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# Modeling based on NeflgArd 2-year eGFR total slope predicts long-term clinical benefit of Nefecon in a real-world IgAN population



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#### INTRODUCTION

- IgAN is a chronic autoimmune kidney disease associated with a very high lifetime risk of kidney failure<sup>1,2</sup>
- Kidney failure severely compromises patients' quality of life,<sup>3</sup> with poor long-term outcomes and high economic burden.<sup>4,5</sup> It is vital to delay the time to kidney failure as long as possible in patients with IgAN
- Nefecon is a novel, oral, targeted-release budesonide formulation designed to treat IgAN<sup>6</sup>
- Results from the full 2-year Phase 3 NeflgArd study demonstrated an eGFR treatment benefit vs placebo and durable proteinuria reduction after 9 months of treatment and 15 months of observational follow-up<sup>7</sup>

#### AIN

• To predict **the median time to the clinical outcome** of kidney failure, eGFR <15 mL/min/1.73 m<sup>2</sup>, or sustained doubling of serum creatinine with Nefecon compared with supportive care only based on the Nefecon 2-year eGFR total slope treatment effect<sup>7</sup>

#### METHODS

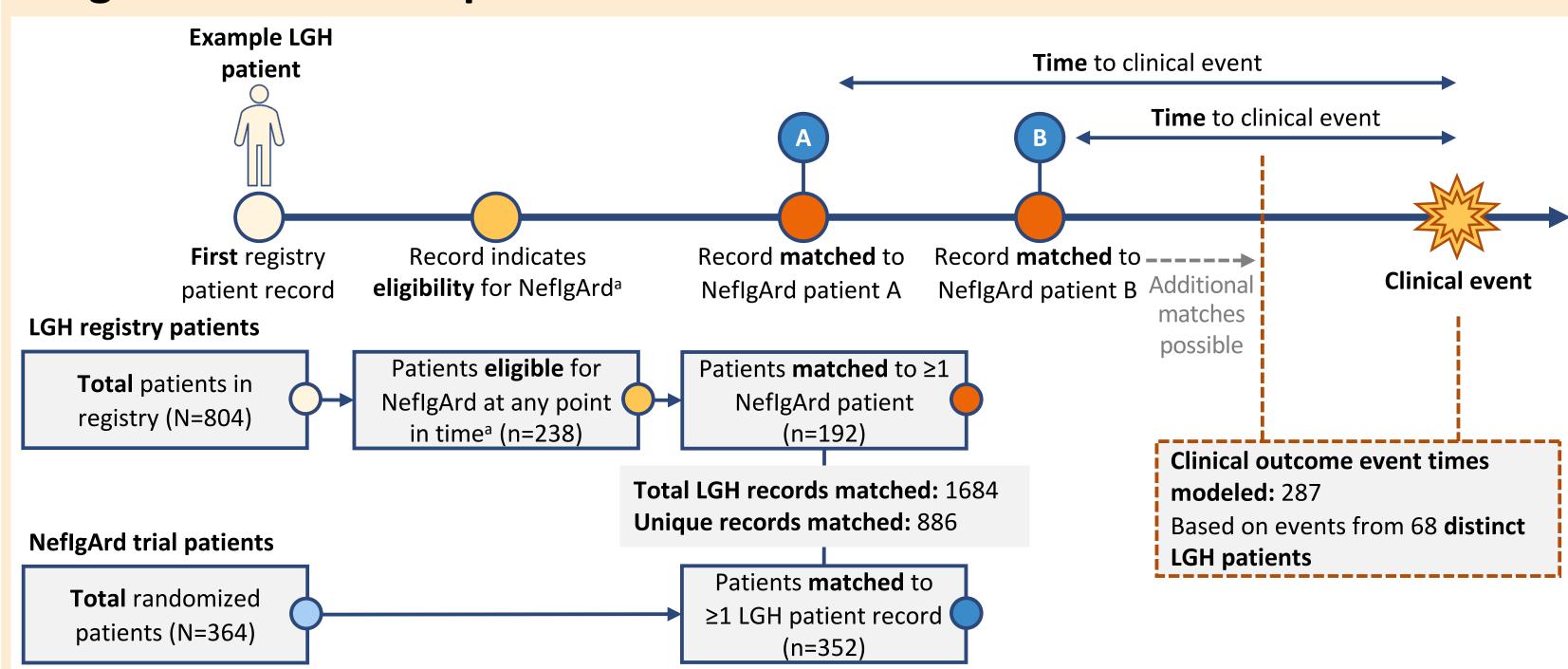
- Patient records from a long-term Leicester General Hospital (LGH) registry (n=804 patients), collected between 1992 and 2020, were used to model the estimated median time to the clinical outcome for a reference group receiving supportive care only (including renin—angiotensin system inhibitors, lifestyle modifications and blood pressure control). Each LGH patient generated multiple records over time with differing eGFR and UPCR values
- A total of 352 of the 364 patients recruited in the NeflgArd trial were each matched to a maximum of 5 distinct patients from the LGH registry, when their baseline UPCR was within 25% and their eGFR within 5 mL/min/1.73 m<sup>2</sup> of an LGH patient record<sup>a</sup>
  - If the same LGH patient record was matched to >1 NeflgArd patient, it was used only once in the modeling of LGH data
- The treatment benefit for 2-year eGFR total slope with Nefecon 16 mg per day vs placebo was applied to **the linear regression analysis** of 2-year eGFR total slope with the log HR of clinical outcome, from a published meta-analysis involving **60,620 patients** with chronic kidney disease to calculate an associated HR for time to clinical outcome<sup>8</sup>
- A Weibull model was fitted to the matched LGH data and the HR used to predict time to clinical outcome for Nefecon assuming a common shape parameter

<sup>a</sup>12 patients in the NeflgArd trial were either not randomized to treatment or did not have baseline eGFR/UPCR values matching LGH patient records.

#### RESULTS

A total of **352 patients from the NeflgArd trial** were matched to 886 unique records from **192 patients from LGH** based on UPCR and eGFR values **(Figure 1)** 

Figure 1: Cohort disposition



<sup>a</sup>Based on UPCR and eGFR eligibility criteria.

**Baseline** eGFR and UPCR values were **similar** between the NeflgArd patients and matched LGH records (**Table 1**)

**Table 1: Cohort demographics** 

	NeflgArd (n=352)	LGH (n=886)	Total (N=1238)
eGFR (mL/min/1.73 m <sup>2</sup> ), n	352	886	1238
Mean (SD)	52.5 (13.1)	53.7 (13.1)	53.4 (13.1)
Median (IQR)	51.0 (42.5-62.0)	52.0 (43.0-62.0)	51.6 (43.0-62.0)
UPCR (g/g), n	352	852 <sup>a</sup>	1204
Mean (SD)	1.47 (0.83)	1.64 (0.94)	1.59 (0.91)
Median (IQR)	1.26 (0.90-1.74)	1.37 (0.98-2.09)	1.32 (0.96-2.00)

MDRD equation used for eGFR.

<sup>a</sup>In a small number of cases, if UPCR records were not available from patients from the LGH registry, matching was based on UACR.

- In the full 2-year NeflgArd trial, 2-year eGFR total slope was improved by **2.78 mL/min/1.73 m<sup>2</sup> per year** (95% CI 1.39, 4.17) when analyzed using the 2-phase linear spline mixed-effect model. When applied to the linear regression of Inker *et al.*,<sup>8</sup> **a HR of 0.38** (95% CI 0.21, 0.63) was predicted for the clinical outcome (i.e., **a 62% reduction**) (**Figure 2**)
- This is consistent with the significantly reduced time to 30% eGFR reduction from baseline or kidney failure (HR 0.45 [95% CI 0.26, 0.75]) seen with Nefecon vs placebo in the NeflgArd trial<sup>7</sup>

### RESULTS (CONT.)

# Figure 2: Relationship between treatment effects on 2-year eGFR slope and clinical outcome

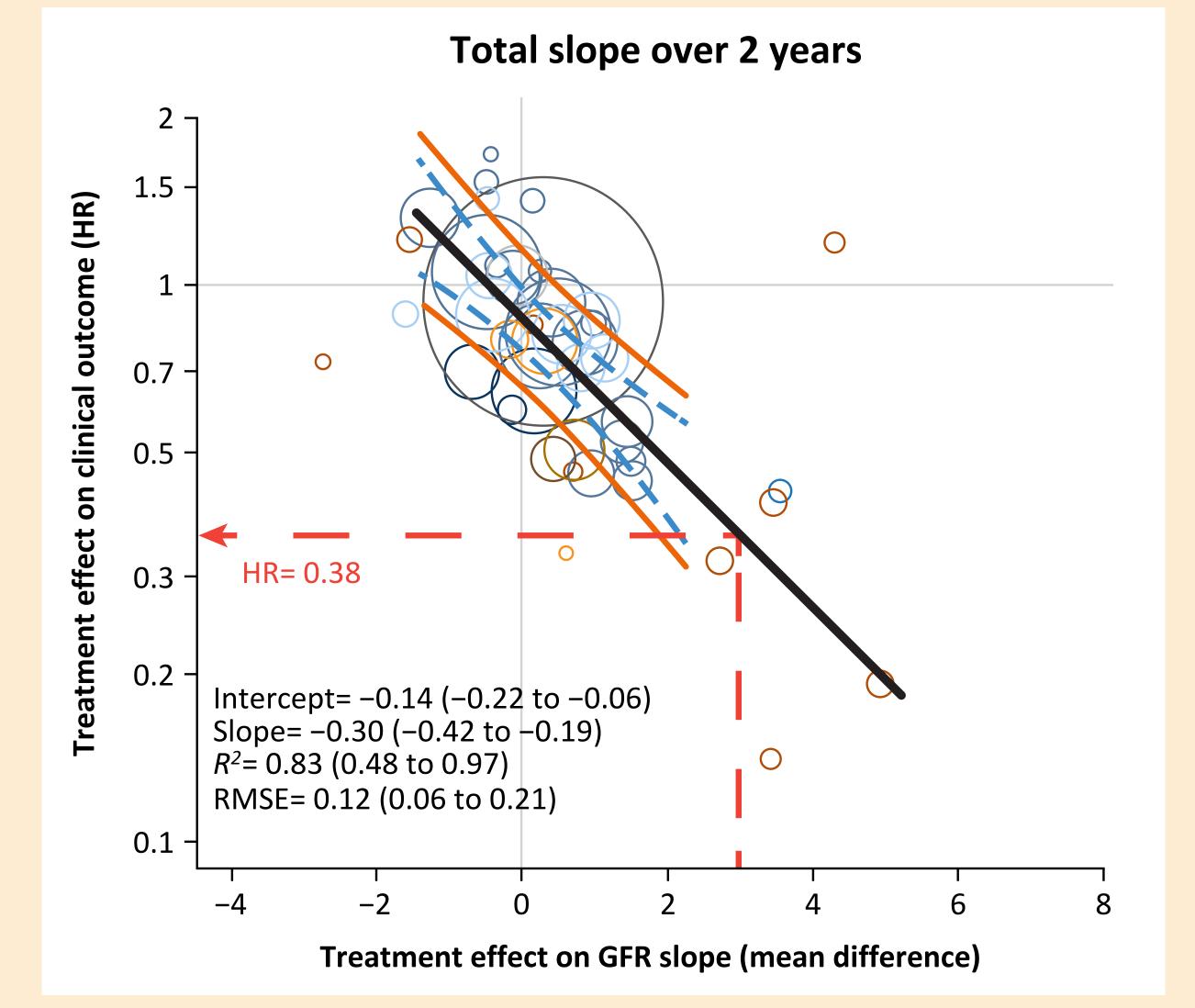
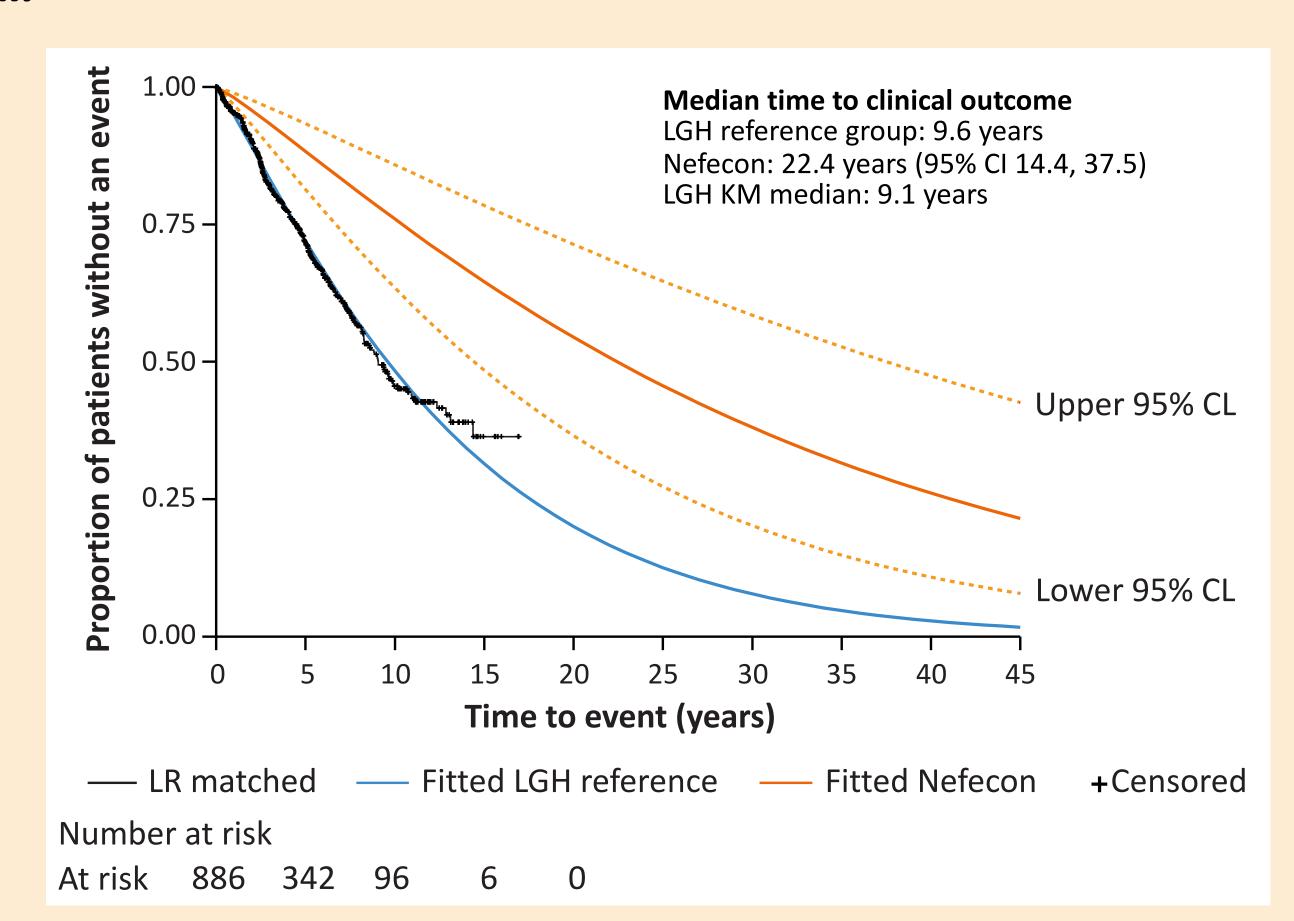


Figure adapted from Inker et al. 2019.<sup>8</sup> Black line represents the line of best fit between the treatment effects on 2-year eGFR slope and the clinical outcomes. The dashed blue lines are the associated 95% CIs for the mean effect, and the dotted orange lines represent the 95% prediction intervals for outcomes from the individual trials.

 The best estimate of the median delay to clinical outcome attributed to Nefecon was 12.8 years (95% CI 4.8, 27.9)
 (Figure 3)

Figure 3: Time to clinical outcome estimate from LGH registry data and estimated outcomes for Nefecon 16 mg based on the difference in 2-year eGFR total slope in NeflgArd<sup>7</sup> and the meta-analysis by Inker et al.<sup>8</sup>



#### RESULTS (CONT.)

 The proportion of patients who would be expected to have a clinical outcome event within 10 years was 24% in patients treated with Nefecon, compared with 52% in patients receiving supportive care only, a relative reduction of approximately 50%

#### CONCLUSIONS

These modeling analysis findings, along with the positive impact seen on clinical endpoints in the full 2-year NeflgArd trial data, indicate that Nefecon exerts a substantial disease-modifying effect on IgAN, potentially delaying the onset of clinical outcomes by many years

#### REFERENCES

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#### ABBREVIATIONS

rate; GFR, glomerular filtration rate; HR, hazard ratio; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; KM, Kaplan—Meier; LGH, Leicester General Hospital; LR, linear regression; MDRD, Modification of Diet in Renal Disease; RMSE, root mean squared error; SD, standard deviation; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio; vs, versus.

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CI, confidence interval; CL, confidence level; eGFR, estimated glomerular filtration

**DISCLOSURES** 

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