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REVIEW

# Insights on Nefecon®, a Targeted-Release Formulation of Budesonide and Its Selective Immunomodulatory Effects in Patients with IgA Nephropathy

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**Abstract:** Immunoglobulin A nephropathy (IgAN) is a chronic, immune-mediated kidney disease characterized by the deposition of galactose-deficient immunoglobulin A1 (Gd-IgA1) in the kidneys. Excess Gd-IgA1 production in patients with IgAN is located within the mucosa-associated lymphoid tissue, particularly within the lamina propria in the distal ileum. Nefecon® is a targeted-release formulation of the corticosteroid budesonide, which became the first treatment approved by the US Food and Drug Administration (FDA; brand name, TARPEYO®) and European Medicines Agency (EMA; KINPEYGO®) for patients with primary IgAN at risk of rapid disease progression, after demonstrating clinically significant reduction of proteinuria in an interim analysis of the Phase III NefIgArd trial. After showing a significant reduction in estimated glomerular filtration rate decline in the full 2-year analysis of the trial, Nefecon was granted full approval by the FDA to reduce the loss of kidney function. Nefecon was specifically designed to deliver budesonide to the distal ileum, selectively targeting excess Gd-IgA1 production in the gut-associated lymphoid tissue. In this review, we describe the properties of Nefecon and the evidence to date that confirms its localized treatment effect. We also present unpublished evidence from Phase I trials investigating the pharmacokinetics and cortisol suppression effects of Nefecon in healthy participants. These studies demonstrated that Nefecon has a distinct pharmacokinetic profile from other budesonide products, allowing for targeted, localized action in the distal ileum. When considered alongside existing clinical trial data showing the effect of Nefecon on gut-associated biomarkers, available evidence indicates that Nefecon has a selective immunomodulatory mechanism of action and a direct disease-modifying effect in patients with IgAN, while having low systemic exposure and adverse effects.

**Keywords:** drug delivery, biomarkers, pharmacokinetics, GALT

## Introduction

Despite being considered relatively rare, with a global incidence of approximately 2.5 per 100,000 individuals, immunoglobulin A (IgA) nephropathy (IgAN), a chronic, immune-mediated kidney disease, is the most common primary glomerular disease and a major cause of chronic kidney disease (CKD) and kidney failure worldwide.[1–5]

Most patients with IgAN are diagnosed in their 20s and 30s and up to 50% of patients are expected to develop kidney failure within 20 years of diagnosis, resulting in patients with IgAN facing a considerable lifetime risk of kidney failure. In a study of data from the UK National Registry of Rare Kidney Diseases (RaDaR), mean age at kidney failure or death was 49 years.[1,5] Therefore, IgAN places a substantial burden on patients and is associated with a reduced life expectancy.[4–6]

IgAN is characterized by the deposition of galactose-deficient IgA1 (Gd-IgA1) antibodies in the glomerular mesangium, either alone or in complex with immunoglobulin G (IgG) and/or IgA auto-antibodies. These initiate a cascade of inflammatory events, eventually causing irreversible glomerulosclerosis and loss of kidney function.[3,7,8]



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Although IgAN manifests in the kidney, there is now consensus supporting a pivotal role of the gut-associated lymphoid tissue (GALT) in the pathogenesis of the condition.[3,7,9–11] In patients with IgAN, B cells located in Peyer's patches in the distal ileum are primed to initiate production of Gd-IgA1 which, when in excess in the circulation, can lead to an autoimmune response, with the formation of anti–Gd-IgA1 IgG and IgA antibodies that ultimately drive IgA immune complex formation (Figure 1).[7,8,12–15] These complexes deposit in the glomerular mesangium, leading to a local inflammatory response and glomerular injury, which are exacerbated by complement activation, and ultimately lead to loss of kidney function.[8,13] The mucosa-associated lymphoid tissue (MALT) of the distal ileum is, therefore, a key source of the immune dysfunction driving IgAN pathophysiology.[8,13]

Despite this, since its first description in 1968, therapies have primarily addressed the downstream consequences of mesangial IgA accumulation in the kidneys of patients with IgAN, with guidelines focusing on providing optimized supportive kidney care with renin–angiotensin system (RAS) inhibition to reduce proteinuria, blood pressure management, lifestyle modification, and further measures to reduce cardiovascular risk.[16–19]

As the underlying disease mechanism of IgAN is immune-mediated, systemic corticosteroids have long been used to reduce inflammation in the kidney.[8,20–22] In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommended RAS inhibitors for the treatment of patients with IgAN and, in certain patients, suggested the use of corticosteroids.[19,23] However, recent studies evaluating the efficacy and safety of systemic corticosteroids in patients with IgAN have led to debate on their use in these patients.[19] The Supportive Versus Immunosuppressive Therapy for the Treatment Of Progressive IgA Nephropathy (STOP-IgAN) and Therapeutic Effects of Steroids in IgA Nephropathy Global (TESTING) trials have reported mixed efficacy outcomes and significantly increased risks of serious adverse events and severe infections, challenging the benefit–risk profile of systemic corticosteroids in IgAN.[21,22] The current KDIGO guidelines from 2021 suggest systemic corticosteroids only be considered in patients with persistent proteinuria who are unable to join a clinical trial after a thorough toxicity risk assessment has been undertaken.[18]

An evolving understanding of the pathophysiology of IgAN has allowed for the potential to develop new therapeutic approaches which address the upstream immune processes underlying IgAN pathophysiology, as well as approaches which address the generic CKD drivers of nephron loss. Specifically designed to target Gd-IgA1 production in the GALT of the distal ileum, Nefecon® (Calliditas Therapeutics AB, Stockholm, Sweden) is the development name of a novel, oral, targeted-release formulation of the topically active corticosteroid budesonide.[8,24–26] Developed over many years with the purpose of providing a disease-modifying therapeutic option, the commercial formulation of Nefecon was investigated in the Phase III Efficacy and Safety of Nefecon in Patients With Primary Immunoglobulin A Nephropathy

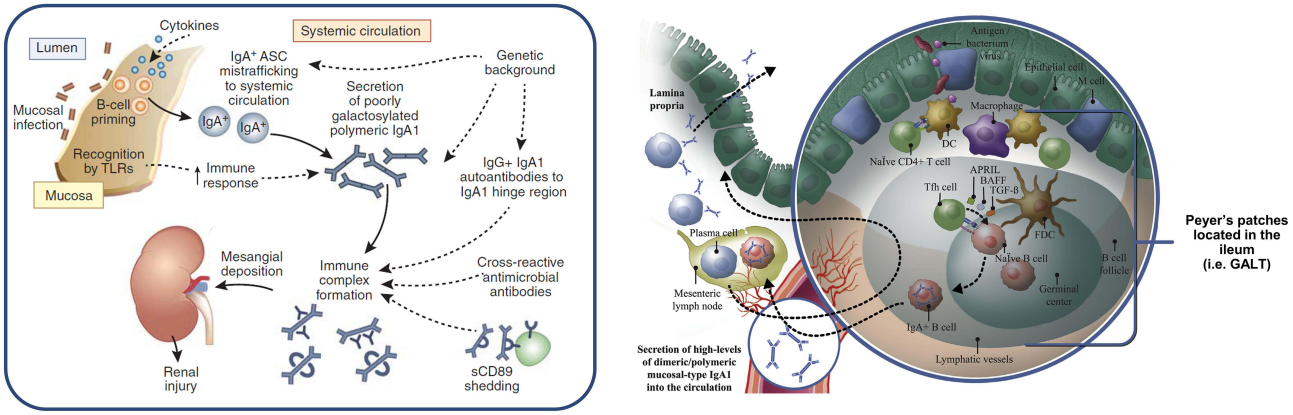


**Figure 1** Targeting mucosal IgA synthesis in the GALT. Image on the left is adapted from *Kidney Int*, volume 81(9), Boyd JK, Cheung CK, Molyneux K, Feehally J, Barratt J. An update on the pathogenesis and treatment of IgA nephropathy. 833–843, Copyright 2012, with permission from Elsevier[10] and image on the right is adapted from *Kidney Int Rep*, volume 5(10), Barratt J, Rovin BH, Cattran D, Trimarchi H, Zhang H. Why target the gut to treat IgA nephropathy? 1620–1624, Copyright 2020, with permission from Elsevier.[7]

**Abbreviations**: APRIL, a proliferation-inducing ligand; ASC, antibody-secreting cells; BAFF, B-cell–activating factor; CD, cluster of differentiation; DC, dendritic cell; FDC, follicular dendritic cell; GALT, gut-associated lymphoid tissue; IgA, immunoglobulin A; IgG, immunoglobulin G; sCD, soluble cluster of differentiation; Tfh, T follicular helper; TGF-β, transforming growth factor-β; TLR, Toll-like receptor.

(NefIgArd) randomized trial, which evaluated the efficacy and safety of 9 months of treatment with Nefecon 16 mg/d compared with placebo, followed by a 15-month off-drug observational period, in patients with IgAN receiving optimized RAS inhibition.[27] Based on the 1-year interim results of the NefIgArd trial,[28] Nefecon became the first approved treatment for patients with primary IgAN at risk of rapid disease progression, receiving accelerated approval in the United States in December 2021 (thereby becoming commercially available in January 2022 as TARPEYO®, and receiving full approval in December 2023) and receiving conditional marketing authorization in the European Union in July 2022 (KINPEYGO®).[24,25] The full 2-year trial results provided evidence that Nefecon 16 mg/d led to a significant and clinically relevant reduction in kidney function decline, as measured by a reduction in time-weighted average change in estimated glomerular filtration rate (eGFR) over 2 years, of 5.1 mL/min/1.73 $m^2$.[27] The eGFR benefit of Nefecon accrued by the end of 9 months of treatment was maintained over the 15-month observational follow-up (Figure 2).[27] This was supported by a reduction in the rate of eGFR decline with Nefecon, with a 2-year total eGFR slope difference versus placebo of 3.0 mL/min/1.73 $m^2$ per year.[27] These results translated to a significant reduction in the risk of a composite endpoint of 30% eGFR reduction or kidney failure in patients receiving Nefecon compared with those receiving placebo (hazard ratio 0.45; 95% confidence interval 0.26–0.75; p=0.0014).[27] A durable reduction in proteinuria was also observed with Nefecon 16 mg/d versus placebo, with a 30% mean reduction in urine protein–creatinine ratio at 9 months, sustained up to 2 years (Figure 2).[27] In addition, during 9 months of treatment, Nefecon 16 mg/d was well tolerated and had a safety profile as expected for a locally acting oral budesonide product.[27] Following the completion of the NefIgArd trial, Nefecon was granted full approval by the US Food and Drug Administration to reduce the loss of kidney function.[25]

Other therapies which target the immune drivers of IgAN pathophysiology are currently under investigation, although, of these, only Nefecon is currently approved.[24,25] Multiple ongoing trials are evaluating the safety and efficacy of inhibitors of B cell–activating factor and a proliferation-inducing ligand, key mediators of B cell activation, maturation, and survival.[29–35] B cell survival is also being explored as a treatment target in studies of an anti–cluster of differentiation 38 (CD38) monoclonal antibody for the treatment of IgAN.[36] Further downstream of IgAN pathogenesis, complement system inhibitors have been shown to reduce proteinuria and markers of pathogenic complement system activation, indicating an effect in reducing inflammation and damage to the kidneys of patients with IgAN.[37–41] In treating the generic CKD drivers of nephron loss, new therapies are now being used to treat IgAN beyond the RAS inhibitors recommended in the 2021 KDIGO guidelines; namely, sodium-glucose cotransporter-2 inhibitors, which have shown efficacy in non-diabetic CKD,[42,43] and sparsentan, a dual endothelin angiotensin receptor antagonist which received accelerated approval in the United States and conditional approval in the European Union to reduce proteinuria in patients with IgAN at risk of disease progression.[44,45]

In this review, we focus on the development of Nefecon's unique formulation as a locally acting oral corticosteroid and describe the evidence supporting its local mechanism of action in the distal ileum.

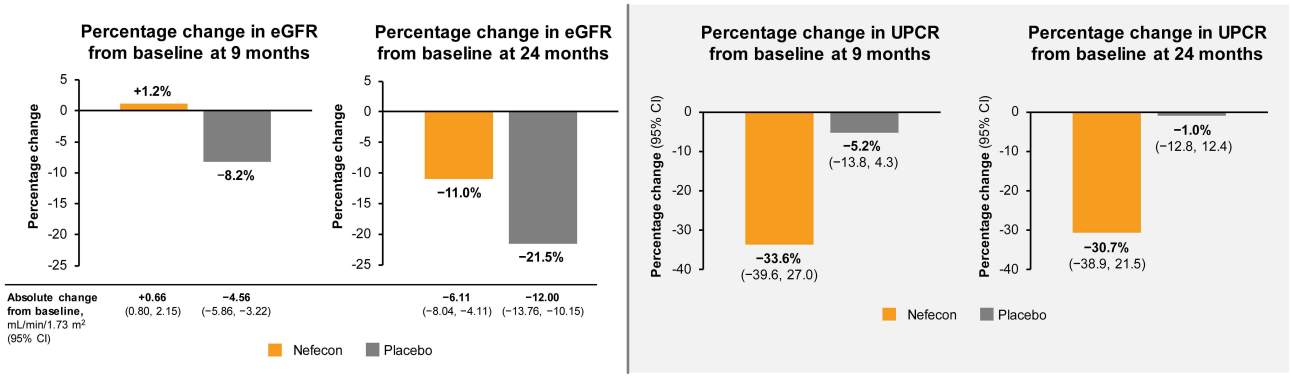


**Figure 2** Effect of Nefecon 16 mg/d on eGFR and UPCR in the NefIgArd trial.[27]
**Abbreviations**: CI, confidence interval; eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio.

## The Formulation of Nefecon and Its Targeted Design

Budesonide is a potent corticosteroid with high receptor affinity that was developed for topical use on mucosal surfaces, showing evidence of deep penetration of mucosal tissues.[46] Following limited metabolism in the mucosa, budesonide undergoes rapid first-pass metabolism in the liver, with its metabolites exhibiting minimal activity, thereby limiting its systemic exposure when administered orally.[46] Nefecon was designed to target the release of budesonide to the GALT of the distal ileum and to enable its sustained, localized immunomodulatory action. Nefecon capsules were therefore developed with an enteric coat that delays the start of release of budesonide, and with triple-coated beads that mediate its sustained release (Figure 3).[47]

The Nefecon capsule shell is covered with an enteric coating which allows for the bypassing of the stomach and upper small intestine and optimizes the release of the budesonide-containing beads in the distal ileum.[47] Following dissolution of the capsule shell, triple-coated beads contained within the Nefecon capsule are released in the ileum. The inner layer contains the active budesonide, while the middle seal coating promotes stability of the budesonide. The outer ethyl-cellulose based coating mediates sustained release, inducing budesonide dissolution over a wider part of the distal ileum. The overall release mechanism of Nefecon differs from that of other oral budesonide formulations, such as Entocort® (Tillotts Pharma UK Limited, Wellingore, UK), which begins to release active budesonide in proximal regions of the small intestine.[47]

## Pharmacokinetic Profile of Nefecon and Its Effects on Cortisol

As a consequence of Nefecon's unique formulation targeting localized delivery of budesonide to the distal ileum, its pharmacokinetic profile demonstrates key differences when compared with other gut-targeted budesonide formulations such as Entocort®, which is indicated in patients with mild to moderate active Crohn's disease at a dose of 9 mg/d.[48]

Two studies in healthy participants (NEF-101 and NEF-105) compared the pharmacokinetics of Nefecon and Entocort®. Detailed methods of the two studies are provided in Supplementary Text 1. Briefly, the NEF-101 study evaluated Nefecon 8 mg and Nefecon 16 mg versus Entocort® 9 mg as single doses in 23 healthy volunteers to evaluate the pharmacokinetics of Nefecon and Entocort® and to compare individual changes from baseline in serum cortisol levels and urine cortisol excretion over a 24-hour period following administration of each product. Serum cortisol was measured frequently during 24 hours before the first dose and after each dose administration, while quantitative cortisol excretion in urine was measured on the same occasions over the 24-hour sampling periods. Budesonide plasma concentrations were followed over a 24-hour period after each dose.

Overall, a slightly lower dose-adjusted suppression of cortisol was demonstrated with Nefecon compared with Entocort®, indicating lower per-milligram systemic cortisol suppression. (Supplementary Figures 1–Supplementary Figures 4). Cortisol suppression was first observed at 2 hours with Entocort® and at 4 hours with Nefecon (Supplementary Figure 2). Nefecon at

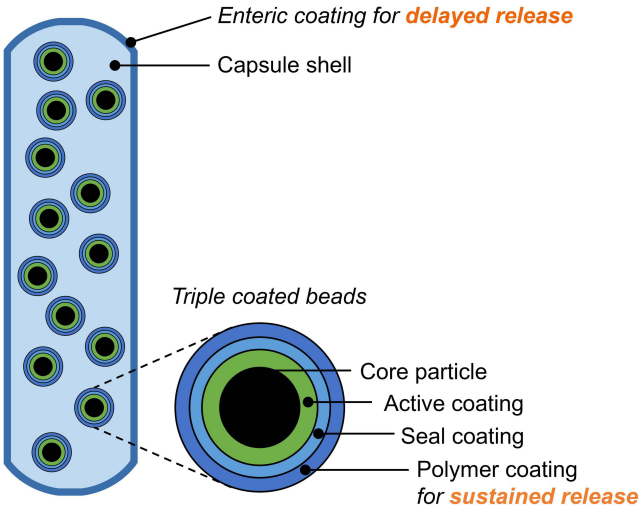


**Figure 3** Schematic image of Nefecon.

a dose of 16 mg was associated with a greater reduction in the mean area under the plasma concentration–time curve over 24 hours ($AUC_{0–24}$) for serum cortisol than Nefecon 8 mg. Based on a linear regression between change in serum cortisol $AUC_{0–24}$ and log dose, the mean change from baseline was −2215.65 nM/h for a 9-mg dose of Entocort®, which corresponded to a dose of 11.7 mg of Nefecon (Table 1). Therefore, per mg budesonide dose, Nefecon gave a 23% lower suppression of serum cortisol over 24 hours compared with Entocort®. Mean change in urine cortisol excretion was similar for Entocort® 9 mg and Nefecon 16 mg and was less pronounced for Nefecon 8 mg (Table 2).

The pharmacokinetic properties of Nefecon were also assessed in the NEF-105 study, which compared the properties of different Nefecon formulations (Nefecon-A 16 mg and Nefecon-F 16 mg) versus Entocort® 9 mg in 25 healthy volunteers, of whom 22 completed all dosing periods. Nefecon-A was the formulation used in Phase II studies, while Nefecon-F was the formulation used from the Phase III studies onward. Nefecon dosing was repeated in patients available on follow-up, providing a total of 47 evaluable pharmacokinetic profiles for each formulation of Nefecon and 23 profiles for Entocort®. Pharmacokinetic sampling started at 1 hour postdose for Nefecon and at 20 minutes postdose for Entocort® to account for the earlier start of drug release from Entocort®.

In both the NEF-101 and NEF-105 studies, maximum plasma concentration ($C_{max}$) was greater with Nefecon than with Entocort®, while simultaneously exhibiting a shorter terminal half-life ($t_{1/2}$). In NEF-101, the $C_{max}$ for budesonide was 3330 pg/mL with Nefecon 8 mg, 6260 pg/mL with Nefecon 16 mg, and 1763 pg/mL with Entocort® 9 mg, while the mean $t_{1/2}$ was 4.27 hours, 4.40 hours, and 4.95 hours, respectively (Table 3). In NEF-105, the $C_{max}$ was 4994–5488 pg/mL across Nefecon formulations and repeated dosing compared with 1188 pg/mL for Entocort® 9 mg, while mean $t_{1/2}$ was 4.74–5.16 hours versus 6.55 hours, respectively (Table 4, Figures 4 and 5, Supplementary Figure 5). This

**Table 1** Serum Cortisol $AUC_{0–24}$ (nmol*h/L) Results in the NEF-101 Study

| | | Baseline (n=24) | Nefecon 8 mg (n=23) | Nefecon 16 mg (n=24) | Entocort® 9 mg (n=24) |
|---|---|---|---|---|---|
| **Observed results** | Observations, n | 24 | 23 | 24 | 23 |
| | Mean (SD) | 5372 (1126) | 3479 (1128) | 2971 (1153) | 3034 (706) |
| | Median (IQR) | 5299 (4811, 5677) | 3183 (2822, 3880) | 2694 (2446, 3142) | 2933 (2702, 3493) |
| | Geometric mean (SE) | 5263 (226) | 3318 (222) | 2798 (204) | 2942 (169) |
| **Individual change from baseline** | Observations, n | N/A | 23 | 24 | 23 |
| | Mean (SD) | N/A | −1901 (710) | −2401 (895) | −2215 (778) |
| | Median (IQR) | N/A | −1949 (−2508, −1361) | −2327 (−2944, −1851) | −2225 (−2655, −1452) |

**Abbreviations**: $AUC_{0–24}$, area under the plasma concentration–time curve over 24 hours; IQR, interquartile range; N/A, not applicable; SD, standard deviation; SE, standard error.

**Table 2** Cortisol Excretion in Urine Over 24 Hours (nmol/d) in the NEF-101 Study

| | | Baseline (n=24) | Nefecon 8 mg (n=23) | Nefecon 16 mg (n=24) | Entocort® 9 mg (n=24) |
|---|---|---|---|---|---|
| **Observed results** | Observations, n | 24 | 23 | 24 | 24 |
| | Mean (SD) | 110 (48) | 65 (35) | 56 (33) | 55 (32) |
| | Median (IQR) | 106 (77, 122) | 59 (40, 84) | 53 (36, 66) | 48 (34, 73) |
| | Geometric mean (SE) | 101 (8.8) | 56 (7.1) | 48 (5.8) | 47 (5.9) |
| **Individual change from baseline** | Observations, n | N/A | 23 | 24 | 24 |
| | Mean (SD) | N/A | −44 (41) | −54 (35) | −55 (36) |
| | Median (IQR) | N/A | −39 (−63, −16) | −54 (−70, −32) | −51 (−71, −34) |

**Abbreviations**: IQR, interquartile range; N/A, not applicable; SD, standard deviation; SE, standard error.

**Table 3** Budesonide Pharmacokinetic Parameters in the NEF-101 Study

| | | Nefecon 8 mg (N=20) | Nefecon 16 mg (N=22) | Entocort® 9 mg (N=24) |
|---|---|---|---|---|
| $t_{lag}$, h | Mean (CV%) | 2.10 (14.6) | 1.91 (19.2) | 0.65 (80.6) |
| | Median | 2.0 | 2.0 | 1.0 |
| | Geometric mean (CV%) | 2.08 (12.5) | 1.87 (20.7) | |
| $t_{max}$, h | Mean (CV%) | 3.80 (20.2) | 3.96 (23.9) | 3.38 (55.8) |
| | Median | 4.0 | 4.0 | 3.04 |
| | Geometric mean (CV%) | 3.73 (20.2) | 3.84 (26.4) | 3.00 (51.6) |
| $C_{max}$, pg/mL | Mean (CV%) | 3330 (75.6) | 6260 (87.3) | 1763 (66.6) |
| | Median | 2887 | 4046 | 1566 |
| | Geometric mean (CV%) | 2451 (110) | 4847 (78.0) | 1455 (70.6) |
| $AUC_{0–24}$, pg/mL*h | Mean (CV%) | 14,138 (55.2) | 27,145 (46.4) | 12,220 (73.2) |
| | Median | 14,358 | 23,582 | 10,088 |
| | Geometric mean (CV%) | 11,472 (89.8) | 24,650 (47.2) | 10,229 (64.6) |
| $t_{1/2}$, h | Mean (CV%) | 4.27 (41.4) | 4.40 (40.8) | 4.95 (26.6) |
| | Median | 3.77 | 4.07 | 4.70 |
| | Geometric mean (CV%) | 3.97 (39.8) | 4.13 (36.4) | 4.78 (27.4) |

**Notes**: Data for profiles with no measurable budesonide concentrations (N=1 for Nefecon 8 mg) or only 1 measurable concentration at 24 h (N=2 for Nefecon 8 mg and N=2 for Nefecon 16 mg) were excluded.

**Abbreviations**: $AUC_{0–24}$, area under the plasma concentration–time curve over 24 hours; $C_{max}$, maximum plasma concentration; CV, coefficient of variation; $t_{1/2}$, half-life; $t_{lag}$, lag time from administration to the start of absorption; $t_{max}$, time to maximum plasma concentration.

**Table 4** Budesonide Pharmacokinetic Parameters in the NEF-105 Study

| Variable | | Nefecon-A 16 mg average[a] | Nefecon-F 16 mg average[a] | Entocort® 9 mg |
|---|---|---|---|---|
| $C_{max}$, pg/mL | Mean (SD) | 5138 (2782) | 5026 (2543) | 1188 (590) |
| | Median | 4593 | 4628 | 1130 |
| | Geometric mean (CV%) | 4611 (48.2) | 4407 (58.3) | 4209 (68.7) |
| $AUC_{0–24}$, pg/mL*h | Mean (SD) | 24,764 (10,642) | 26,615 (11,525) | 9197 (4187) |
| | Median | 23,487 | 28,150 | 8096 |
| | Geometric mean (CV%) | 22,789 (43.8) | 24,131 (49.7) | 21,327 (51.4) |
| $AUC_{0\text{-}inf}$, pg/mL*h | Mean (SD) | 26,089 (11,325) | 28,607 (12,471) | 10,223 (4743) |
| | Median | 24,905 | 28,933 | 9143 |
| | Geometric mean (CV%) | 23,943 (44.7) | 25,929 (49.7) | 22,426 (52.2) |
| $t_{1/2}$, h | Mean (SD) | 4.90 (0.87) | 5.04 (0.82) | 6.55 (1.82) |
| | Median | 4.60 | 4.96 | 6.27 |

(*Continued*)

**Table 4** (Continued).

| Variable | | Nefecon-A 16 mg, 1st dose | Nefecon-A 16 mg, 2nd dose | Nefecon-F 16 mg, 1st dose | Nefecon-F 16 mg, 2nd dose | Entocort® 9 mg |
|---|---|---|---|---|---|---|
| $t_{lag}$, h | Mean (SD) | 2.84 (0.67) | 2.39 (0.74) | 3.08 (1.31) | 3.02 (0.95) | 0.57 (0.32) |
| | Median | 2.5 | 2.5 | 3.25 | 3.0 | 0.67 |
| $t_{max}$, h | Mean (SD) | 5.16 (1.40) | 4.91 (1.18) | 5.73 (1.64) | 5.87 (1.83) | 4.33 (1.70) |
| | Median | 4.52 | 4.5 | 5.25 | 5.0 | 4.0 |

**Notes**: [a]Nefecon-A and Nefecon-F dosing was repeated twice in the majority of subjects. For AUCs and $C_{max}$, the geometric mean of the 2 doses for each subject was used; for $t_{1/2}$, the harmonic mean was used. Average values for repeated doses were not available for $t_{lag}$ or $t_{max}$.
**Abbreviations**: $AUC_{0-24}$, area under the plasma concentration–time curve over 24 hours; $AUC_{0-inf}$, area under the plasma concentration–time curve from baseline to infinity; $C_{max}$, maximum plasma concentration; CV, coefficient of variation; SD, standard deviation; $t_{1/2}$, half-life; $t_{lag}$, lag time from administration to the start of absorption; $t_{max}$, time to maximum plasma concentration.

demonstrated that the duration of systemic exposure to budesonide was shorter with Nefecon than with Entocort®. These results may explain the lower per-milligram suppression of cortisol with Nefecon compared with Entocort® because, even though Nefecon exhibited a high $C_{max}$, the cortisol suppression with corticosteroids is nonlinear and has a "ceiling effect."[49]

The interval between the start of budesonide absorption ($t_{lag}$) and the time of maximum plasma concentration ($t_{max}$) for budesonide in the NEF-105 study was approximately 2.5 hours for Nefecon when based on mean values, and 2 hours when based on median values. For Entocort®, the corresponding intervals were 3.75 hours and 3.3 hours, respectively (Table 4). The shorter intervals with Nefecon indicated a more rapid drug release after onset of drug absorption compared with Entocort®, allowing for budesonide release to be constrained to the ileum upon the dissolution of the capsule.

There was consistency across studies in the minimum individual lag time to onset of budesonide absorption under different conditions, suggesting there is no foreseeable risk of Nefecon administration leading to premature, rapid release of high concentrations of budesonide, ie, "dose dumping." However, it should be noted that these studies only evaluated single doses

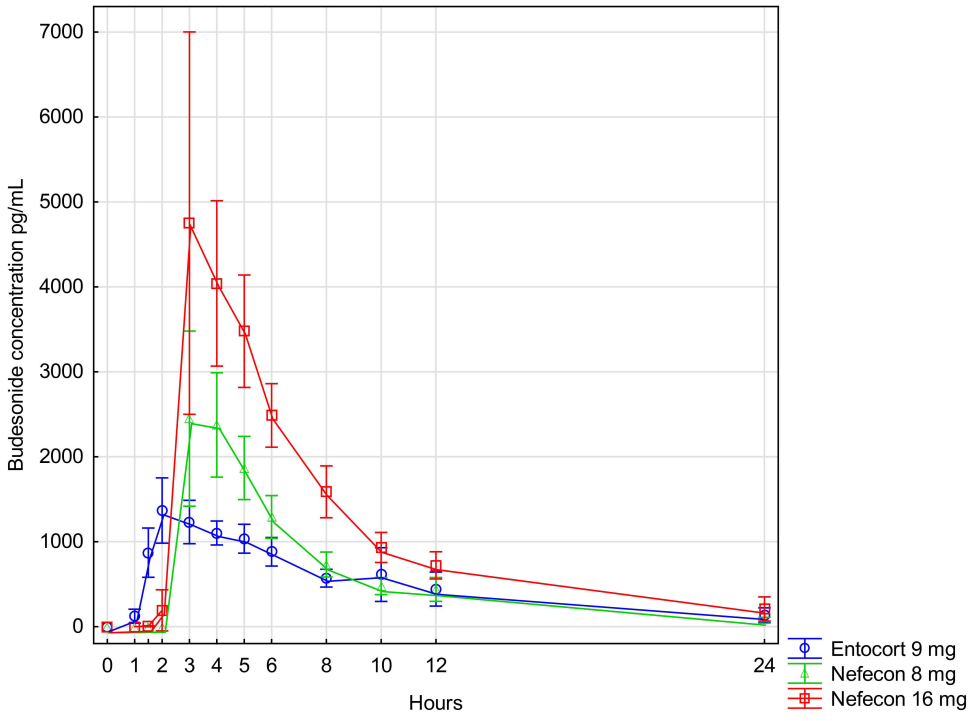


**Figure 4** Arithmetic mean budesonide concentration with 90% CIs over time in the NEF-101 study.
**Abbreviations**: CI, confidence interval.

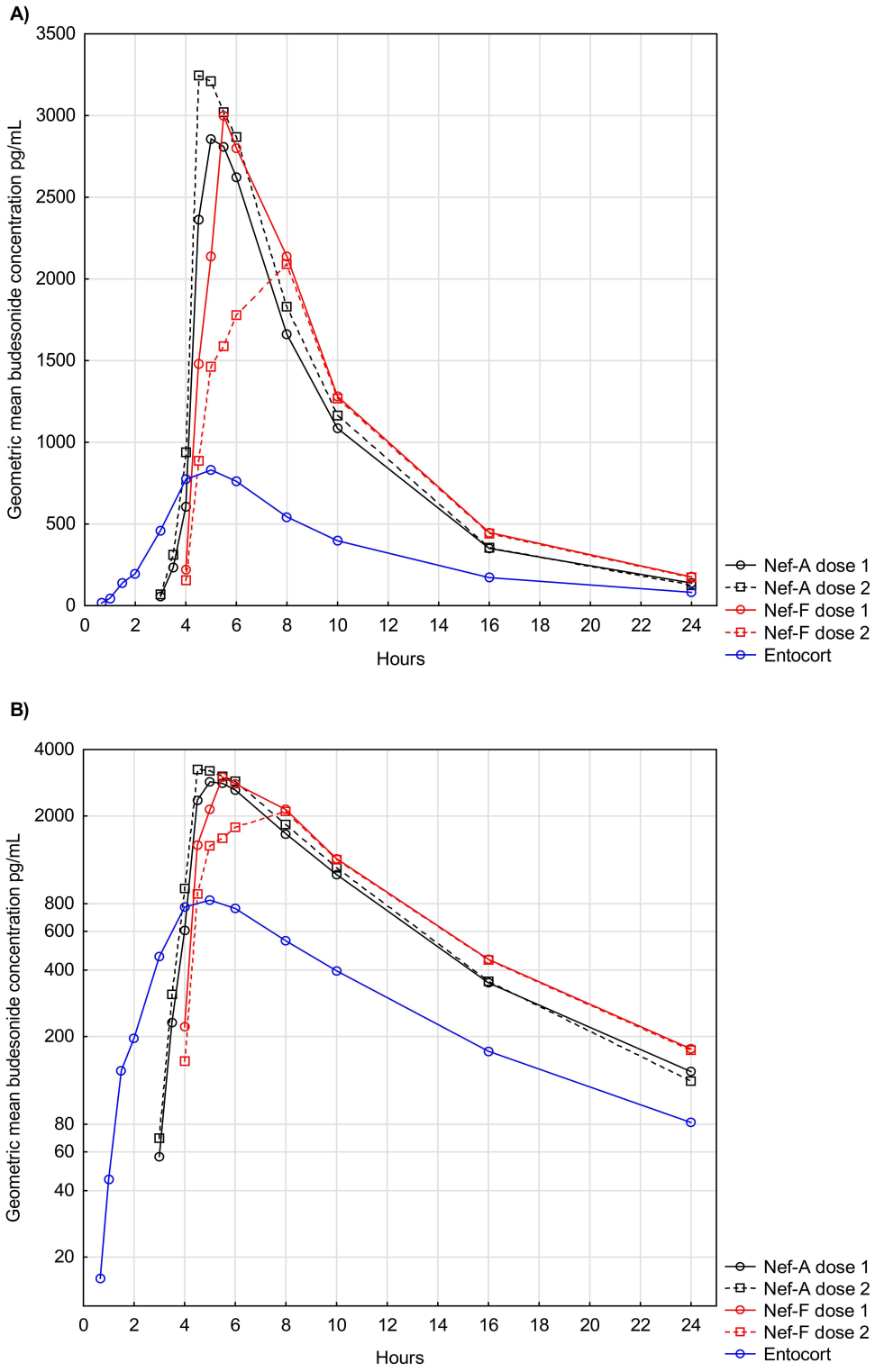


**Figure 5** Geometric mean budesonide concentration over time in the NEF-105 study; **(A)** linear concentration axis and **(B)** logarithmic concentration axis.
**Abbreviations**: Nef-A, Nefecon-A; Nef-F, Nefecon-F.

in healthy volunteers and not repeated doses. Importantly, as budesonide has a short $t_{½}$ of ~5 hours, once-daily dosing every 24 hours is unlikely to lead to systemic accumulation, thereby reducing the likelihood of concentration-dependent adverse effects in nontarget tissues which are commonly associated with the use of systemic corticosteroids in IgAN.[21,22] No accumulation of budesonide has been observed with repeated administration of Entocort®.[46]

There is no reason to believe that the gastrointestinal tract of patients with IgAN differs from that of healthy volunteers in a way that interferes with the release characteristics of budesonide from Nefecon, the rate and extent of budesonide absorption, or the degree of first-pass metabolism of budesonide. The pharmacokinetic results from these studies in healthy volunteers can therefore be deemed representative for patients with IgAN.

## Gastrointestinal Transit Time and Nefecon Delivery to the Distal Ileum

Determining the exact site of drug absorption can prove difficult as there is uncertainty with respect to precise gastrointestinal transit times. Substantial variability exists depending on the methodology used to assess small intestinal transit time.[50,51] Additionally, enterically coated capsules such as Nefecon are subject to the variable effects of gastric motility and dietary regimens.[52] Overall, a typical range of 3–4 hours for small intestinal transit time is provided in the literature, although values from <1 to >10 hours have been observed.[52]

A study by Ibekwe et al that investigated an enteric-coated tablet which does not disintegrate in the stomach estimated that average gastric emptying time was ~1 hour in the fasted state and ~2 hours and 40 minutes in the fed state.[53] Upper small intestine transit time was ~2 hours 20 minutes irrespective of fasting state.[53] Ingestion of a meal 30 minutes following administration of the tablet did not substantially affect transit time.[53] Given that Nefecon 16 mg is enteric coated and currently recommended in clinical practice to be taken in the morning 1 hour before a meal,[24,25] these results indicate that a typical lag time to reach the lower small intestine is ~3.5 hours for a product such as Nefecon.[53] In the NEF-105 study in healthy volunteers, the lag time from administration to the start of drug absorption ($t_{lag}$) for Nefecon was ~3 hours in the fasted state. However, due to the properties of extended-release triple-coated beads, budesonide release is prolonged following dissolution of the Nefecon capsule, which may suggest delivery of budesonide to the lower small intestine in line with the Ibekwe et al enteric-coated tablet study.[53]

The potential time to budesonide absorption was also investigated in an in vitro study which evaluated the differences in budesonide release profiles across different formulations. The budesonide products were first subjected for 2 hours to an acidic environment with pH 1.2 representing the stomach, and then were exposed for 3 hours to a "biorelevant" buffer medium with pH 6.5 representing transit through the small intestine. The study confirmed that Nefecon released no budesonide in the acidic "gastric" phase. In the intestinal buffer medium, Nefecon capsule disintegration and onset of budesonide release occurred after 1 hour, after which budesonide was released over a relatively short period, with the majority of the release occurring over a period of 2 hours from first budesonide release (Figure 6).[47] These results suggest budesonide is likely to be released locally in the distal ileum.

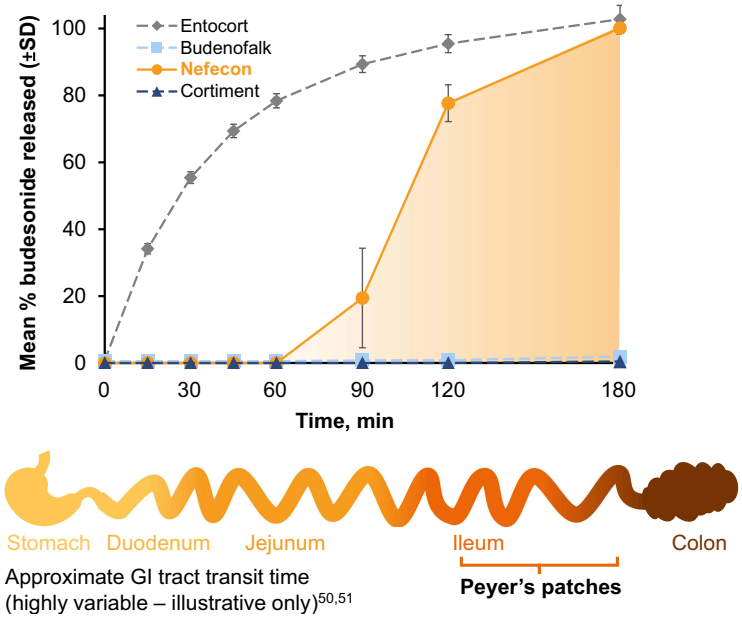


**Figure 6** In vitro budesonide release profiles using the biorelevant method. Adapted with permission from Dressman J, Philipson R, Barratt J. Comparison of the dissolution profile of Nefecon with three other commercially available oral formulations of budesonide: Implications for interchangeability. IIgANN, Tokyo, Japan, 2023.[54]
**Abbreviations**: GI, gastrointestinal; SD, standard deviation.

**Table 5** Summary of Commercially Available Oral Formulations of Budesonide

| | Nefecon | Budenofalk® | Entocort® | Cortiment® |
|---|---|---|---|---|
| **Indication** | IgAN | Crohn's disease; autoimmune hepatitis; microscopic colitis | Crohn's disease; microscopic colitis | UC; microscopic colitis |
| **Target tissue** | GALT of the distal ileum | Ileum and ascending colon | Ileum and ascending colon | Colon |
| **Enteric coat** | EUDRAGIT® L&S | EUDRAGIT® L&S | EUDRAGIT® L55 | EUDRAGIT® L55 & S |
| **What is enteric coated?** | Capsule shell | Beads | Beads | Tablet |
| **Nominal pH of enteric coating** | Proprietary information | 6.4 (RMS AR) | 5.5 (FDA) | 7 (FDA) |
| **Capsule material** | HPMC | Gelatin | Gelatin | Not applicable |
| **What sustains release?** | Ethyl cellulose–based coating on beads | EUDRAGIT® *RS* | Ethyl cellulose | MMX® (stearic acid/HPC matrix) |

**Note**: Adapted with permission from Dressman J, Philipson R, Barratt J. Comparison of the dissolution profile of Nefecon with three other commercially available oral formulations of budesonide: Implications for interchangeability. IIgANN, Tokyo, Japan, 2023.[54]

**Abbreviations**: FDA, US Food and Drug Administration; GALT, gut-associated lymphoid tissue; HPC, hydroxypropyl cellulose; HPMC, hydroxypropyl methylcellulose; IgAN, immunoglobulin A nephropathy; RMS AR, Reference Member State Assessment Report; UC, ulcerative colitis.

The in vitro study also compared the budesonide release profile of Nefecon with that of Entocort® and 2 other oral budesonide formulations which are available commercially for the treatment of Crohn's disease and ulcerative colitis: Budenofalk® (DR. FALK PHARMA GmBH, Freiburg, Germany) and Cortiment® (Ferring Pharmaceuticals Ltd., West Drayton, UK) (Table 5).[47] Similar to the in-human pharmacokinetic studies, budesonide release with Entocort® occurred earlier and over a longer period of time than with Nefecon, indicating release in the proximal small intestine and absorption across the small intestine. Conversely, Budenofalk® and Cortiment® did not release budesonide in the "biorelevant" intestinal medium, consistent with a substantial amount of budesonide being released in the colon. An analysis using the $f_2$ statistic to test similarity between dissolution profiles demonstrated that Nefecon has a strongly dissimilar budesonide release profile compared with the other commercially available budesonide formulations tested, and that none could be considered pharmaceutically or therapeutically interchangeable.[47]

## Evidence Supporting the Local Mechanism of Action of Nefecon

The local effect of Nefecon on the GALT is also demonstrated by its effect on biomarkers indicative of modulation of numerous immune pathways within the GALT (Figure 7). IgAN is characterized by deposition of Gd-IgA1–containing immune complexes in the glomerular mesangium, driven by excess production of Gd-IgA1 in the GALT. Using false discovery rate q-values, Nefecon was shown to significantly reduce serum levels of Gd-IgA1 after 9 months of treatment, as well as IgA-IgG immune complexes. Conversely, it did not significantly reduce levels of total IgA, supporting a local and selective effect of Nefecon on the GALT, while having no or only limited effect on systemic IgA.[55,56]

As the GALT is directly involved in the immune response to antigens encountered in the intestinal mucosa, antibodies specific to gut-derived antigens such as casein are markers of GALT activity. Nefecon was found to substantially reduce levels of anti-casein IgA, while having a less pronounced effect on anti-tetanus toxoid IgA, which is generated following systemic antigen challenge.[55] Further analyses of biomarker data from the Phase III NefIgArd trial will be undertaken to further investigate and validate these observations.

The relative lack of systemic exposure of budesonide with Nefecon is also congruent with the development of budesonide as a topical corticosteroid.[19] The NEF-101 study demonstrated that the cortisol-suppressive effects of 9 mg of Entocort® corresponded to a dose of 11.7 mg of Nefecon.[57] Combined with published estimates of the equivalence between Entocort® and prednisolone doses, a 2:1 dose equivalence between Nefecon and prednisolone can be calculated.[57] Clinical efficacy of Nefecon was demonstrated at a dose of 16 mg/d.[27] In the TESTING study, the maximum daily dose of systemic corticosteroids was equivalent to prednisolone 40 mg and 60 mg in the low- and high-dose protocols, respectively.[21,58]

Because of the high systemic exposure to corticosteroids in trials with systemic corticosteroids, significant rates of side effects were observed, including high rates of serious adverse events, excess hospitalizations, serious infections, and deaths.[21,22] Likely

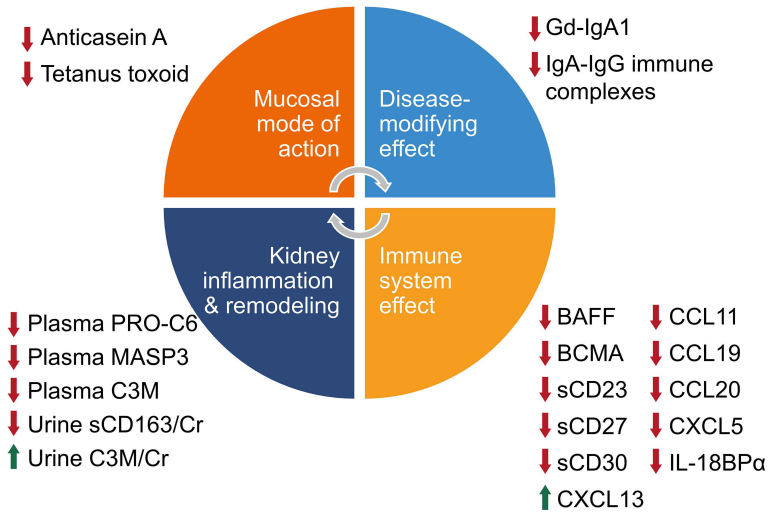


**Figure 7** Biomarker assessments from the Phase IIb NEFIGAN trial with significant changes from baseline at 9 months for Nefecon 16 mg vs standard of care, as measured by FDR q-value. Adapted from *Kidney Int*, volume 105(2), Wimbury D, Muto M, Bhachu JS, et al. Targeted-release budesonide modifies key pathogenic biomarkers in immunoglobulin A nephropathy: insights from the NEFIGAN trial. 381–388, Copyright 2023. Creative Commons.[55]
**Abbreviations**: BAFF, B-cell–activating factor; BCMA, B-cell maturation antigen; C3M, collagen type III degradation marker; CCL, C-C motif chemokine ligand; Cr, creatinine; CXCL, C-X-C motif chemokine ligand; FDR, false discovery rate; Gd, galactose-deficient; Ig, immunoglobulin A; IgG, immunoglobulin G; IL-18BPα, interleukin 18 binding protein isoform α; MASP3, mannose-binding lectin–associated serine protease 3; PRO-C6, propeptide of type VI collagen; sCD, soluble cluster of differentiation.

due to lower systemic corticosteroid exposure, Nefecon was typically associated with milder adverse events, which were generally reversible, and had a safety profile expected for a locally acting corticosteroid.[27] Additionally, while lymphopenia is commonly associated with long-term systemic corticosteroid use,[59–61] levels of circulating lymphocytes were not reduced with long-term use of Nefecon in the NefIgArd trial, with a mean absolute change from baseline at 9 months in lymphocyte count of $0.49 \times 10^9$/L (standard deviation ± 0.75) in Nefecon recipients versus $0.03 \times 10^9$/L (standard deviation ± 0.43) in placebo recipients. These results suggest a reduced systemic impact of Nefecon in patients with IgAN compared with that typically observed with systemic corticosteroids.

Finally, Nefecon's treatment effect on proteinuria in the NefIgArd trial occurred after a delay, with no significant difference in urine protein–creatinine ratio between Nefecon and placebo groups at 3 months, after which durable reductions in proteinuria were observed for Nefecon versus placebo over the remaining 2-year trial period.[27] Conversely, in the TESTING trial, methylprednisolone had a substantial effect on proteinuria at 3 months vs placebo, diminishing over time, reflective of its anti-inflammatory mode of action.[21] This delayed as opposed to immediate reduction in proteinuria supports Nefecon's effect at the source of the disease in the GALT, as opposed to a predominant anti-inflammatory mechanism of action in the kidneys.

## Conclusions

Nefecon, a targeted-release formulation of the topically acting corticosteroid budesonide, was specifically designed to deposit budesonide in the distal ileum, targeting the Gd-IgA1–producing cells in the ileal GALT. Its unique formulation results in a pharmacokinetic profile distinct from other budesonide products that allows for targeted, local action. The high first-pass metabolism of budesonide also distinguishes it from systemic corticosteroids, limiting its systemic exposure. The release of budesonide to the ileum and its subsequent effect on gut-associated biomarkers indicates that Nefecon is likely to act locally on the GALT, resulting in a selective immunomodulatory mechanism of action with a direct disease-modifying effect in patients with IgAN. This is further corroborated by the NefIgArd trial, the results of which showed that 9 months of Nefecon treatment on top of RAS inhibition provided a statistically significant and clinically relevant preservation of eGFR and durable reduction in proteinuria compared with RAS inhibition alone. Additionally, Nefecon was associated with low rates of adverse events, which were generally mild to moderate in severity, as expected for a locally acting corticosteroid with limited systemic exposure.

## Abbreviations

$AUC_{0–24}$, area under the plasma concentration–time curve over 24 hours; CD, cluster of differentiation; $C_{max}$, maximum plasma concentration; eGFR, estimated glomerular filtration rate; GALT, gut-associated lymphoid tissue; Gd-IgA1, galactose-deficient IgA1; IgA, immunoglobulin A; IgAN, IgA nephropathy; IgG, immunoglobulin G; KDIGO, Kidney Disease: Improving Global Outcomes; MALT, mucosa-associated lymphoid tissue; NefIgArd, Efficacy and Safety of Nefecon in Patients With Primary Immunoglobulin A Nephropathy; RaDaR, National Registry of Rare Kidney Diseases; RAS, renin–angiotensin system; STOP-IgAN, Supportive Versus Immunosuppressive Therapy for the Treatment Of Progressive IgA Nephropathy; $t_{1/2}$, half-life; TESTING, Therapeutic Effects of Steroids in IgA Nephropathy Global; $t_{lag}$, lag time from administration to start of absorption; $t_{max}$, time to maximum plasma concentration.

## Data Sharing Statement

Data sharing requests will be considered from research groups that submit a research proposal with a valuable research question and an appropriate statistical analysis and dissemination plan. Proposals will be assessed by a committee formed from the trial management group, including senior statistical and clinical representation. Requests are to be sent to Richard Philipson (Calliditas Therapeutics AB, Stockholm, Sweden). Data will be shared via a secure data access system.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The study steering committee led the design of the Phase I trials, with support from the sponsor (Calliditas Therapeutics AB). The sponsor was responsible for the preparation of the trial protocol and the statistical analysis plan, and the collection and analysis of data. The sponsor assisted the authors in data interpretation and in reviewing the manuscript.

## Disclosure

**JB** is a consultant to Calliditas Therapeutics AB and reports grants and consultancy and personal fees from Calliditas Therapeutics, Everest Medicines, and STADA Arzneimittel AG. **JK** and **MJ** are consultants for Calliditas Therapeutics. **CP** is an employee of Calliditas Therapeutics. The authors report no other conflicts of interest in this work.

## References

1. Schena FP, Nistor I. Epidemiology of IgA nephropathy: a global perspective. *Semin Nephrol*. 2018;38(5):435–442. doi:10.1016/j.semnephrol.2018.05.013
2. McGrogan A, Franssen CF, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. *Nephrol Dial Transplant*. 2011;26(2):414–430. doi:10.1093/ndt/gfq665
3. Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med*. 2013;368(25):2402–2414. doi:10.1056/NEJMra1206793
4. Lai KN, Leung JC, Tang SC. Recent advances in the understanding and management of IgA nephropathy. *F1000Res*. 2016;5:161. doi:10.12688/f1000research.7352.1
5. Pitcher D, Braddon F, Hendry B, et al. Long-term outcomes in IgA nephropathy. *Clin J Am Soc Nephrol*. 2023;18(6):727–738. doi:10.2215/CJN.0000000000000135
6. Moriyama T, Tanaka K, Iwasaki C, et al. Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. *PLoS One*. 2014;9(3):e91756. doi:10.1371/journal.pone.0091756
7. Barratt J, Rovin BH, Cattran D, Trimarchi H, Zhang H. Why target the gut to treat IgA nephropathy? *Kidney Int Rep*. 2020;5(10):1620–1624. doi:10.1016/j.ekir.2020.08.009

8. Barratt J, Lafayette RA, Rovin BH, Fellstrom B. Budesonide delayed-release capsules to reduce proteinuria in adults with primary immunoglobulin A nephropathy. *Expert Rev Clin Immunol*. 2023;19(7):699–710. doi:10.1080/1744666X.2023.2206119
9. Kiryluk K, Novak J. The genetics and immunobiology of IgA nephropathy. *J Clin Invest*. 2014;124(6):2325–2332. doi:10.1172/JCI74475
10. Boyd JK, Cheung CK, Molyneux K, Feehally J, Barratt J. An update on the pathogenesis and treatment of IgA nephropathy. *Kidney Int*. 2012;81(9):833–843. doi:10.1038/ki.2011.501
11. McCarthy DD, Kujawa J, Wilson C, et al. Mice overexpressing BAFF develop a commensal flora-dependent, IgA-associated nephropathy. *J Clin Invest*. 2011;121(10):3991–4002. doi:10.1172/JCI45563
12. Coppo R. The gut–renal connection in IgA nephropathy. *Semin Nephrol*. 2018;38(5):504–512. doi:10.1016/j.semnephrol.2018.05.020
13. Selvaskandan H, Barratt J, Cheung CK. Immunological drivers of IgA nephropathy: exploring the mucosa-kidney link. *Int J Immunogenet*. 2022;49(1):8–21. doi:10.1111/iji.12561
14. Smith AC, Molyneux K, Feehally J, Barratt J. O-glycosylation of serum IgA1 antibodies against mucosal and systemic antigens in IgA nephropathy. *J Am Soc Nephrol*. 2006;17(12):3520–3528. doi:10.1681/ASN.2006060658
15. Tomana M, Novak J, Julian BA, Matousovic K, Konecny K, Mestecky J. Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies. *J Clin Invest*. 1999;104(1):73–81. doi:10.1172/JCI5535
16. Feehally J, Cameron JS. IgA nephropathy: progress before and since Berger. *Am J Kidney Dis*. 2011;58(2):310–319. doi:10.1053/j.ajkd.2011.03.024
17. Berger J, Hinglais N. [Intercapillary deposits of IgA-IgG]. *J Urol Nephrol (Paris)*. 1968;74(9):694–695.
18. Kidney Disease: Improving Global Outcomes Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4S):S1–S276.
19. Del Vecchio L, Rimoldi C, Pozzi C. Nefecon (targeted-release formulation-budesonide) for the treatment of IgA nephropathy. *Future Rare Dis*. 2021;1(4):FRD14.
20. Cunningham AM, Reich H. Corticosteroids should be used to treat slowly progressive IgA nephropathy: PRO. *Kidney360*. 2021;5(2):1078–1080. doi:10.34067/KID.0007192020
21. Lv J, Wong MG, Hladunewich MA, et al. Effect of oral methylprednisolone on decline in kidney function or kidney failure in patients with IgA nephropathy: the TESTING randomized clinical trial. *JAMA*. 2022;327(19):1888–1898. doi:10.1001/jama.2022.5368
22. Rauen T, Eitner F, Fitzner C, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. *N Engl J Med*. 2015;373(23):2225–2236. doi:10.1056/NEJMoa1415463
23. Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl*. 2012;2:139–274.
24. Kinpeygo (budesonide) [European summary of product characteristics]. Bad Vilbel; STADA Arzneimittel AG; 2024. Available from: https://www.ema.europa.eu/documents/product-information/kinpeygo-epar-product-information_en.pdf. Accessed July 22, 2024.
25. Tarpeyo (budesonide) [US prescribing information]. Stockholm; Calliditas Therapeutics AB; 2024. Available from: https://www.tarpeyo.com/prescribinginformation.pdf. Accessed July 22, 2024.
26. Smerud HK, Bárány P, Lindström K, et al. New treatment for IgA nephropathy: enteric budesonide targeted to the ileocecal region ameliorates proteinuria. *Nephrol Dial Transplant*. 2011;26(10):3237–3242. doi:10.1093/ndt/gfr052
27. Lafayette R, Kristensen J, Stone A, et al. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial. *Lancet*. 2023;402(10405):859–870. doi:10.1016/S0140-6736(23)01554-4
28. Barratt J, Lafayette R, Kristensen J, et al. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. *Kidney Int*. 2022;103(2):391–402. doi:10.1016/j.kint.2022.09.017
29. Mathur M, Barratt J, Suzuki Y, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of VIS649 (sibeprenlimab), an APRIL-neutralizing IgG2 monoclonal antibody, in healthy volunteers. *Kidney Int Rep*. 2022;7(5):993–1003. doi:10.1016/j.ekir.2022.01.1073
30. Barratt J, Kooienga L, Agha I, et al. Updated interim results of a phase 1/2 study of BION-1301 in patients with IgA nephropathy. European Renal Association (ERA). Milan, Italy, 2023, Abstract 4337. Available from: https://academic.oup.com/ndt/article/38/Supplement_1/gfad063c_4337/7196269. Accessed June 14, 2024.
31. Lafayette R, Barbour S, Israni R, et al. A phase 2b, randomized, double-blind, placebo-controlled, clinical trial of atacicept for treatment of IgA nephropathy. *Kidney Int*. 2024;105(6):1306–1315. doi:10.1016/j.kint.2024.03.012
32. Lv J, Liu L, Hao C, et al. Randomized phase 2 trial of telitacicept in patients with IgA nephropathy with persistent proteinuria. *Kidney Int Rep*. 2023;8(3):499–506. doi:10.1016/j.ekir.2022.12.014
33. Tumlin JA, Singh H, Cortazar FB, et al. Povetacicept, an enhanced dual BAFF/APRIL antagonist, in autoantibody-associated glomerulonephritis (GN). American Society of Nephrology Kidney Week. Philadelphia, PA, USA, 2023, TH-PO1125. Available from: https://www.asn-online.org/education/kidneyweek/2023/program-abstract.aspx?controlId=3977579. Accessed June 14, 2024.
34. Alpine Immune Sciences Inc. An open-label study of povetacicept (ALPN-303) in autoimmune kidney diseases (RUBY-3). Available from: https://clinicaltrials.gov/study/NCT05732402. Accessed June 14, 2024.
35. RemeGen Co Ltd. A study of telitacicept in patients with primary IgA nephropathy. Available from: https://clinicaltrials.gov/study/NCT05799287. Accessed June 14, 2024.
36. Floege J, Lafayette R, Barratt J, et al. Felzartamab (anti-CD38) in patients with IgA nephropathy—interim results from the IGNAZ study. European Renal Association (ERA). Stockholm, Sweden, 2024, Abstract 425. Available from: https://academic.oup.com/ndt/article/39/Supplement_1/gfae069-0139-425/7678088. Accessed June 14, 2024.
37. Barratt J, Rovin B, Zhang H, et al. Efficacy and safety of iptacopan in IgA nephropathy: results of a randomized double-blind placebo-controlled phase 2 study at 6 months. ISN World Congress of Nephrology (WCN). Kuala Lumpur, Malaysia, 2022, POS–546. Available from: https://www.kireports.org/article/S2468-0249(22)00577-0/fulltext. Accessed June 14, 2024.
38. Barratt J, Flöge J, Duggal V, et al. IMAGINATION: a global phase 3 trial of RO7434656, an antisense oligonucleotide inhibitor of complement factor B, in IgA nephropathy. American Society of Nephrology (ASN) Kidney Week. Philadelphia, PA, USA, 2023, SA–PO885. Available from: https://medically.roche.com/content/dam/pdmahub/restricted/haematology/asn-kidney-week-2023/ASN-Kidney-Week-2023-poster-barratt-IMAGINATION-A-global-phase-3-trial.pdf. Accessed June 14, 2024.

39. Barbour SJ, Makris A, Hladunewich M, et al. An exploratory trial of an investigational RNA therapeutic, IONIS-FB-LRx, for treatment of IgA nephropathy: new interim results. American Society of Nephrology (ASN) Kidney Week. Philadelphia, PA, USA, 2023, SA–PO926. Available from: https://dam.ionisph.com/portals/9s1vyd3c/ASN-2023_An-Exploratory-Trial-of-IONIS-FB-lrx. Accessed June 14, 2024.
40. Barratt J, Rocha Castilla JL, Roccatello D, Garlo K, Rice K, Lafayette R. Efficacy and safety of ravulizumab in a phase 2 randomized controlled trial in IgA nephropathy. American Society of Nephrology (ASN) Kidney Week. Philadelphia, PA, USA, 2023, TH–PO1127. Available from: https://www.asn-online.org/education/kidneyweek/2023/program-abstract.aspx?controlId=3979029. Accessed June 14, 2024.
41. Bruchfeld A, Magin H, Nachman P, et al. C5a receptor inhibitor avacopan in immunoglobulin A nephropathy—an open-label pilot study. *Clin Kidney J*. 2022;15(5):922–928. doi:10.1093/ckj/sfab294
42. Wheeler DC, Toto RD, Stefansson BV, et al. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. *Kidney Int*. 2021;100(1):215–224. doi:10.1016/j.kint.2021.03.033
43. EMPA-KIDNEY Collaborative Group. Impact of primary kidney disease on the effects of empagliflozin in patients with chronic kidney disease: secondary analyses of the EMPA-KIDNEY trial. *Lancet Diabetes Endocrinol*. 2024;12(1):51–60. doi:10.1016/S2213-8587(23)00322-4
44. Filspari (sparsentan) [US prescribing information]. San Diego; Travere Therapeutics Inc; 2023. Available from: https://www.filspari.com/igan/filspari-prescribing-information.pdf. Accessed July 22, 2024.
45. Filspari (sparsentan) [Summary of product characteristics]. Vifor France; 2024. Available from: https://www.ema.europa.eu/en/documents/product-information/filspari-epar-product-information_en.pdf. Accessed July 22, 2024.
46. Edsbacker S, Andersson T. Pharmacokinetics of budesonide (Entocort EC) capsules for Crohn's disease. *Clin Pharmacokinet*. 2004;43(12):803–821. doi:10.2165/00003088-200443120-00003
47. Dressman J. Comparative dissolution of budesonide from four commercially available products for oral administration: implications for interchangeablity. *Dissolution Technol*. 2023;30(4):224–229. doi:10.14227/DT300423P224
48. Entocort (budesonide) [Summary of product characteristics]. Wellingore; Tillots Pharma UK Ltd; 2023. Available from: https://www.medicines.org.uk/emc/product/872/smpc#gref. Accessed July 22, 2024.
49. Allen A. The relationship between fluticasone furoate systemic exposure and cortisol suppression. *Clin Pharmacokinet*. 2013;52(10):885–896. doi:10.1007/s40262-013-0078-1
50. Szarka LA, Camilleri M. Methods for the assessment of small-bowel and colonic transit. *Semin Nucl Med*. 2012;42(2):113–123. doi:10.1053/j.semnuclmed.2011.10.004
51. O'Grady J, Murphy CL, Barry L, Shanahan F, Buckley M. Defining gastrointestinal transit time using video capsule endoscopy: a study of healthy subjects. *Endosc Int Open*. 2020;8(3):E396–E400. doi:10.1055/a-1073-7653
52. Vinarov Z, Abdallah M, Agundez JAG, et al. Impact of gastrointestinal tract variability on oral drug absorption and pharmacokinetics: an UNGAP review. *Eur J Pharm Sci*. 2021;162:105812. doi:10.1016/j.ejps.2021.105812
53. Ibekwe VC, Fadda HM, McConnell EL, Khela MK, Evans DF, Basit AW. Interplay between intestinal pH, transit time and feed status on the *in vivo* performance of pH responsive ileo-colonic release systems. *Pharm Res*. 2008;25(8):1828–1835. doi:10.1007/s11095-008-9580-9
54. Dressman, J, Philipson, R, Barratt, J. Comparison of the dissolution profile of Nefecon with three other commercially available oral formulations of budesonide: Implications for interchangeability. IIgANN, Tokyo, Japan, 2023.
55. Wimbury D, Muto M, Bhachu JS, et al. Targeted-release budesonide modifies key pathogenic biomarkers in immunoglobulin A nephropathy: insights from the NEFIGAN trial. *Kidney Int*. 2023;105(2):381–388. doi:10.1016/j.kint.2023.11.003
56. Molyneux K, Nawaz N, Taylor S, Barratt J. Treatment with Nefecon reduces circulating levels of galactose-deficient IgA1 in patients with IgA nephropathy in the NefIgArd clinical trial. American Society of Nephrology Kidney Week. Orlando, FL, USA, 2022, SA-PO654. Available from: https://www.asn-online.org/education/kidneyweek/2022/program-abstract.aspx?controlId=3770895. Accessed 22 July, 2024.
57. Jerling M Systemic GCS exposure from NEFECON administration, estimated from suppression of endogenous cortisol production. American Society of Nephrology Kidney Week. Washington, DC, USA, 2019, TH-PO1029. Available from: https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3236815. Accessed July 22, 2024.
58. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol*. 2013;9(1):30. doi:10.1186/1710-1492-9-30
59. Yang H, Zhang W, Li Y, Li R. Neutrophil-to-lymphocyte ratio: an effective predictor of corticosteroid response in IgA nephropathy. *Int Immunopharmacol*. 2019;74:105678. doi:10.1016/j.intimp.2019.105678
60. Chiang JL, Patterson R, McGillen JJ, et al. Long-term corticosteroid effect on lymphocyte and polymorphonuclear cell function in asthmatics. *J Allergy Clin Immunol*. 1980;65(4):263–268. doi:10.1016/0091-6749(80)90153-0
61. Hanson RG, Peters MG, Hoofnagle JH. Effects of immunosuppressive therapy with prednisolone on B and T lymphocyte function in patients with chronic type B hepatitis. *Hepatology*. 1986;6(2):173–179. doi:10.1002/hep.1840060204