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Budesonide delayed-release capsules to reduce proteinuria in adults with primary immunoglobulin A nephropathy

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ABSTRACT

Introduction: Immunoglobulin A nephropathy (IgAN) is characterized by mesangial deposition of immune complexes containing galactose-deficient IgA1 (Gd-IgA1). This Gd-IgA1 is believed to originate from mucosally sited B cells, which are abundant in the Peyer's patches-rich distal ileum. Nefecon is a targeted-release form of budesonide developed to act in the distal ileum, thereby exerting a direct action on the mucosal tissue implicated in the pathogenesis of the disease.

Areas covered: This review discusses IgAN pathophysiology and provides an overview of the current therapeutic landscape, focusing on Nefecon, the first drug to receive accelerated US approval and conditional EU approval for the treatment of patients with IgAN at risk of rapid disease progression.

Expert opinion: Nefecon trial data thus far have demonstrated a promising efficacy profile, with a predictable pattern of adverse events. Treatment with Nefecon for 9 months reduces proteinuria substantially (Part A of the Phase 3 trial and the Phase 2b trial). A nearly complete prevention of deterioration of renal function has been observed at 12 months in patients at greatest risk of rapid disease progression. Long-term data from Part B of the Phase 3 study will provide 24-month data, furthering understanding of the durability of the 9-month treatment course.

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Budesonide; glomerular filtration rate; glomerulonephritis; glucocorticoids; Immunoglobulin A; nephropathy; Peyer's patches; proteinuria

1. Introduction

Immunoglobulin A nephropathy (IgAN) is a rare, chronic autoimmune kidney disease with an incidence of approximately 2.5 per 100,000 individuals worldwide [1,2]. Despite its relative rarity, IgAN is the most common primary glomerular disease globally [3]. The incidence of IgAN varies by country, with China experiencing the highest rates; IgAN accounts for nearly half of all glomerular disease in this population [1,4–7]. This disparity is hypothesized to be due to differences in underlying pathogenic and immune regulatory pathways in different populations [6].

As a chronic autoimmune disease with no current cure, IgAN results in progressive kidney scarring and damage, frequently leading to kidney failure in the long term, with up to half of diagnosed patients progressing to kidney failure within 20 years of diagnosis [8–10]. Often asymptomatic in its early stages, IgAN is mostly diagnosed following episodes of visible hematuria or as an incidental finding of non-visible hematuria and/or proteinuria during health screening [10,11]. Among patients with proteinuria or renal insufficiency at diagnosis, 30–40% and 50–70%, respectively, are expected to progress to kidney failure within 20 years from diagnosis [8,10]. It is important to recognize that most patients are diagnosed in their 20s and 30s, and so a 20-year time frame means that most patients will still only be in their 40s and 50s and still have on average another 30–40 years of life expectancy. One must consider lifetime risk of kidney failure in all patients with IgAN, which is likely to be considerable, although current epidemiological data are lacking in this regard. Although kidney transplantation is the treatment option of choice for patients with kidney failure, up to 50% of patients with IgAN will experience a disease recurrence following transplantation [9,12].

2. Role of inflammation and immunity in IgA nephropathy

2.1. The 4-hit hypothesis

Our current understanding of the pathology of IgAN is that there are at least 4 distinct pathological 'hits' resulting in kidney injury and scarring; this is termed the 4-hit hypothesis [12,13].

The first 'hit' refers to an excess of poorly *O*-galactosylated IgA1 in the circulation. Gd-IgA1 is prone to self-aggregation and formation of circulating IgA immune complexes with other serum proteins. In susceptible individuals, the presence of Gd-IgA1 elicits an autoimmune response with the production of specific anti-Gd-IgA1 IgG and IgA antibodies (the second 'hit'), which amplifies the formation of circulating immune complexes, constituting the third 'hit' [12–14]. The fourth and final 'hit' is the deposition of these circulating IgA-containing immune complexes in the glomerular mesangium, which occurs due to a combination of mesangial trapping and

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Article highlights

- IgA nephropathy (IgAN) is a rare, chronic kidney disease that frequently progresses to kidney failure; effective and well-tolerated treatment options have been lacking
- Nefecon is a unique formulation of budesonide designed to be released in the Peyer's patches-rich distal ileum, where initial key pathogenic steps occur. The improvement in proteinuria and stabilization of estimated glomerular filtration rate in patients with IgAN at risk of rapid disease progression suggests Nefecon is a potentially disease-modifying treatment with a favorable safety profile compared with systemic glucocorticoids currently used in clinical practice
- Nefecon is the first accelerated FDA-approved and conditionally EMA-approved treatment for patients with IgAN
- An increased understanding of the pathophysiology of the disease, combined with a change in the regulatory landscape, has stimulated development of several new therapeutic approaches that are currently in development and will likely reshape the treatment landscape for patients with IgAN

an increased affinity of IgA immune complex constituents for the extracellular mesangial matrix [12–14]. The accumulation of IgA-containing immune complexes in the mesangium leads to mesangial cell activation with release of proinflammatory and profibrotic mediators, which in turn promote glomerular inflammation and subsequent scarring. Simultaneous glomerular complement activation through both the lectin and alternative pathways amplifies these inflammatory and fibrotic responses and promotes glomerular and downstream tubulointerstitial injury. The extent of the mesangial reaction to IgA immune complex deposition is highly variable for uncertain reasons, but this variability likely explains the marked heterogeneity in rates of disease progression seen in patients with IgAN [13].

2.2. The contribution of gut-associated lymphoid tissue to the development of IgA nephropathy

The mucosal-associated lymphoid tissue generates the majority of IgA in the body, with gut-associated lymphoid tissue (GALT) being responsible for a daily secretion of approximately 40–60 mg/kg of IgA in the intestinal lumen (mucosal IgA represents 15% of total immunoglobulins produced throughout the body) [15].

The most important immunological element of the GALT is the Peyer's patches [16–18]. They comprise at least five aggregated lymphoid follicles, are located in the mucosal layer of the intestine, and serve as the major antigen sampling and inductive sites of the GALT [18,19]. Almost half of all Peyer's patches are located in the distal 25 cm of the ileum [20]. Peyer's patches are thought to be the main source of IgA class-switched mucosal B cells and terminally differentiated IgA-secreting plasma cells. These plasma cells reside in the intestinal lamina propria and secrete IgA, which is typically transported across the mucosal epithelium [18,21].

A number of observations support the importance of mucosal-derived IgA as a major source of pathogenic IgA in IgAN. Elevated serum levels of mucosally derived secretory IgA have been demonstrated in IgAN, levels increase after mucosal immunization, and secretory IgA has been identified in mesangial IgA deposits [22,23]. Elevated serum levels of IgA antibodies specific for food antigens, mucosal vaccines, and gut-associated bacteria have also been reported in patients with IgAN, which may be indicative of GALT dysregulation [24–26]. Recent research shows increased levels of gut-homing IgA-positive B cells in patients with IgAN compared with healthy individuals; moreover, modulating the gut microbiota in a mouse model of IgAN was observed to positively influence IgAN phenotype [27,28]. It has been shown that the physicochemical properties of mucosally derived IgA are the same as Gd-IgA1 [29,30]. Mucosal IgA is polymeric, low affinity, and poorly *O*-galactosylated, and its expression is elevated in the serum of patients with IgAN. Of note, the intestinal immune cascade leading to IgA production has been found to be the most enriched Kyoto Encyclopedia of Genes and Genomes pathway in IgAN [18,31]. Additionally, several alleles identified through genome-wide association studies have been found to be directly associated with an increased risk of inflammatory bowel disease, with intestinal epithelial barrier integrity, or with response to mucosal pathogens. Collectively, this evidence is in line with the current knowledge on secondary causes of IgAN, including disorders such as inflammatory bowel disease and celiac disease [32]. Therefore, although not yet proven conclusively, the body of information accumulated to date strongly suggests a role for mucosal immune dysregulation in the pathogenesis of IgAN.

3. IgA nephropathy treatment landscape overview

The 2021 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on Glomerular Disease outlines that the primary focus of management of IgAN should be optimized goal-directed supportive care [33]. This comprises lifestyle modification, including smoking cessation, weight loss or control, exercise, and restriction of salt intake; other preventive cardiovascular interventions where necessary; tight control of blood pressure; and, irrespective of the presence of hypertension, use of maximal tolerated doses of renin-angiotensin system (RAS) inhibitors to reduce proteinuria.

The 2021 KDIGO guideline defines patients with persistent proteinuria >1 g/24 hours despite at least 90 days of optimized goal-directed supportive care as being at increased risk of progression to kidney failure. The guideline recommends that these patients should be offered the opportunity to take part in a clinical trial; should this option not be feasible, systemic glucocorticoids may be considered after a discussion with the patient regarding the important risk of treatment-emergent toxicity [33].

The guideline also acknowledges that there is no evidence of benefit from use of traditional immunosuppressive agents such as cyclophosphamide, azathioprine, mycophenolate mofetil, and rituximab and that the long-term efficacy and safety of systemic glucocorticoids are uncertain [33,34]. The use of tonsillectomy as a purported treatment for IgAN (by eliminating exposure to tonsil-derived IgA) is also referred to in the guideline; however, supportive data for this strategy (outside of specific geographic regions) are very limited.

The KDIGO group identified a number of critical research recommendations based on current unmet need in IgAN and strongly endorsed the evaluation of therapeutic strategies that minimize or avoid systemic glucocorticoid exposure.

3.1. Therapeutic options in development

An increased understanding of the pathophysiology of IgAN, combined with a change in the regulatory landscape, has strongly stimulated the development of several new therapeutic approaches that will likely transform the treatment landscape for patients with IgAN [35]. Both immunological and non-immunological approaches are currently being evaluated.

From a non-immunological perspective, 2 endothelin type A receptor antagonists are being studied in Phase 3 trials: sparsentan in the PROTECT trial and atrasentan in the ALIGN trial [36]. Recent data presented on the sodium-glucose cotransporter-2 inhibitors (SGLT2is) dapagliflozin and empagliflozin demonstrated significant kidney function protection in non-diabetic kidney disease, and a large meta-analysis of all SGLT2i clinical trial data supports a renoprotective effect [37–39]. Although not approved specifically for IgAN, the use of SGLT2is in patients with IgAN is increasing.

In parallel, immunological approaches are currently being evaluated to inhibit B cell synthesis of Gd-IgA1 and anti-Gd-IgA1 autoantibodies (Hits 1–3), and include drugs that target the B cell-activating factor (BAFF/BLyS)/a proliferation-inducing ligand (APRIL) axis (atacicept, telitacicept, sibeprenlimab, and BION1301) [40–43]; CD38 (felzartamab and TAK-079) [44,45]; and co-stimulatory signaling (tegoprubart) [46]. A separate immunological approach is aimed at targeting the downstream pathogenic pathway of complement activation within the kidneys. Glomerular complement activation through both the lectin and alternative pathways amplifies the inflammatory and fibrotic responses to mesangial IgA immune complex deposition and promotes glomerular injury (Hit 4). Inhibitors of the lectin pathway (narsoplimab), the alternative pathway (iptacopan, IONIS-FB-LRx, and ALXN2050), and the common terminal pathway (pegcetacoplan, cemdisiran, ravulizumab, and avacopan) are at various stages of development [43,47–50].

4. Introduction to Nefecon

The active ingredient in Nefecon is budesonide, which is a highly potent, locally acting glucocorticoid that has been widely used in a number of products where it can be locally applied to a mucosal surface. Budesonide has not been developed for systemic treatment due to its extensive metabolism in the gut mucosa and the liver, limiting the systemic exposure [51]. Budesonide was originally developed for inhaled treatment of bronchial asthma in 1981 and later formulated for enteric use for the treatment of inflammatory bowel disease [52].

4.1. Mechanism of action

Budesonide works by binding to glucocorticoid receptors, leading to upregulation of anti-inflammatory processes and downregulation of pro-inflammatory ones, and ultimately blocking the immune mechanisms that lead to the generation of Gd-IgA1. Due to the increasing recognition of the role of the GALT, particularly the B cell-containing Peyer's patches, in the generation of pathogenic Gd-IgA1 and subsequent formation of IgA-containing immune complexes, Nefecon was developed with the intent to achieve a local pharmacological effect by directing release of budesonide to the Peyer's patch-rich distal ileum before being rendered mostly inactive during its passage through the portal circulation, thus minimizing the risk of side effects associated with systemic glucocorticoids [53]. The question of what level of systemic budesonide patients are exposed to with Nefecon is a complex one; however, comparative analyses based on the suppression of endogenous cortisol suggest that 16 mg of Nefecon would result in the approximate level of suppression as 8 mg of prednisolone [54].

The intended target of Nefecon is mucosal resident B cells in the ileal GALT. Specifically, Nefecon is designed to inhibit B cell proliferation, IgA class-switch recombination, and B cell maturation in the ileal Peyer's patches, as well as to inhibit plasma cell secretion of Gd-IgA1 in the ileal lamina propria. Consequently, it is hypothesized that this will lead to reductions in the levels of Gd-IgA1 and nephrotoxic immune complexes in the systemic circulation, thereby preventing the downstream mesangial IgA deposition (Figure 1).

This mechanism of action of Nefecon is supported by exploratory analyses of patient serum samples that were collected in the Phase 2b NEFIGAN study. Analyses published to date have shown dose-dependent reductions in Gd-IgA1 (Hit 1) and IgA-containing immune complexes (Hit 3), alongside changes in multiple biomarkers of GALT activity, including gut antigen-specific IgA antibodies, GALT-directing chemokines, and B cell survival factors including BAFF [55–57].

5. Clinical trial evidence

5.1. Efficacy

5.1.1. The proof-of-concept and Phase 2b study

A proof-of-concept study was undertaken in 16 patients with IgAN who received the enteric formulation of budesonide (Nefecon) 8 mg once daily for 6 months, followed by a 3-month follow-up period. On-treatment, median urinary albumin excretion decreased by 23% relative to baseline, with further reductions that reached 40% 2 months after treatment discontinuation. No major corticosteroid-related adverse events were reported [53].

These data led to the design and delivery of the randomized, double-blind, placebo-controlled Phase 2b NEFIGAN study (NCT01738035), which evaluated 2 doses of Nefecon (16 mg once daily and 8 mg once daily), given for 9 months in patients with primary IgAN on a background of optimized RAS inhibitor therapy [58].

Consistent with STOP-IgAN, the largest randomized controlled trial in IgAN at the time, a 6-month run-in phase was implemented to optimize RAS inhibition. Following this run-in phase, only those patients who still had proteinuria levels at 0.75 g/day or above were randomized in a 1:1:1 ratio to

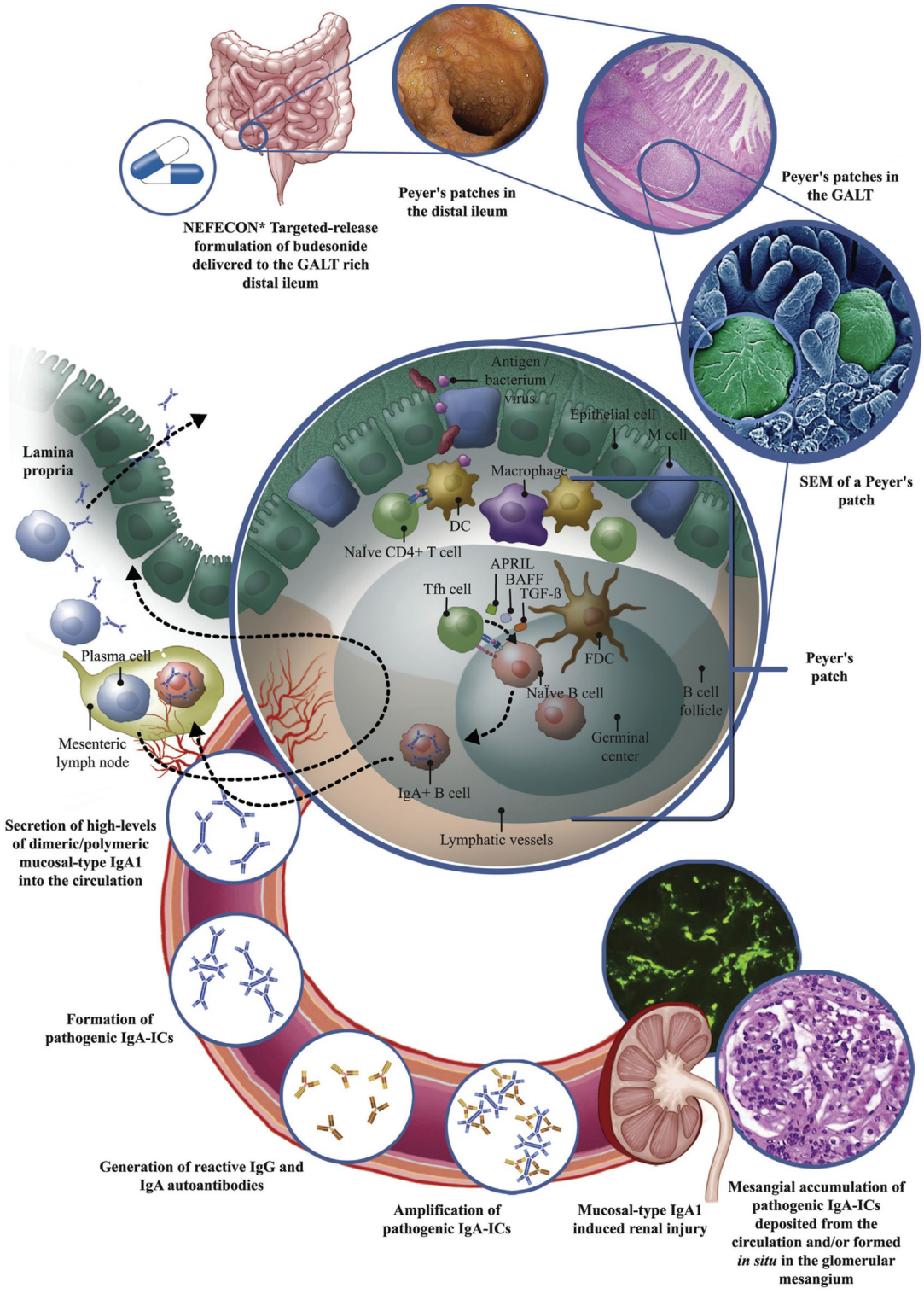

Figure 1. The role of Payer's patch targeting by Nefecon in the treatment of IgAN.

Note: Figure from Barratt et al., 2020, Kidney Int Rep. [18].

APRIL, a proliferation-inducing ligand; BAFF, B-cell–activating factor; CD, cluster of Differentiation; DCs, dendritic cells; FDC, follicular dendritic cell; GALT, gut-associated lymphoid tissue; IgAN, IgA nephropathy; IL, interleukin; M, microfold; SEM, scanning electron microscope; Tfh, T follicular helper; TGF-β, transforming growth factor; TLR, toll-like receptor.

receive Nefecon 8 mg/day, Nefecon 16 mg/day, or placebo, for 9 months; patients then underwent a 3-month follow-up period. Nefecon dosing was not based on body weight because of its site of action locally in the ileum, where body weight is not expected to substantially affect mucosal surface area. The 9-month duration was selected to assess whether a longer

duration of treatment could be beneficial and was based on studies considered relevant to estimate urine protein-creatinine ratio (UPCR) variance and effect size [59,60]. In this study, the primary objective was met at an interim analysis when a statistically significant 26% reduction in UPCR at 9 months was observed for the combined Nefecon 16 mg/day and 8 mg/day dose groups compared with placebo (1-sided $p = 0.0066$). Having met the primary objective, the 16 mg and 8 mg doses were individually compared with placebo. Patients treated with the 16 mg/day dose showed a statistically significant 29% reduction in UPCR versus placebo ($p = 0.0092$), whereas the 24% reduction in UPCR observed with the 8 mg/day dose versus placebo ($p = 0.0290$) was not statistically significant, in accordance with the adjusted p-value cutoff of ≤0.0158 used for interim analysis.

In the final analysis conducted once all 149 patients in the full analysis set had completed the study, those treated with Nefecon 16 mg/day showed a statistically significant 32% reduction in UPCR at 12 months ($p = 0.0005$ vs placebo). In addition to this improvement in proteinuria reduction, Nefecon treatment resulted in stabilization of estimated glomerular filtration rate (eGFR) during the 9-month treatment period and 3 months of follow-up compared with a baseline proteinuria-related decrease in the placebo group [58]. A summary of the Phase 2b NEFIGAN trial key efficacy results is provided in Table 1.

5.1.2. Design of the Phase 3 study

In addition to being a rare disease, a key challenge for the evaluation of new treatments for IgAN is that the progression to kidney failure typically develops over many years. Therefore, early surrogate end points that can reliably predict long-term clinical benefit are essential for clinical trials and the regulatory approval process. The two main end points that have been evaluated as potential early surrogates in chronic kidney disease are proteinuria reduction and change in eGFR.

In patients with IgAN, persistent proteinuria is widely accepted as a key risk factor for progression of the disease [33,61]. Prior to the commencement of the Phase 3 study, an individual patient-level meta-analysis of randomized controlled trials in IgAN showed that a decline in proteinuria at 9 months in association with study treatment correlated with a lower risk for the clinical endpoint of the composite time to the first occurrence of a doubling of serum creatinine, kidney failure, or death [62,63]. At the end of Phase 2b, health authorities endorsed the ratio change in UPCR at 9 months from baseline as the primary end point for the Phase 3 study, representing a surrogate end point that was likely to be a reliable predictor for the treatment effect on long-term kidney outcomes in IgAN. However, to confirm that the trial was adequately powered to determine whether there was a clinical benefit of treatment based on proteinuria reduction, supportive analyses of eGFR were required for the early approval. These principles were later endorsed by a Kidney Health Initiative project workgroup, which was convened to help identify reliable, long-term predictors of the treatment effect in IgAN that could be used to support approval: the experts involved agreed on the use of proteinuria reduction as a reasonably likely surrogate end point to assess the treatment effect on progression to kidney failure in patients with IgAN [63].

In March 2018, after the Phase 3 study had commenced, the National Kidney Foundation (NKF), along with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) held a scientific workshop 'Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of Chronic Kidney Disease,' with the objective of improving the understanding of change in proteinuria and change in GFR slope as measures of kidney disease progression in early stages of kidney disease [64–66]. In addition to the use of proteinuria as a valid surrogate end point, the analyses presented showed that treatment effects on eGFR slope over 2 years were strongly predictive of treatment effects on the clinical composite end point of dialysis, eGFR <15 mL/min/1.73 m^2, or doubling of serum creatinine, and results were consistent across disease subgroups, including patients with IgAN. Following this workshop, further consultation with FDA and EMA led to the original Phase 3 protocol being amended to more closely align the Part B analyses with these findings and to include an analysis of the 2-year eGFR slope.

Therefore, the Phase 3 study was designed on the basis that early demonstration of a significant reduction in UPCR of a sufficient magnitude could support an initial approval, with confirmation of clinical benefit for conversion to full approval based on 2-year eGFR data.

Table 1. Phase 2b NEFIGAN key efficacy summary.

	Treatment Effects	
	Nefecon 8 mg/day versus placebo	Nefecon 16 mg/day versus placebo
Proteinuria		
Reduction from baseline in 24-hour UPCR at 9 months (*Interim)	24%; 95% CI: −1 to 42%; $p = 0.0290$	29%; 95% CI: 6% to 47%; $p = 0.0092$
Reduction from baseline in 24-hour UPCR at 12 months	23%; 95% CI: 4 to 38%; $p = 0.0101$	32%; 95% CI: 4 to 43%; $p = 0.0005$
Reduction from baseline in 24-hour UACR at 9 months	18%; 95% CI: −9 to 39%; $p = 0.0818$	32%; 95% CI: 9 to 50%; $p = 0.0053$
Reduction from baseline in 24-hour UACR at 12 months	28%; 95% CI: 7 to 44%; $p = 0.0068$	38%; 95% CI: 18 to 53%; $p = 0.0004$
eGFR [CKD-EPI]		
Change in eGFR from baseline at 9 months	10%; 95% CI: 2 to 18%; $p = 0.0064$	12%; 95% CI: 3 to 21%; $p = 0.0026$
Change in eGFR from baseline at 12 months	3%; 95% CI: −6 to 13%; $p = 0.2508$	11%; 95% CI: 1 to 23%; $p = 0.0134$

All p-values are 1-sided.
CI, confidence interval; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio; UPCR, urine protein-creatinine ratio.
*Adjusted alpha level of ≤0.0158 used at the interim analysis.
Source data: Fellström et al, 2017, Lancet, Supplementary tables S5 and S6 [58].

5.1.3. Phase 3 study

Nefecon has been studied in the largest commercially sponsored study in IgAN of its time: the Phase 3 NefIgArd (NCT03643965) study [67]. NefIgArd is a randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, and tolerability of Nefecon 16 mg once daily compared with placebo in patients with primary IgAN on a background of optimized RAS inhibitor therapy. Approximately 360 patients were required to be randomized, and patients have been enrolled across sites in Europe, North America, South America, and Asia Pacific, including China [68].

The NefIgArd study design was aligned to the KDIGO 2012 guideline that described the optimal use of RAS inhibitor treatment, and considerations based on clinical practice [61]. The proteinuria values required at entry were also based on the KDIGO 2012 guideline, in which persistent proteinuria ≥1 g per day was noted to be associated with an accelerated decline in kidney function. Therefore, patients had to have biopsy-verified primary IgAN and persistent proteinuria of ≥1 g per day (or UPCR ≥0.8 g/g), despite optimized RAS inhibition.

The NefIgArd study consists of two parts: Part A and Part B. In Part A, eligible patients are randomized in a 1:1 ratio to Nefecon 16 mg/day or placebo for 9 months, followed by a 3-month observational follow-up period (including a 2-week tapering-off period to reduce the dose). In Part B, patients are observed off-treatment for a further 12 months while continuing optimized RAS blockade [68].

The final 2-year efficacy and safety results will be reported at the completion of the trial in 2023 [68].

The Part A analysis included data from 199 patients among the first 201 patients randomized, regardless of whether the patients received study drug (per intention to treat) [68].

UPCR results from NefIgArd Part A reaffirmed those observed in NEFIGAN; after 9 months of treatment, patients assigned to Nefecon had a 27% reduction in UPCR compared with placebo (1-sided $p = 0.0003$). At the end of the 3-month follow-up period, a 48% reduction in UPCR compared with placebo was observed at 12 months ($p < 0.0001$). In both NEFIGAN and NefIgArd, the UPCR treatment effect was found to be highly consistent across different baseline demographic and disease characteristics, including baseline eGFR and proteinuria/UPCR levels [58,68].

When considering eGFR as an end point for evaluation of an intervention, it should be noted that a treatment benefit can, at most, be a stabilization, because previously lost kidney function cannot be expected to be restored. This means that an eGFR treatment benefit is unlikely to be larger than the eGFR decline observed in a similar group of untreated patients.

Although eGFR data are so far only available for the 199 patients analyzed in Part A, treatment with Nefecon was shown to provide a statistically significant 7% treatment benefit on eGFR compared with placebo at 9 months ($p = 0.0014$), with a 7% treatment benefit maintained at 1 year ($p = 0.0106$). This 3.87 mL/min/1.73 m^2 treatment benefit at 9 months corresponded to a slight reduction from baseline of 0.17 mL/min/1.73 m^2 in patients who received Nefecon 16 mg once daily, compared with a deterioration from baseline of 4.04 mL/min/1.73 m^2 in patients who received placebo. In a supportive analysis of 1-year total eGFR slope benefit, the improvement for Nefecon versus placebo was 3.37 mL/min/1.73 m^2 per year in the overall population ($p = 0.0111$), a 73% improvement compared with the 1-year total slope of −4.63 mL/min/1.73 m^2 per year observed in placebo recipients.

In addition, the rate of eGFR decline in patients on supportive care alone is known to be dependent on the severity of the disease, which is tightly correlated with the level of proteinuria [69]. Therefore, in IgAN patients with higher levels of proteinuria, a faster rate of eGFR decline is to be expected. Consistent with this, patients in the placebo group of NefIgArd who had higher levels of baseline proteinuria showed a much faster decline in eGFR compared with the overall study population, placing them at particularly high risk for developing kidney failure. A predefined subgroup analysis of patients with baseline UPCR ≥1.5 g/g demonstrated an improvement in a 1-year eGFR total slope of 9.31 mL/min/1.73 m^2 per year ($p = 0.0005$) [68,70]. This reflects an 88% improvement in the 1-year eGFR total slope compared with the −10.61 mL/min/1.73 m^2 per year deterioration observed in the placebo group.

These data point to a highly effective prevention of the IgAN-induced eGFR decline in the study group as a whole and most notably for the subgroup of patients with the most aggressive disease.

Evaluation of eGFR data for patients with UPCR <1.5 g/g is more challenging. First, the slower rate of decline of eGFR in untreated patients requires substantially more power and longer follow-up for evaluation of an eGFR treatment effect [71]. Second, there is a modest acute eGFR effect observed with Nefecon, observed in all patients, particularly evident at 3 months [68]. When the underlying deterioration in eGFR is slower, this acute effect interferes with the interpretation of smaller IgAN-related changes in eGFR expected over 1 year.

Therefore, the results from part B of NefIgArd, where both more patients (360 vs 199) and a longer observation period (24 months rather than 9–12 months) will be available, are expected to provide a more reliable evaluation of eGFR in patients with lower levels of baseline UPCR. There is no scientific reason to question the assumption that Nefecon would also provide stabilization of eGFR in these patients, given the effect of Nefecon on proteinuria reduction was similar for the 2 subgroups (below and above UPCR 1.5 g/g) (Figure 2, Table 2).

The final analysis of the NefIgArd study will seek to confirm whether the substantial reduction in proteinuria achieved with 9 months of Nefecon treatment, irrespective of baseline proteinuria levels, will translate into a clinically relevant benefit on eGFR for a broader population of patients once patients have been followed for longer, and the cumulative immunomodulatory effect of Nefecon treatment has had time to impact eGFR in all patients.

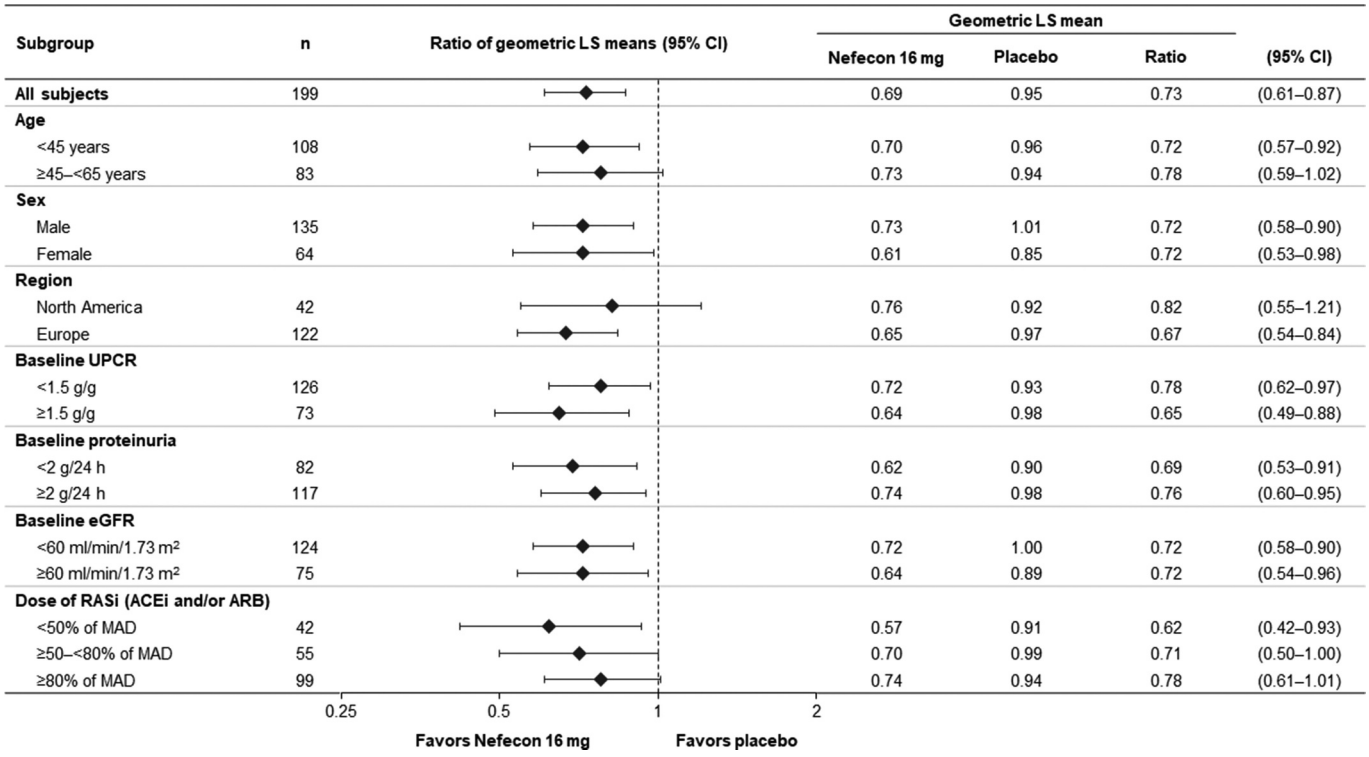

Figure 2. Ratio of UPCR (g/g) at 9 months compared with baseline across predefined subgroups.

Note: Figure from Barratt et al., 2022, Kidney Int. [68].

For patients who took both an ACEi and ARB, the categorization was applied to the sum of the percentage of maximum allowed dose of each RASi therapy. Patients who were not recorded as having received either an ACEi or an ARB were included in the <50% category. It was not possible to assign a category to some patients where the dose was not recorded.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least-squares; MAD, maximum allowable dose; RASi, renin-angiotensin system inhibitor; UPCR, urine protein-creatinine ratio.

Table 2. Phase 3 NeflgArd key efficacy summary.

	Treatment effects (Nefecon 16 mg/day versus placebo)
Proteinuria	
Reduction from baseline in 24-hour UPCR at 9 months	27%; 95% CI 13 to 39%; $p = 0.0003$
Reduction from baseline in 24-hour UPCR at 12 months	48%; 95% CI 36 to 58%; $p < 0.0001$
Reduction from baseline in 24-hour UACR at 9 months	31%; 95% CI 14 to 45%; $p = 0.0005$
Reduction from baseline in 24-hour UACR at 12 months	54%; 95% CI 40 to 64%; $p < 0.0001$
eGFR (CKD-EPI)	
Percentage change in eGFR from baseline to 9 months vs placebo (corresponding difference in absolute change [mL/min/1.73 m^2])	7%; 95% CI 3 to 13% [3.87]; $p = 0.0014$
Percentage change in eGFR from baseline to 12 months vs placebo (corresponding difference in absolute change [mL/min/1.73 m^2])	7%; 95% CI 1 to 13% [3.56]; $p = 0.0106$
1-year total eGFR slope benefit (difference between Nefecon and placebo)	3.37 mL/min/1.73 m^2 per year; $p = 0.0111$

Note: All *p*-values are 1-sided. All analyses (apart from eGFR slope) were performed on the log-scale. Treatment effects are expressed as percentage change for Nefecon compared with placebo, derived from the ratio of geometric LS means at the respective timepoint. For eGFR, results have additionally been presented in terms of the mean difference in absolute change from baseline, which were derived from the geometric LS means.

CI, confidence interval; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LS, least-squares; UACR, urine albumin-creatinine ratio; UPCR, urine protein-creatinine ratio.

Source data: Barratt et al, 2022, Kidney Int. [68].

5.2. Safety and tolerability

In both randomized placebo-controlled trials, 9 months of Nefecon 16 mg once daily was seen to be generally well tolerated, with a safety profile consistent with that expected for an oral budesonide product [58,68].

Treatment-emergent adverse events (TEAEs) were predominantly mild or moderate and reversible, with only 1% of events in Part A of NeflgArd classified as severe. The overall number of serious adverse events reported with Nefecon treatment has been low (Table 3).

Table 3. NeflgArd key safety data (Part A, full analysis set).

	Placebo ($n = 100$)		Nefecon 16 mg/day ($n = 97$)	
	n (%)	Events	n (%)	Events
All TEAEs	73 (73.0)	300	84 (86.6)	429
AE of infection	41 (41.0)	–	38 (39.2)	–
Any AESI	0	–	2[a] (2.1)	–
Any treatment-emergent SAE	5 (5.0)	5	11 (11.3)	16
Any study treatment-related treatment-emergent SAE	2 (2.0)	2	2 (2.1)	2
Any AE leading to death	0	0	0	0
Any TEAE leading to discontinuation of study treatment[b]	1 (1.0)	5	9 (9.3)	27

Note: AEs were coded using the Medical Dictionary for Regulatory Activities (Version 22.0). AEs were considered to have been reported during the 'on-treatment' period if the start date was after the first dose of study treatment until 14 days after completion of the tapering period. AEs that started >14 days after the last dose of study treatment were attributed to follow-up (not reported herein). TEAEs were defined as AEs that occurred for the first time after dosing with study drug or existed before but worsened in severity or relationship to study drug after dosing. AESIs were defined as severe infections requiring hospitalization, new onset of diabetes mellitus, confirmed fracture, new osteonecrosis, gastrointestinal bleeding requiring hospitalization, reported occurrence of cataract formation, and reported onset of glaucoma.

[a]New onset of diabetes mellitus. These patients had levels of FBG or HbA1c prior to the start of treatment that indicated a pre-diabetic condition, defined as FBG ≥100 mg/dl or HbA1c ≥5.7%, according to the American Diabetes Association 2020 guidelines.

[b]Note that for 1 Nefecon-treated patient with a TEAE leading to discontinuation of study treatment, this was not their primary reason for withdrawal.

AE, adverse event; AESI, adverse event of special interest; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Source data: Barratt et al, 2022, Kidney Int. [68].

Supporting the good tolerability profile, most patients treated with Nefecon completed the 9-month treatment regimen; in NeflgArd, although higher than that in the placebo group, the frequency of TEAEs leading to discontinuation of study drug was <10% in Nefecon-treated patients. This is lower than what had been observed with the 16 mg dose in the NEFIGAN trial [58,68]. It may be that, following the results of NEFIGAN showing treatment benefit, patients included in NeflgArd were more willing to continue study treatment for the potential benefit. The solicitation of glucocorticoid-related adverse effects at every visit in NEFIGAN may also have led to some biased reporting of glucocorticoid-related adverse effects, and a consequent impact on withdrawal rates.

In Part A of the Phase 3 NeflgArd trial, the most common TEAEs reported with increased frequency compared with placebo were hypertension, peripheral edema, muscle spasms, and acne [68]. In contrast to results with high-dose systemic corticosteroids from the TESTING and STOP-IgAN studies [72,73], there was no increase in infections with the use of Nefecon (39% vs 41% with placebo), and no severe infections were reported in either treatment group; furthermore, there were no deaths in either the NEFIGAN study or in Part A of NeflgArd [58,68].

The NeflgArd study allowed patients with type 1 or type 2 diabetes mellitus to be included if the condition was adequately controlled. Of note, after randomization, a higher proportion of patients in the Nefecon group had a medical history of diabetes or were identified as having pre-diabetes compared with the placebo group (9.3% vs 1.0% and 45.4% vs 29.4%, respectively). In Part A of NeflgArd, glycated hemoglobin (HbA1c) levels were generally unchanged throughout treatment, with the exception of 11 Nefecon-treated patients who all either had a pre-enrollment diagnosis of diabetes or who had HbA1c values at baseline above thresholds indicative of pre-diabetes (typically defined as an HbA1c level of ≥5.7%). Reversibility to baseline levels was generally seen within 3 months after the end of treatment. New onset diabetes mellitus was reported in 2 patients during treatment; both met the American Diabetes Association criteria for pre-diabetes at baseline [68].

6. Approval status

Nefecon received accelerated approval from the FDA in December 2021, with an indication to 'reduce proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a UPCR ≥1.5 g/g' [74,75]. Nefecon was granted conditional approval by the EMA in July 2022 in adults at risk of rapid disease progression with a UPCR ≥1.5 g/g [70,76].

Other regulatory submissions are now ongoing, and confirmatory data from the final analysis of the NeflgArd trial are expected to provide the evidence of preservation of kidney function needed to convert these early approvals to full approval.

7. Limitations

Prolonged administration of Nefecon (beyond 9 months) has not been tested, nor is there currently any information on the efficacy of repeated courses of Nefecon treatment following the initial treatment period. IgAN is a chronic autoimmune disease, and it is not foreseen that one 9-month treatment cycle will cure patients. Based on current data, it is anticipated that one treatment cycle, which offers durable proteinuria reduction, may delay disease progression, thereby prolonging the time to kidney failure. NeflgArd was designed to provide confirmatory data for treatment benefit following a 9-month cycle. A Phase 3b open-label extension study is now ongoing to evaluate the efficacy and safety of a second cycle of Nefecon treatment in patients who have completed treatment and follow-up in NeflgArd [77]. The intention is for all patients who enter this extension study to remain on their stable dose of optimized RAS inhibitor therapy and receive 9 months of Nefecon 16 mg/day, with follow-up at 12 months. Part B of NeflgArd and the open-label extension study will provide additional

information on duration of efficacy for both single and repeated 9-month treatment cycles.

Much may still be learned about the pathophysiology of IgAN. Further understanding of how Nefecon modulates the different components of the pathogenic cascade in IgAN may also be gleaned from additional biomarker analyses of the Phase 3 study to help inform the future use of Nefecon in clinical practice.

8. Conclusions

Nefecon is a delayed-release formulation of budesonide specifically designed to deliver the drug to the B cell-rich distal ileum. It is the first treatment option to be approved by the FDA, the EMA, and the UK Medicines and Healthcare products Regulatory Agency for the reduction of proteinuria in patients with IgAN at risk of rapid disease progression [70,74,78] and is, to date, the only one commercially available in both the US and Europe. Thanks to its intended action as a topical agent, Nefecon has been shown to reduce proteinuria and slow the rate of decline of kidney function in patients at risk of rapid disease progression, without exhibiting the serious adverse events characteristic of systemic glucocorticoids [58,68].

9. Expert opinion

As our understanding of the pathophysiology of IgAN has improved, it has opened up new possibilities for therapeutic targets for this disease. New therapies have been developed to address these targets, options that are sorely needed, as the natural history of IgAN is one of progressive disease, with a high potential for life-altering or life-limiting consequences.

With systemic glucocorticoids, we have a class of drugs that, despite showing some efficacy in terms of proteinuria reduction, cannot be confidently recommended due to a challenging safety and tolerability profile and uncertainty regarding long-term efficacy [33]. Nefecon has been developed with the intent of being disease modified by targeting its release to the B cell-rich distal ileum, which appears to play a crucial role in the pathophysiology of IgAN [53]. To date, clinical trial results have been promising: Nefecon has been shown to effectively reduce UPCR and urine albumin-creatinine ratio, as well as to significantly slow kidney function decline compared with placebo; importantly, these achievements have been accompanied by a limited rate of mostly mild or moderate TEAEs typical of an oral budesonide product with limited systemic glucocorticoid exposure [58,68]. One-year data have resulted in the granting of accelerated approval by the FDA and conditional approval by the EMA for adult patients with IgAN at risk of rapid disease progression [70,74–76], a population that represents an important unmet need. We look forward to the completion of the Phase 3 study, because confirmatory results at 2 years would solidify confidence in this approach and its mechanism of action and confirm the approval status, allowing continued provision of a novel treatment option to a population otherwise at considerable risk of kidney failure [70,74].

The ultimate goal of IgAN treatment is to arrest disease progression or at least delay it to the point where patients are unlikely to develop kidney failure in their natural lifetime. Biomarker data have provided insights into some facets of the mechanism of action of Nefecon, suggesting that it may have multi-modal, disease-modifying effects [79,80]. Clinical data to date have shown a considerable reduction in UPCR and in the rate of eGFR decline over 1 year after 9 months of treatment, and the 2-year follow-up results are therefore awaited with great interest.

The currently approved indications for Nefecon are for patients at risk of rapid disease progression, (generally) with UPCR ≥1.5 g/g. Placebo recipients with lower levels of proteinuria at baseline in NefIgArd had a much smaller deterioration in eGFR over the first year, which limited the opportunity to demonstrate a treatment effect on eGFR during Part A. The substantial improvement in UPCR that was observed for all patients, irrespective of baseline UPCR, suggests benefits on eGFR will be observed for all patients when followed for longer. One important point raised in both the NEFIGAN and NefIgArd primary publications is the fact that both studies included mainly Caucasian patients [58,68]. Although the efficacy and safety profile of Nefecon is not expected to differ substantially between patients of different ethnicities, these study findings will also need to be confirmed across diverse patient populations.

The evolving understanding of IgAN pathophysiology has led to the exploration of new therapeutic options, such as endothelin type A receptor antagonists, complement inhibitors, and B cell modulators. These options are in various stages of development and have so far demonstrated promising efficacy in reducing proteinuria in patients with IgAN with manageable safety profiles. There is great anticipation on the potential benefit of these new therapeutic options, either alone or in combination, when added to standard of care, to preserve kidney function in patients with IgAN.

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