**Introduction**

- **Nefcon** is the first treatment approved by the FDA and EMA for adult patients with primary IgAN at risk of rapid disease progression.1
- This target-oriented 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 NEFISEAN and the Phase 3 Nefcon clinical trials.2
- 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).3,4
- These IgA-IC have a propensity to deposit within the glomerular mesangium, where they can trigger glomerular inflammation and scarring.5,6
- 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.7
- Results from the Phase 2a NEFISEAN trial (NCT03723835) and the interim (Part A) results from the Phase 3 Nefcon trials (NCT03643985) showed that 9 months' treatment with Nefcon 16 mg/day significantly reduced circulating levels of Gd-IgA1.8
- In the NEFISEAN trial, this reduction in Gd-IgA1 was also associated with a significant reduction in circulating IgA-IC.9

**Objectives**

- This study investigated the effect of Nefcon on circulating levels of IgA-IC in patients of the interim (Part A) section of the Nefcon clinical trial.

**Materials and methods**

- The Nefcon 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:
  - **Part (A):** 9-month treatment period with 3-month observational follow-up period off study drug
  - **Part (B):** 12-month additional observational follow-up period off study drug

**Results**

- Levels of IgA-IC were not significantly different in the Nefcon 16 mg/day and placebo groups at baseline (Fig. 2A)
- Treatment with Nefcon 16 mg/day significantly reduced levels of circulating IgA-IC compared with baseline at 3 months (p=0.0005; 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 Nefcon 16 mg/day group returned to levels seen in the placebo group at the 3-month follow-up (Fig 2E)

**Discussion**

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