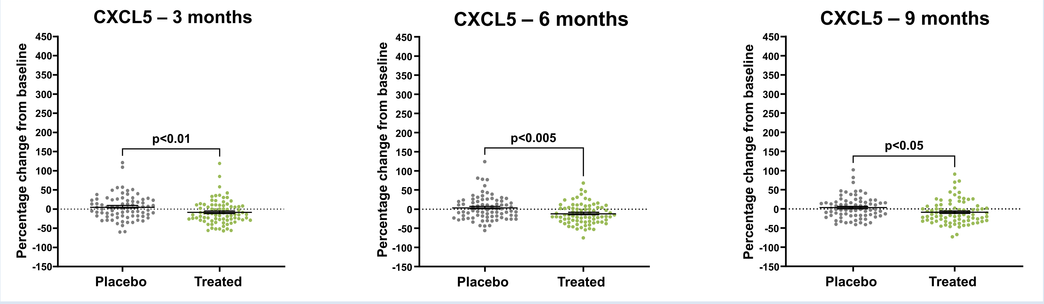
- Levels of CXCL5, CCL11, and CCL13 were measured in serum samples (at baseline, 3-, 6-, and 9-months post-randomization) from 160 participants in the NefIgArd trial (interim Part A results) using Luminex technology
- Comparisons between placebo- and Nefecon-treated groups were made at each study time point using unpaired t-tests, with a **significance level of p<0.05**

Results

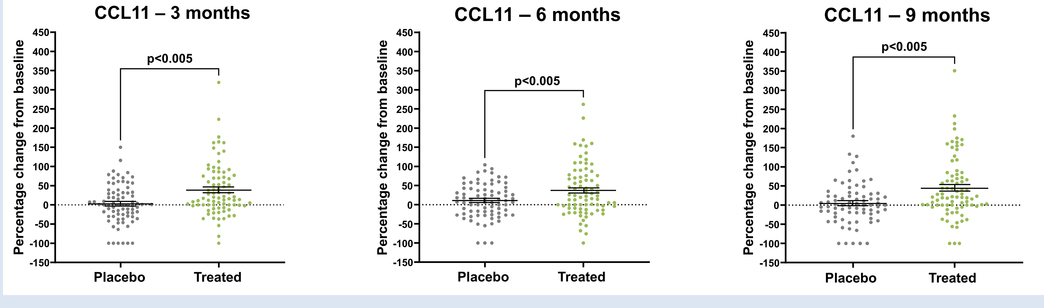
- Treatment with Nefecon resulted in a **significant reduction in the levels of CCL13** at end of treatment, compared with placebo (3 months, p=0.022; 6 months, p=0.0004; 9 months, p=0.04)



- **Levels of CXCL5 were also significantly reduced by Nefecon** compared with placebo (3 months, p=0.009; 6 months, p=0.001; 9 months, p=0.0128)



- By contrast, Nefecon treatment resulted in **significant increases in the levels of CCL11** compared with placebo (3 months, p=0.003; 6 months, p=0.0037; 9 months, p=0.0004)



- **These data confirm findings from the NEFIGAN study** that show treatment with Nefecon results in a coordinated pattern of responses in chemokines, cytokines, and B-cell survival factors that map to the Kyoto Encyclopedia of Genes and Genomes pathway for the intestinal immune network for IgA production
- Further work will add to these analyses and validate Nefecon-mediated modulation of other key members of this network

Conclusion

- These data provide further evidence for a **mucosal mechanism of action of Nefecon in IgAN** and support previous observations that disordered lymphocyte trafficking and mucosal dysregulation are fundamental pathogenic pathways in IgAN

eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GALT, gut-associated lymphoid tissue; Gd-IgA1, poorly *O*-galactosylated immunoglobulin A type 1; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IgG, immunoglobulin G.

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. Lafayette R, *et al. Lancet* 2023;402:859-870. 5. Barratt J, *et al. Kidney Int* 2023;103:391-402.
6. Barratt J, *et al. Kidney Int Rep* 2020;5:1620-1624.
7. Bhachu JS, *et al.* Presented at the 15th International Symposium on IgA Nephropathy, Buenos Aires, Argentina. 27-29 September 2018; abstract 0038. 8. Molyneux K, *et al.* Presented at ASN Kidney Week, 22-25 October 2020; abstract FR-OR37.
9. Molyneux K, *et al.* Presented at ASN Kidney Week, 27-28 November 2021; abstract PO1453.

Scan to view Nefecon presentations, posters, and materials

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