B-Cell Directed Therapies for IgA Nephropathy: Effectiveness and Value

Final Report

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Prepared for

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Jason H. Wasfy served as the lead author on the report. Avery McKenna led the systemic review and authorship of the comparative clinical effectiveness section of this report with support from Sophia Cassim. R. Brett McQueen, Michael J. DiStefano, Antal Zemplenyi, and Deepika Paratane developed the cost-effectiveness model and authored the corresponding sections of the report in collaboration with Woojung Lee. Marie Phillips conducted the analysis for the budget impact model. David M. Rind provided methodologic guidance on the clinical and economic sections. We would also like to thank Madeline Booth, Anna Geiger, and Chloe Fandetti for their contributions to this report.

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The funding for this report comes from non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers (PBMs), or life science companies. ICER receives approximately 22% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include: Otsuka Holdings Co., Ltd. A complete list of funders and more information on ICER's support, is available on the funding page of the ICER website.

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In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:

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None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions or iterations of the report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from whom we requested input, or who have submitted public comments so far, please visit: https://icer.org/assessment/iga-nephropathy-2025/

Conflict of Interest Disclosures for the Report

Table 1. ICER Staff and External Collaborators Conflict of Interest Disclosures

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Table 2. Expert Reviewers of the Draft Evidence Report Conflict of Interest Disclosures

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Jonathan Barratt, PhD, FRCP Professor of Renal Medicine University of Leicester, UK	Dr. Barratt has received income in the last 36 months from health care companies relevant to this review including Calliditas, Otsuka, Vera Therapeutics, Argenx, Alexion, Vertex Pharmaceuticals, Takeda Pharmaceutical, Biohaven, Novartis, and Roche.
Phil McEwan, PhD Chief Executive Officer Health Economics and Outcomes Research, Ltd.	No conflicts to disclose
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Bonnie Schneider Founder and Executive Director IgA Nephropathy Foundation	The IgA Nephropathy Foundation received 95% of funding from health care companies including Calliditas, Otsuka, and Vera Therapeutics.

These pages include conflict of interest disclosures for ICER staff, external collaborators, and expert reviewers of the report. For all public meeting participant disclosures, please refer to Supplement I.

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List of Acronyms and Abbreviations Used in this Report

AE	Adverse event
ACEi	Angiotensin-converting enzyme inhibitor
AHRQ	Agency for Healthcare Research and Quality
APRIL	A Proliferation-Inducing Ligand
ARB	Angiotensin receptor blocker
BAFF	B-cell Activating Factor
BLA	Biologic License Application
CKD	Chronic Kidney Disease
CI	Confidence interval
DEARA	Dual endothelin and angiotensin receptor antagonist
dL	Deciliter
eGFR	Estimated glomerular filtration rate
ESKD	End-stage kidney disease
evLYs	Equal value life years
FDA	Food and Drug Administration
g/g	Grams per grams
HR	Hazard ratio
IgA	Immunoglobulin A
IgAN	Immunoglobulin A Nephropathy
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
LYs	Life years
mg	Milligram
mL/min/1.73m^2	Milliliter per minute per 1.73 meters squared
N	Total number
NC	Not calculated
NR	Not reported
OLE	Open-label extension
PDUFA	Prescription drug fee user act
PPPM	Per person per month
QALYs	Quality-adjusted life years
RASi	Renin-angiotensin inhibitor
SC	Subcutaneous
SD	Standard deviation
SGLT2i	Sodium-glucose cotransporter-2 inhibitor
TBD	To be determined
TEAE	Treatment-emergent adverse event
uACR	Urine albumin-creatinine ratio
uPCR	Urinary protein-to-creatinine ratio
WAC	Wholesale acquisition cost

Executive Summary

IgA nephropathy (IgAN) is a disorder that occurs when abnormal complexes of the antibody immunoglobulin A (IgA) are deposited in the kidneys, causing inflammation and damage. When the kidneys can no longer filter blood and clear toxins from the body, either kidney transplantation or dialysis is required to avoid death. There are uncertainties about how often this happens with IgAN: for many patients, either death or end-stage kidney disease (ESKD) occurs within 15-20 years after IgAN diagnosis, although other reports suggest more than two-thirds still have functioning kidneys at 25 years.[1,2] In the United States (US), an estimated 200,000 individuals have IgAN. IgAN is more common in males than in than females in the US and many new diagnoses occur in young adults.

Patients have told us that their lives change substantially after IgAN diagnosis. By time of recognition, kidney damage has occurred for many. Current treatments have important toxicities and so far do not stop deterioration of kidney function, so patients are often faced with an uncertain tradeoff between drug toxicities in the short term to reduce the risk of kidney failure in the longer term. Since recognition of IgAN in the 1960s, the main treatment to reduce IgA deposition has been systemic oral glucocorticoids, which have substantial side effects.

Nefecon, an oral preparation of the glucocorticoid budesonide in a delayed-release formulation intended to target release to the distal ileum (Tarpeyo®, Calliditas Therapeutics AB; sometimes referred to as "*delayed release*" [FDA label] or "*targeted release*") is administered daily for nine months and was approved by the US Food and Drug Administration (FDA) in 2023.[3] Nefecon has "first-pass" metabolism in the liver, and is thought to therefore have lower risk of systemic side effects. Sibeprenlimab (Voyxact®, Otsuka Holdings Co., Ltd.) is a monoclonal antibody that binds to and neutralizes a proliferation-inducing ligand (APRIL) that regulates immune cell activity and the production of IgA antibodies.[4] The drug is administered subcutaneously every four weeks. Sibeprenlimab was approved by the FDA under accelerated approval on November 25, 2025.[5] Atacicept (Vera Therapeutics, Inc.) is a recombinant fusion protein that can bind to and neutralize APRIL as well as B-cell Activating Factor (BAFF), another regulator of immune activity.[6] The drug is administered subcutaneously and has a Prescription Drug Fee User Act (PDUFA) date of July 7, 2026.[7]

Clinical evidence includes high-quality Phase II and Phase III randomized comparisons of systemic glucocorticoids, Nefecon, atacicept, and sibeprenlimab against no specific immunomodulatory therapy. All these treatments appear to slow the deterioration in kidney function in IgAN, although interim Phase III results for atacicept and sibeprenlimab focus on reduction in urine protein (proteinuria) rather than loss of kidney function; final Phase III results will present data on kidney function. The trajectory of placebo arms differ across the various trials, showing that enrolled trial populations differ. As such, effect estimates from interventions in trials have limited ability to be compared against each another. The harms of systemic glucocorticoids are well known. Atacicept

and sibeprenlimab appear well tolerated but have a new mechanism of action and so rare and/or longer-term harms could emerge. Nefecon produces systemic glucocorticoid side effects in at least some patients, and it is unclear how effective a single nine-month course is over a lifetime; repeated courses of treatment are being evaluated. Given the strengths and limitations of these data, we have high confidence of at least a small net health benefit for all these interventions and the comparator relative to no specific immunomodulatory therapy but less confidence about the comparative effectiveness of the intervention and comparator against one another.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
B-Cell Directed Therapies Compared with No Specific Immunomodulatory Therapy		
Sibeprenlimab	No specific immunomodulatory therapy	B+
Atacicept	No specific immunomodulatory therapy	B+
Nefecon	No specific immunomodulatory therapy	B+
B-Cell Directed Therapies Compared to Systemic Glucocorticoids		
Sibeprenlimab	Systemic Glucocorticoids	P/I
Atacicept	Systemic Glucocorticoids	P/I
Nefecon	Systemic Glucocorticoids	P/I
B-Cell Directed Therapies Compared to Each Other		
Sibeprenlimab	Atacicept	I
Sibeprenlimab	Nefecon	I
Atacicept	Nefecon	I

B+: 'Incremental or Better' – Moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit, I: 'Insufficient' – Any situation in which the level of certainty in the evidence is low, P/I: 'Promising but Inconclusive' – Moderate certainty of a small or substantial net health benefit with a small likelihood of a negative net health benefit

To estimate the cost-effectiveness of these new therapies, we developed a *de novo* Markov model (Figure 4.1) with a cycle length of one month, informed by key clinical trials and prior relevant economic models.[8-10,11,12]

Our analysis has substantial uncertainties given that IgAN can progress over many years while available data on new therapies are short-term. Our best estimates suggest that at its current price, a single course of Nefecon is more expensive but more effective than systemic glucocorticoids with base-case findings meeting the upper bound of commonly cited cost-effectiveness thresholds. However, in probabilistic sensitivity analyses, there was uncertainty in whether Nefecon would meet commonly cited cost-effectiveness thresholds. For example, varying inputs related to adverse effects from systemic glucocorticoids led to either increases in the incremental cost-effectiveness ratios or decreases to a point where Nefecon may be more effective and less costly. We also estimate that sibeprenlimab compared to systemic glucocorticoids leads to extensions to life and improvements in quality of life but, at the current estimated net price, far exceeds commonly used cost-effectiveness thresholds. The cost-effectiveness of atacicept will depend on its actual price, though would also far exceed commonly used cost-effectiveness thresholds if atacicept is priced

similarly to sibeprenlimab. The annual Health Benefit Price Benchmark (HBPB) is $61,000 to $81,000 for sibeprenlimab, $60,000 to $80,000 for atacicept, $110,900 to $143,000 for a single treatment course of Nefecon.

At the current net price of sibeprenlimab ($292,500 per year), 6% of the eligible population could be treated before reaching the ICER potential budget impact threshold of $821 million. Therefore, ICER is issuing an access and affordability alert for sibeprenlimab. For atacicept, ICER is issuing an alert based on a placeholder price of $292,500 per year, but no alert would be needed if atacicept is actually priced within the HBPB range. ICER is not issuing an alert for Nefecon.

Key policy recommendations include:

- If the price of sibeprenlimab is reduced to a price aligned with value, and if the initial price of atacicept is aligned with value, payers should not require step therapy with systemic glucocorticoids or Nefecon before authorizing use of sibeprenlimab or atacicept for treatment of IgAN.
- Manufacturers should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. In the case of IgAN, substantial new hope with the availability of these therapies is diminished by the extremely high price of sibeprenlimab. Nefecon is priced slightly above a value-based price.
- Manufacturers should create a cross-trial repository of blood and urine data and permit access by academic researchers to assist in better understanding how to identify patients with IgAN who are more or less likely to progress on and off various therapies.
- Research funding organizations should support pragmatic analyses assessing the feasibility and the effectiveness of large-scale screening for IgAN and other kidney diseases including among children, which would inform public health practices like school-based screening programs.

Appraisal committee votes on questions of comparative effectiveness and value, along with other key policy recommendations regarding pricing, access, and future research are included in the main report.

1. Background

IgA nephropathy (IgAN, known as Berger's disease) occurs when abnormal complexes of immunoglobulin A (IgA) antibodies are deposited in the glomeruli of the kidneys, resulting in inflammation (glomerulonephritis) and kidney damage. Some patients with IgAN note recurrent episodes of blood in the urine (gross hematuria), often coinciding with upper respiratory infections, while others are diagnosed after evaluation for the disorder when urine studies show microscopic protein and/or blood in the urine.[13] Presentations with gross hematuria are more common in children and young adults than in older adults.[13] Over time, kidney damage can progress to end-stage kidney disease (ESKD) where patients require dialysis or renal transplant. Although blood and urine tests can suggest IgAN, confirming the diagnosis requires a biopsy of the kidney. An estimated 200,000 individuals in the United States (US) have IgAN, and in American cohorts, IgAN is more than twice as common among males as females.[14,15] In the US, IgAN is more commonly diagnosed in Asian individuals and less commonly diagnosed in Black individuals.[16] For many patients, either death or ESKD occurs within 15-20 years after IgAN diagnosis, although other reports suggest more than two-thirds still have functioning kidneys at 25 years.[1,2] Integrating the reported prevalence of ESKD caused by IgAN, the current US population, and the cost of ESKD per year, we estimate that care for ESKD caused by IgAN costs $1.3 billion dollars annually.[1,17,18]

The patient experience with chronic kidney disease (CKD) varies with the stage of disease. After diagnosis, more than half of patients experience worry or shock. As the CKD progresses, most patients report fatigue and muscle cramps and over one-third report anxiety or depression. Once CKD reaches ESKD, nearly half of patients report inability to sleep and more than three-quarters report difficulty with the ability to work.[19] Patients being treated with hemodialysis typically need to have a surgical procedure to create vascular access, go to a specialized center three times per week for hours of dialysis, and have limitations on their ability to travel because of the need for dialysis. For patients with ESKD who receive kidney transplantation, patients report substantial needs for self-care, financial concerns, health systems obstacles, and limitations in social activities.[20]

New guidelines, as well as our discussions with clinical experts, emphasize the importance of simultaneously (1) reducing the production of IgA antibodies that eventually deposit in the kidneys with immunosuppressive therapies that inhibit B-cell function as well as (2) protecting glomerular function in the kidneys once deposition of pathogenic IgA has already occurred. Both novel and existing medications are generally directed at achieving one or the other of these clinical purposes. For goal #2, treatments to protect glomerular function in IgAN include general measures for kidney protection in people with chronic kidney disease (CKD), including blood pressure control and the use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) in patients with substantial proteinuria. More recent management guidelines include the use of dual

endothelin and angiotensin receptor antagonist (DEARA) therapy and/or sodium-glucose cotransporter-2 inhibitor (SGLT2i) therapy in some patients.[21] General supportive care is also recommended, including smoking cessation, weight management, exercise, and reduction in salt intake. In terms of goal #1, for patients with higher levels of protein in the urine and other poor prognostic markers, immunosuppressive drugs can be considered; side effects of these therapies can be substantial. For many years, systemic glucocorticoids (typically prednisone or methylprednisolone) were used as main immunosuppressants although additional medications such as cyclophosphamide and azithothioprine were recommended in specific circumstances. Nefecon, an oral preparation of the glucocorticoid budesonide, was approved by the US Food and Drug Administration (FDA) in 2023. Nefecon is a delayed-release formulation intended to target release to the distal ileum (Tarpeyo®, Calliditas Therapeutics AB; sometimes referred to as "*delayed release*" [FDA label] or "*targeted release*"). Since Nefecon is released in the distal ileum and has "first-pass" metabolism in the liver, therefore is thought to have lower risk of systemic side effects.

In addition to the above options, other treatments targeting B-cell activity are becoming available. Sibeprenlimab (Voyxact®, Otsuka Holdings Co., Ltd.) is a monoclonal antibody that binds to and neutralizes a proliferation-inducing ligand (APRIL) that regulates immune cell activity and the production of IgA antibodies.[4] The drug is administered subcutaneously. The FDA approved sibeprenlimab under accelerated approval on November 25, 2025.[5] Atacicept (Vera Therapeutics, Inc.) is a recombinant fusion protein that can bind to and neutralize APRIL as well as B-cell Activating Factor (BAFF), another regulator of immune activity.[6] The drug is administered subcutaneously. The manufacturer announced the biologics license application (BLA) submission through the Accelerated Approval Program in November 2025 with a PDUFA date of July 7, 2026.[7]

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Sibeprenlimab	Monoclonal antibody that binds to and neutralizes APRIL	Subcutaneous injection	400 mg every 4 weeks
Atacicept	Recombinant fusion protein that inhibits APRIL and BAFF	Subcutaneous injection	TBD
Nefecon	Formulation of the glucocorticoid budesonide targeted to act locally in the distal ileum	Daily oral capsule	16 mg/day

APRIL: A Proliferation-Inducing Ligand, BAFF: B-cell Activating Factor, mg: milligram, TBD: to be determined

2. Patient and Other Stakeholder Input

During this review, we sought input from diverse stakeholders, including patients and patient advocates, clinicians, researchers, and manufacturers of the treatments under consideration. This section summarizes feedback gathered during calls with patient community stakeholders (patients and patient advocacy organizations) and clinical experts. ICER looks forward to continued engagement with stakeholders throughout the review to refine our understanding of the clinical effectiveness and value of treatments for IgAN.

2.1 Patient Community Insights

Nearly all patients with IgAN described to us that they experienced delayed diagnosis and inadequate access to subspecialty expertise. Many patients reported histories of clinical hematuria and findings on urinalysis that were thought at the time to suggest urinary tract infections or other clinical conditions. We heard that for diagnosis with kidney biopsy, many patients face challenges in finding nephrologists with appropriate expertise, and this can interfere with obtaining a timely diagnosis. These delayed diagnoses are harmful because they lead to worse kidney function by the time IgAN is diagnosed. We also heard from multiple patients about fractured care from changes in providers or gaps in insurance coverage that contributed to additional delays in diagnosis. Given that the initial diagnosis is often difficult and delayed, once diagnosed, many patients perceive the need to adopt a "self-advocacy" approach to IgAN care. Many diagnoses of IgAN occur in younger patients previously thought to be healthy. One patient shared with us that "there is a clear divide of life before diagnosis and after diagnosis." Another patient discussed how "life after IgAN" creates tremendous uncertainty and changes in plans for careers and building families.

Discussions with patient advocacy groups emphasized the difficulty of accessing care even after diagnosis, particularly at earlier stages of disease before dialysis is needed. More broadly, availability of nephrologists who have specific expertise in clinical management of glomerulopathies is limited, and better access to expertise at an earlier stage of disease might improve patient outcomes and reduce patients' anxiety and uncertainty. It could potentially also reduce some patient costs, such as the costs of traveling to see various specialists. Patients prioritize avoiding dialysis, and stress for family and caregivers increase when patients develop ESKD.

Even with access to appropriate expertise after diagnosis, patients must balance the risks of difficult choices such as certainties of medication side effects with uncertainties of later disease course. Toxicities of steroids include weight gain, insulin resistance, osteopenia, sleep and mood changes, and potentially serious infections. Even though Nefecon is thought to have less systemic effects (and thus potentially fewer and less severe side effects) than systemic glucocorticoids, some patients report typical steroid side effects while receiving Nefecon. Other choices pose different

risks. Some immunosuppressive agents, such as cyclophosphamide, can cause cancers, hair loss, and infertility. The risk of infertility with some treatments is one of several aspects of IgAN care that differentially affects women (discussed in greater detail among health equity considerations below). Immunosuppressive therapy increases the risk of opportunistic infections, some of which can be fatal. Even if those feared complications do not occur, patients may need to make life and employment decisions to avoid the risk of infections or being away from care if infection were to occur. More options are needed, since standard first-line treatments lead to remission in some patients but not others. Especially in the absence of many direct comparisons between options, expected side effect profiles and life circumstances are important in decision making.

Despite hope for improved side effect profiles with newer options, cost and access are potential difficulties. Many patients report difficulty accessing Nefecon as well as other IgAN treatments that do not affect B-cell function (such as sparsentan), in part due to high patient-facing cost sharing. Similar challenges appear likely for atacicept and sibeprenlimab as they enter clinical practice.

A Voice of the Patient Report for IgA Nephropathy highlighted the importance of measures including kidney function, rate of damage to kidney function (proteinuria/albuminuria), and the time to dialysis or transplant.[22] Patients would be more enthusiastic about trying a novel medication that reduces proteinuria, slows deterioration in kidney function, or improves the way patients feel, function, or survive. Halting progression of disease and/or delaying need for dialysis were core hopes for any new therapies, although managing fatigue and anxiety are also core unmet needs for patients. Patients also note that trials should include children. Any requirement for annual kidney biopsies would reduce interest in trial enrollment. Conversely, patients expressed willingness to participate in clinical trials for many years and expressed high tolerance for risk given the expected trajectory of IgAN.[22] Patients do not feel that their treatments adequately reduce important symptoms, including fatigue, anxiety/depression, or intolerance to heat/cold. Systemic glucocorticoids are commonly noted to have substantial side effects. Patients also report difficulties with social isolation, difficulty maintaining relationships, uncertainty about trajectory, and the ability to attend important recreational and life events.[22]

2.2 Health Equity Considerations

Women face specific challenges with both diagnosis and treatment for IgAN. Although IgAN can occur at any age, median age at diagnosis is between 30 and 40. As such, the disorder affects many women of childbearing age and some of the treatment options affect fertility. The 2025 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest that many IgAN treatments including Nefecon, SGLT2i, RAS inhibitors, and sparsentan should be discontinued in women who may become pregnant.[23] Additionally, the initial clinical symptoms and findings on urinalysis of IgAN can mimic a urinary tract infection, a syndrome much more common in young women than young

men. As such, conceptually, the challenges that all patients faced with timely diagnosis may affect women even more.

We reviewed challenges with insurance coverage with a dialysis social worker. She shared that patients receiving home dialysis immediately become eligible for Medicare although patients who receive hemodialysis at a center are not eligible for Medicare until they have been receiving dialysis for three months. Financial stress can be important for patient decisions regarding coverage. For example, some patients enroll in Medicare earlier within a coordination period given higher patient-facing costs from private insurance plans. Conversely, others cannot afford Medicare premium costs and therefore enroll in Medicare later. Patients with fewer financial resources therefore may have more difficulty navigating the transition from private to Medicare insurance with the development of ESKD.

2.3 Clinical Expert Insights

Discussions with clinical experts emphasized the importance of evolving treatment paradigms for IgAN. Given rapid development of new therapeutic options, clinical experts are currently reviewing and debating potential new therapeutic pathways. Clinical experts emphasized that neither traditional (ACE/ARB) or novel (DEARA) inhibitors of the renin-angiotensin system like sparsentan are alternatives to inhibitors of APRIL and/or BAFF. Discussions with clinical experts also emphasized the magnitude of unmet need for individuals with IgAN. Many patients are at high risk for developing ESKD over the course of years, even with lower levels of proteinuria.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Scope of Review

We evaluated the clinical effectiveness of B-cell directed therapies compared to systemic glucocorticoids, no specific immunomodulatory treatment, and to each other, for people with IgAN. All groups were expected to receive renal protective therapies that could include renin-angiotensin inhibitors (RASis), sodium-glucose cotransporter (SGLT2) inhibitors, and/or endothelin receptor antagonists (ERAs), as well as lifestyle modification. We sought and reviewed evidence on patient-important outcomes, including the development of end-stage kidney disease, hospitalization, quality of life, and serious adverse events such as infections, injection site reactions, and common corticosteroid adverse effects (e.g., metabolic effects, bone loss) as well as measures that may predict these outcomes, such as glomerular filtration rate and proteinuria. The full protocol for the review is available in Supplement Section D1.

Evidence Base

The evidence informing our review of B-cell directed treatments for IgAN was primarily derived from Phase II and Phase III randomized controlled trials (RCTs). We prioritized Phase III trials unless key endpoints (i.e., eGFR) were only reported in the corresponding Phase II trials. Data sources include peer-reviewed publications, conference presentations, and clinicaltrials.gov. Key trial characteristics are outlined below and in Table 3.1. Additional details are in Supplement Section D2.

Across the main trials, key inclusion criteria were: biopsy-confirmed IgAN, baseline urine protein-creatinine ratio (uPCR) ranging from ≥0.75 to 1.0 g/g (urinary protein excretion ≥1 g/day for the key glucocorticoid trial), baseline eGFR ranging from ≥30 to ≥35 mL/min/1.73m^2 (see Table 3.1 for ranges across trials), and a stable and maximally tolerated dose of ACEi or ARBs for a period of time before screening. Common exclusion criteria were: secondary forms of IgAN, nephrotic syndrome, rapidly progressive glomerulonephritis, and prior use of chronic systemic immunosuppression during a designated period of time before randomization. Detailed trial criteria and baseline characteristics are outlined below in Table 3.1, Supplement Section D2, and Supplement Tables D3.1-7.

Sibeprenlimab

The evidence informing our review of sibeprenlimab includes data from the ongoing Phase III VISIONARY trial and the published Phase II ENVISION trial.[8,24]

VISIONARY is an ongoing Phase III RCT that is evaluating the efficacy and safety of sibeprenlimab 400 mg subcutaneously (SC) every four weeks versus placebo for 100 weeks. A total of 510 participants have been randomized. Currently available data include results for 320 participants who received either sibeprenlimab (n=152) or placebo (n=168) and have completed nine months of follow-up. An exploratory cohort of 20 participants with IgAN and an eGFR between 20 and 30 is being evaluated but data are not available at this time.[25] A pre-specified interim analysis reports on the primary efficacy endpoint of the ratio of 24-hour uPCR ratio at month nine compared with baseline.[24] Data on annualized eGFR slope over 24 months are expected in 2026.[26]

ENVISION is a published Phase II RCT that evaluated the efficacy and safety of three weight-based doses of sibeprenlimab compared to placebo. Participants were randomized to sibeprenlimab 2 mg/kg (n=38), 4 mg/kg (n=41), 8 mg/kg (n=38), or placebo (n=38) and received intravenous treatment or matched placebo once a month for 12 months. Participants were followed for an additional four months of observation.[8] The results presented below will primarily focus on the 4 mg/kg dose of sibeprenlimab since modeling showed that the 400 mg subcutaneous (SC) dose being evaluated in the Phase III trial led to similar levels of exposure and IgA reduction as the intravenous (IV) administration.[26-28]

Baseline characteristics are presented in Supplement Table D3.2.

Atacicept

The evidence informing our review of atacicept primarily comes from the published Phase II ORIGIN and Phase III ORIGIN 3 trials.[9,29] This was supplemented by data from the Phase IIa JANUS study, a published open-label extension (OLE) study, and an integrated safety profile of atacicept across indications, which are described in Supplement Section D2.[30-32]

ORIGIN 3 is an ongoing Phase III RCT evaluating the efficacy and safety of atacicept compared to placebo. Enrolled participants were randomized to receive either atacicept 150 mg (n=214) or placebo (n=214) subcutaneously once weekly for 104 weeks. A pre-specified interim analysis reports on data up to week 36, with a focus on the primary endpoint of change in 24-hour uPCR.[29]

ORIGIN was a Phase II RCT that evaluated the efficacy and safety of three doses of atacicept compared to placebo. Enrolled participants were randomized to receive atacicept 25 mg (n=16), 75 mg (n=33), 150 mg (n=33), or placebo (n=34) subcutaneously once weekly for 36 weeks.[9] Participants who completed the trial were enrolled in an open-label extension trial and received

atacicept 150 mg for 60 additional weeks, for a total follow-up time of 96 weeks.[31] While the primary outcome focused on data from the combined 75 mg and 150 mg atacicept group, we primarily focused on the 150 mg atacicept dose as this is the dose studied in the Phase III ORIGIN 3 trial and is the anticipated approval dose.[29]

Baseline characteristics are presented in Supplement Tables D3.3-4.

Nefecon

The evidence informing our review of Nefecon is primarily derived from the Phase III NefIgArd trial.[10] These data were supplemented by data from the NefIgArd OLE, the Phase II NEFIGAN trial, a publication of a China cohort from NefIgArd, and a post marketing safety study.[33-37] In this case, we prioritized the Phase III trial since there were not important endpoints reported in the Phase II trial that were not also reported in the Phase III trial. We also identified one publication and five abstracts related to small real-world observational studies.[38-44] This supporting evidence is described in Supplement Section D2.

NefIgArd was a Phase III RCT that evaluated the efficacy and safety of Nefecon versus placebo. Participants were randomized to either Nefecon 16 mg (n=182) or placebo (n=182) via oral capsule once daily for nine months. The trial consisted of two parts: Part A and Part B. Part A reported on an initial analysis of uPCR at month nine for 199 patients who had nine months of treatment and three months of follow-up.[45] Part B presented final results for 364 participants who received nine months of Nefecon or placebo and had 15 months of follow-up for a total trial period of two years.[10] The primary outcome for Part B was the time-weighted change in eGFR over two years. The OLE of NefIgArd enrolled participants who met the proteinuria eligibility (≥1 g/day at end of NefIgArd) from the double-blind period to receive a nine-month course of Nefecon; this was either a second nine-month course for those who had been in the treatment arm (n=45) or a first course for those who initially received placebo (n=74).[36]

Baseline characteristics are presented in Supplement Tables D3.5-6.

Systemic Glucocorticoids

Our review highlighted systemic glucocorticoids as a comparator of interest. The evidence informing our review of systemic glucocorticoids was primarily derived from the TESTING trial, as this is the largest and most recent randomized trial that reports on steroid efficacy for individuals with IgAN.[46-48] This was supported by evidence from previously published randomized trials evaluating the efficacy of corticosteroids or other immunosuppressants for IgAN (e.g., STOP-IgAN).[49-54] The STOP-IgAN trial included combinations of immunosuppressive therapies and so does not provide direct evidence on glucocorticoids alone compared to supportive care. As such, our review focused on the TESTING trial.

TESTING was an RCT initiated in 2012 that evaluated the safety and efficacy of oral methylprednisolone compared to placebo.[47] The trial enrolled predominantly Asian participants (93%), most of whom were from China. Initially, 263 participants were randomized to either methylprednisolone 0.6 to 0.8 mg/kg per day for two months with doses tapering by 8 mg per day or matching placebo for a treatment period of six to eight months. Due to cases of serious infections in the methylprednisolone group, two of which led to death, the study was halted. After a 2017 protocol revision to randomize participants to a lower dose (0.4 mg/kg for two months with dose tapering of 4 mg each day for a total of six to nine months), 241 additional participants were randomized.

Two publications that reported the results of the TESTING trial were Lv 2022 and Kim 2024. Lv 2022 reported data from 503 participants from both the initial full-dose cohort and the reduced-dose cohort. At the time of the publication, the median follow-up time for the overall cohort was 3.5 years (6.1 years for full-dose, 2.5 years for reduced-dose).[47] Kim 2024 reported data from the 241 participants who received a reduced-dose of methylprednisolone and data from this publication are the focus of our review below as we heard from clinical experts that this aligns with current clinical care.[48]

Baseline characteristics are presented in Supplement Table D3.7.

Table 3.1. Key Trial Characteristics[8-10,24,29,48]

Trial	Population	Primary Outcome	Treatment and Follow-Up Time	Key Baseline Characteristics‡
Sibeprenlimab				
VISIONARY*	Adults with biopsy confirmed IgAN with uPCR ≥0.75 g/g and eGFR ≥30 mL/min/1.73m^2 N=510†	Change from baseline in 24h-uPCR at month 9	Treatment: 100 weeks Follow-up: 12 weeks	% Male: 63 % Asian: 59 Median age: 42.5 Mean eGFR: 63.45 Median uPCR: 1.25 Mean proteinuria: NR
ENVISION	Adults with biopsy confirmed IgAN with uPCR ≥0.75 g/g and eGFR ≥30 mL/min/1.73m^2 N=155	Change from baseline in the 24h-uPCR at month 12	Treatment: 12 months Follow-up: 4 months	% Male: 57 % Asian: 74 Median age: 39 Median eGFR: 63.25 Mean uPCR: 1.6 Median proteinuria: 1.9
Atacicept				
ORIGIN 3*	Adults with biopsy confirmed IgAN with uPCR ≥ 1.0 g/g and eGFR ≥30 mL/min/1.73m^2 N=428†	Change from baseline in 24h-uPCR at month 9	Treatment: 104 weeks	% Male: 57 % Asian: 55 Mean age: 40.5 Mean eGFR: 65.1 Mean uPCR: 1.75 Mean proteinuria: 2.25

Trial	Population	Primary Outcome	Treatment and Follow-Up Time	Key Baseline Characteristics‡
ORIGIN	Adults with biopsy confirmed IgAN with uPCR ≥0.75 g/g and eGFR ≥30 mL/min/1.73m^2 N=116	Change from baseline in 24h-uPCR at week 24 (~month 6)	Treatment: 9 months	% Male: 59 % Asian: 44 Mean age: 39 Mean eGFR: 63 Mean uPCR: 1.6 Mean proteinuria: 2.2
Nefecon				
NefIgArd	Adults with biopsy confirmed IgAN with uPCR ≥0.8 g/g and eGFR 35 – 90 mL/min/1.73m^2 N=364	Time-weighted mean eGFR over two years	Treatment: 9 months Off-treatment Follow-up: 15 months	% Male: 66 % Asian: 23 Mean age: 42.5 Median eGFR: 55.6 Median uPCR: 1.48 Mean proteinuria: 2.7
Systemic Glucocorticoids				
TESTING, Reduced-dose	Adults with biopsy confirmed IgAN with a UPE ≥1 g/day and eGFR 30 – 120 mL/min/1.73m^2 N=241	First occurrence of a sustained 40% eGFR decrease, kidney failure, or death due to kidney disease.	Treatment: 6 – 9 months Median total follow-up: 2.5 years	% Male: 58 % Asian: 93 Mean age: 36.7 Mean eGFR: 65.0 Mean uPCR: NR Mean proteinuria: 2.48

eGFR: estimated glomerular filtration rate, g/g: gram per gram, mL/min/1.73m^2: milliliter per minute per 1.72 meters squared, N: total number, uPCR: urinary protein-to-creatinine ratio, UPE: urinary protein excretion, NR: not reported

*Trials are ongoing, final data not available at the time of review.

†Results from pre-specified interim analysis are for 320 participants for VISIONARY trial and 203 participants for ORIGIN 3.

‡Units: age: years, eGFR: mL/min/1.73m^2, uPCR: g/g, proteinuria: g/day

Evaluation of Clinical Trial Diversity

We rated the demographic diversity (race/ethnicity, sex, age) of the participants in the trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[55] The VISIONARY, ORIGIN 3 and ORIGIN trials achieved a "fair" diversity rating for race and ethnicity. The remainder of the key trials achieved a "poor" diversity rating for race and ethnicity. Trials for IgAN were multi-national and predominantly enrolled participants from Asian countries. In the absence of requested US specific demographic data, these trials appeared have a greater percentage of Asian participants than what would be observed in the US and therefore appear to under enroll other racial/ethnic groups when compared to prevalence estimates of people with IgAN in the US. All trials achieved a "good" diversity rating for sex. We did not calculate diversity ratings on age due to lack of demographic data on participants older than 65 in the trials. See Supplement D1 for full details of CDR methods and results.

Table. 3.2. Diversity Ratings for Key Trials

Trial	Race and Ethnicity	Sex	Age (Older Adults)
VISIONARY	Fair	Good	NC
ENVISION	Poor	Good	NC
ORIGIN 3	Fair	Good	NC
ORIGIN	Fair	Good	NC
NEFIGARD	Poor	Good	NC
NEFIGAN	Poor	Good	NC
TESTING	Poor	Good	NC

NC: not calculated

3.2. Results

Clinical Benefits

Data on outcomes of estimated glomerular filtration rate (eGFR), 24-hour urinary protein-to-creatinine ratio (uPCR), and hematuria, and patient-important outcomes including composite endpoints around ESKD and health-related quality of life are described below. Additional endpoints related to proteinuria, such as spot uPCR, urine protein excretion, and urinary albumin-to-creatinine ratio (uACR), and IgAN biomarkers (e.g., Gd-IgA1, IgG, APRIL) and need for rescue medication are detailed in Supplement Section D2. Definitions for outcomes described below are in Supplement Section A.

Estimated Glomerular Filtration Rate (eGFR)

eGFR was presented both as changes over time and as annualized slopes. Where reported, both measures are described below.

Sibeprenlimab

At the time of this review, data on eGFR was not available for the Phase III VISIONARY trial. In the Phase II ENVISION trial, there was a change of +0.2 mL/min/1.73m^2 in eGFR in the sibeprenlimab 4 mg/kg group compared to a change of -7.4 mL/min/1.73m^2 in the placebo group at month 12. The annualized eGFR slope was +0.1 mL/min/1.73m^2/year for sibeprenlimab 4 mg/kg and -5.9 mL/min/1.73m^2/year for placebo (see Table 3.3).[8]

Atacicept

At the time of this review, data on eGFR was not available for the Phase III ORIGIN 3 trial. In the Phase II ORIGIN trial, there was a change of +0.92 mL/min/1.73m^2 (95% CI: -3.2 to 5.2) in eGFR in the atacicept 150 mg group compared to a change of -4.9 mL/min/1.73m^2 (95% CI: -8.5 to -1.1) in the placebo group at month nine (~36 weeks).[9] Over 96 weeks of follow-up from ORIGIN OLE, mean

eGFR levels for all atacicept-treated participants were above baseline levels up until week 96; at week 96, the mean change in eGFR was approximately -2.02 mL/min/1.73m^2.[31] A conference abstract reported that at 26 weeks of follow-up after the last dose of atacicept in the OLE, the mean change in eGFR was -3.9 mL/min/1.73m^2.[56]

The annualized eGFR slope was +2.6 mL/min/1.73m^2/year for atacicept 150 mg and -3.2 mL/min/1.73m^2/year for placebo (see Table 3.3).[9] However, this was estimated in an exploratory analysis using nine months of available data. Using a total of 96 weeks of data (36 weeks from double-blind treatment period, 60 weeks from OLE), there was an annualized eGFR slope of -0.6 mL/min/1.73m^2/year, which included all patients who received any atacicept dose or placebo in the double-blind trial who enrolled in the extension and received atacicept 150 mg.[31]

Nefecon

In NefIgArd, there was a change of +0.66 mL/min/1.73m^2 in the Nefecon group compared to a change of -4.56 mL/min/1.73m^2 in the placebo group at month nine. After the nine-month treatment period until month 24, the rate of worsening in eGFR was similar in Nefecon and placebo groups, although the absolute change eGFR was better in the Nefecon group at month 24 (-6.11 for Nefecon, -12 for placebo). These findings were consistent across subgroups based on baseline eGFR and baseline proteinuria levels, however there was numerically less decline in eGFR in individuals who had a baseline uPCR <1.5 g/g compared with ≥1.5 g/g, regardless of being treated with Nefecon or placebo (see Supplement Table D3.21).[10,57] The time-weighted average reduction of eGFR between months 12 and 24 was -4.1 mL/min/1.73m^2 in the Nefecon group and -9.1 mL/min/1.73 m^2 in the placebo group (difference: 5; 95% CI: 2.9 to 7.7; p<0.0001).[10]

The annualized eGFR slope was -3.06 mL/min/1.73m^2/year for Nefecon 16 mg and -6 mL/min/1.73m^2/year for placebo, resulting in a difference of 2.95 mL/min/1.73m^2/year (see Table 3.3).[10]

In the OLE, eGFR was stabilized in both the participants who received a second course of Nefecon and the participants who received a first course. At month nine, the change in eGFR from baseline was -1.28 mL/min/1.73m^2 in the second course group and -1.53 mL/min/1.73m^2 in the first course group.[36]

Systemic Glucocorticoids

In reduced dose cohort of TESTING, there was an eGFR change of +5.0 mL/min/1.73m^2 in the methylprednisolone group and -3.0 mL/min/1.73m^2 in the placebo group at month 12 (difference: 7.9; 95% CI: 4.3 to 11.5; p<0.001). There were significantly fewer participants who received methylprednisolone that had an eGFR reduction of 30%, 40%, and 50%, compared to placebo (see Supplement Section D2 and Supplement Table D3.13).[48]

For the reduced-dose cohort, the annualized eGFR slope was -0.7 mL/min/1.73m^2/year in the methylprednisolone group and -3 mL/min/1.73m^2/year in the placebo group (see Table 3.3).[48] Similar differences versus placebo were observed in the full-dose cohort and the combined full and reduced dose cohort (see Supplement Section D2).[46,47]

Table 3.3. Annualized eGFR Slope for Key Trials[8-10,48]

Outcome	Annualized eGFR slope, mL/min/1.73m^2/year							
Intervention	**Sibeprenlimab**		**Atacicept**		**Nefecon**		**Methylprednisolone**	
Trial	**Ph II ENVISION**		**Ph II ORIGIN***		**Ph III NefIgArd†**		**TESTING‡**	
Arm	**Sibe 4 mg/kg**	**Placebo**	**Ata 150 mg**	**Placebo**	**Nefecon 16 mg**	**Placebo**	**Reduced-Dose Methyl-prednisolone**	**Placebo**
N	38	38	33	34	182	182	117	113
Mean Change (SE)	+0.1 (1.6)	-5.9 (1.7)	+2.6 (2.4)	-3.2 (2.4)	-3.06 (NR)	-6 (NR)	-0.7 (NR)	-3.0 (NR)
Difference vs. Placebo (95% CI); p-value	5.96 (1.5, 10.4); NR		5.9 (-0.75, 12.5); NR		2.95 (1.67, 4.58); p<0.0001		2.3 (-0.03, 4.6); p=0.054	

CI: confidence interval, Ata: Atacicept, eGFR: estimated glomerular filtration rate, kg: kilogram, mg: milligram, mL/min/1.73m^2/year: milliliter per minute per 1.73 meters squared per year, N: number, NR: not reported, Ph: Phase, Sibe: Sibeprenlimab, SE: standard error, vs.: versus

*Exploratory analysis using nine-month data cut-off. Annualized slope from atacicept-treated participants using 96 weeks of data from randomized period and OLE = -0.6.

†Annualized data from two years (nine months on treatment, 15-month follow-up)

‡Median follow-up: 2.5 years

Proteinuria

Sibeprenlimab

In the VISIONARY trial, both sibeprenlimab and placebo groups had a baseline mean urinary protein to creatinine ratio (uPCR) of 1.3 g/g. Participants who received sibeprenlimab had a mean change of -50.2% in 24-hour uPCR at month nine compared to a change of +2.1% in participants who received placebo (see Table 3.4).[24] Reductions in proteinuria were consistent across subpopulations defined

by key demographic subgroups (age, sex, and race) and risk of disease progression (baseline uPCR and eGFR). Similar reductions in the sibeprenlimab groups compared to placebo were observed in the ENVISION trial at month nine and 12 and were maintained four months after treatment at month 16, aside from the lowest sibeprenlimab dose group that began to return towards baseline levels. Of note, the placebo arm in the Phase II trial had greater reductions in uPCR than were observed in the placebo group in the Phase III trial.[8] See Supplement Section D2 and Supplement Tables D3.8 and D3.19 for additional details.

In VISIONARY, remission of proteinuria was defined as having a total urinary protein of <0.5 g/day at month 12. At month 12, proteinuria remission was observed in 34.3% of sibeprenlimab treated participants and 12.7% of placebo treated participants.[24]

Atacicept

In the Phase III ORIGIN 3 trial, participants who received atacicept 150 mg had a mean change of -45.7% in 24-hour uPCR compared to a change of -6.8% in the placebo group at month nine (see Table 3.4).[29] Reductions in proteinuria were consistent across subpopulations defined by key demographic subgroups (age, sex, and race) and risk of disease progression (baseline uPCR and eGFR). Similar reductions were observed in the ORIGIN and ORIGIN OLE trials.[9,31] See Supplement Section D2 and Supplement Tables D3.9 and D3.20 for additional details.

Nefecon

In NefIgArd, the mean percent change in 24-hour uPCR for Nefecon-treated participants was -33.6% compared to -5.2% in placebo-treated participants at month nine (see Table 3.4). The change for Nefecon-treated participants was greater at month 12 (-51.3%) but slowly decreased by month 24 (-30.7%). The time-averaged percent change in uPCR between months 12 and 24 was -40.3% for those who received Nefecon and +1% for those who received placebo. (Percent difference: 40.9; 95% CI: 31.9 to 48.7; p<0.0001).[10] A uPCR response of ≤0.5 g/g was achieved by more patients who received Nefecon compared to placebo (34.6% vs. 10.4%).[37] These results were consistent across subgroups defined by baseline eGFR.[57] See Supplement Section D2 and Supplement Tables D3.11-12 for additional details.

In the OLE, the second treatment course and first treatment course groups had similar reductions in uPCR at month nine (-33% and -31% change, respectively).[36]

Systemic Glucocorticoids

The TESTING trial did not report the 24-hour uPCR outcome but reported on proteinuria using the time-averaged mean 24-hour urine protein excretion. In the reduced-dose cohort, there was a change in proteinuria of -1.01 grams per day in the methylprednisolone group and +0.10 grams per day in the placebo group at month 12 (Mean difference: -1.15 g/day; 95% CI: -1.68 to -0.62; p<0.001). In the reduced-dose methylprednisolone group, this translates to a 45.8% reduction in proteinuria at 12 months. This treatment effect waned by month 24 and returned to similar levels as the placebo group by month 48, although few participants reached four years of follow-up (methylprednisolone n=14, placebo n=12).[48]

Table 3.4. Percent Reduction in 24-Hour uPCR for Key Trials at Month Nine[8-10,24,29]

Intervention	Trial	Arm	N	Geometric Percent Change, %	Difference vs. Placebo, % (95% CI); p-value*
Sibeprenlimab	VISIONARY	Sibe 400 mg SC	152	-50.2	51.2 (42.9, 58.2); p<0.0001†
		Placebo	168	+2.1	
	ENVISION	Sibe 4 mg/kg IV	38	-56.7	NR
		Placebo	38	-12.7	
Atacicept	ORIGIN 3	Ata 150 mg	214	-45.7	41.8 (28.9, 52.3); p<0.001
		Placebo	214	-6.8	
	ORIGIN	Ata 150 mg	33	-33	35 (9.13, 53.1); p=0.012
		Placebo	34	+3	
Nefecon	NefIgArd	Nefecon 16 mg	182	-33.6	30 (19.9, 38.8); NR
		Placebo	182	-5.2	

Ata: Atacicept, CI: confidence interval, IV: intravenous, mg: milligram, mg/kg: milligram per kilogram, N: total number, NR: not reported in trial, SC: subcutaneous, Sibe: Sibeprenlimab

*Difference values may not align with percent change column due to rounding / statistical analysis from trial

†Placebo-adjusted treatment effect, reports 96.5% CI

Note: Geometric mean percentages calculated using the log-transformed scale

Composite Endpoints & End Stage Kidney Disease

There were no composite endpoints reported for sibeprenlimab or atacicept trials regarding end stage kidney disease.

Nefecon

The NefIgArd trial had a composite endpoint of time to confirmed 30% eGFR reduction or kidney failure. There were significantly more participants who received placebo who met the composite endpoint compared to participants treated with Nefecon (21% vs. 12%; HR: 0.45; 95% CI: 0.26 to 0.75; p=0.0028). This was consistent across baseline uPCR groups, although not significant in those with a baseline uPCR <1.5 g/g. (uPCR <1.5 g/g HR: 0.51; 95% CI: 0.21 to 1.12; uPCR ≥1.5 g/g HR: 0.42; 95% CI: 0.21 to 0.83).[10]

Systemic Glucocorticoids

The primary endpoint of the TESTING trial was a composite endpoint of the first occurrence of a sustained 40% eGFR decrease, kidney failure, or death due to kidney disease. In the reduced-dose cohort, the annual event rate of this endpoint was significantly lower in the methylprednisolone group compared to placebo (annual event rate %: 2.2 vs. 7.1; HR: 0.24; 95% CI: 0.10 to 0.58; p=0.002). There were no differences among subgroups classified by baseline proteinuria, baseline kidney function, histological lesion scoring, race, age, or time between biopsy and randomization.[48] Additional data on the combined dose cohort and other key subgroups are described in Supplement Section D2.

There were three events of kidney failure in the methylprednisolone group and 10 events in the placebo group, although this difference was not statistically significant (HR: 0.26; 95% CI: 0.07 to 1.03; p=0.056).[48]

Health-Related Quality of Life (HRQoL)

Data on quality of life were not reported in trials for sibeprenlimab, atacicept, or the primary systemic glucocorticoid trial, TESTING.

Nefecon

The NefIgArd trial reports data on the eight categories of short form 36 (SF-36) questionnaire that range from bodily pain, general health, mental health, physical functioning, social function, and vitality. At both months nine and 24, there were little-to-no differences in the quality-of-life domains for both Nefecon and placebo groups.[58] Detailed results are reported in Supplement Table D3.24.

Hematuria

Sibeprenlimab

In VISIONARY, among the 78.3% (119/152) sibeprenlimab-treated participants who had hematuria at baseline, 19.8% (22/111) still had hematuria at week 48. In the placebo group, there were 70.8% (119/168) who had hematuria at baseline and 69% (89/129) at week 48. The different denominators at baseline and week 48 are due to missing measurements for 41 participants in the sibeprenlimab group and 39 participants in the placebo group.[24] Hematuria data for ENVISION are in Supplement Section D2.

Atacicept

In ORIGIN 3, there were 60.1% (122/203) of participants who had hematuria at baseline. At week 36, 81% (51/63) in the atacicept group and 20.7% (12/58) in the placebo group had hematuria resolution.[29] Similarly, there were greater reductions in hematuria in atacicept-treated participants in the ORIGIN and ORIGIN OLE trials (see Supplement Section D2).[9,31]

Nefecon

Of the participants with two or more valid urine dipstick results during the follow-up period of the NefIgArd trial, 34% (53/158) of Nefecon-treated participants and 32% (49/152) of placebo-treated participants did not have microhematuria at baseline. During the follow-up period, a higher percentage of participants treated with Nefecon did not have microhematuria present compared to placebo (59.5% vs. 39%).[10]

Systemic Glucocorticoids

Data on hematuria in the reduced-dose cohort were not reported.

Harms

Sibeprenlimab

Interim analyses from the VISIONARY trial report that serious treatment-emergent adverse events (TEAEs) were observed in 3.5% of sibeprenlimab-treated participants and 4.4% of placebo-treated participants. Treatment-related adverse events were reported by 29% who received sibeprenlimab and 26.7% who received placebo. Infections or infestations were reported by 39% and 32.7% of the sibeprenlimab and placebo groups, respectively. These were most commonly upper respiratory tract infections, nasopharyngitis, Covid-19, and influenza. There was one person who discontinued due to an AE in the sibeprenlimab group compared to four in the placebo group. No deaths were reported (see Table 3.5).[24] A similar safety profile was observed in the ENVISION trial, described in Supplement Section D2 and Supplement Table D3.30.[8]

Atacicept

In ORIGIN 3, serious TEAEs were reported by one person (0.5%) who received atacicept and 11 (5.1%) who received placebo. Treatment-related AEs were reported by 29.4% in the atacicept group and 10.3% in the placebo group, of which two in the placebo group were serious. The largest difference in treatment-related AEs was mild injection site reactions (26.2% in the atacicept group vs. 4.7% in the placebo group). There were fewer participants in the atacicept group who

discontinued treatment due to an adverse event than in the placebo group (0.9% vs. 3.7%). There were similar rates of infections or infestations between the atacicept and placebo groups, (31.8% and 28.0%), two of which were serious in the placebo group (see Table 3.5).[29] There were no deaths across any of the atacicept trials, including the Phase II ORIGIN and ORIGIN OLE.[9,31,59] A similar safety profile was observed in the Phase II ORIGIN trial, OLE, and an integrated safety analysis across indications, which are described in Supplement Section D2 and Supplement Tables D3.31-32.

Nefecon

In the treatment period of the NefIgArd trial, serious TEAEs were reported by 10% and 5% of participants in the Nefecon and placebo groups, respectively. These serious events were treatment-related in 2% of participants in each group. During the follow-up period, serious TEAEs were reported by 8% of participants in each group, with one event (1%) being treatment-related in the placebo group. A higher percentage of participants in the Nefecon group had TEAEs that led to discontinuation of the study treatment (9% vs. 2%). Infection-related TEAEs were reported by 35% of the Nefecon group and 31% of placebo group (see Table 3.5). Among those treated with Nefecon, two people had serious hypertension, one had serious peripheral and facial edema (swelling), and one person had a severe case of peripheral edema. Three Nefecon-treated participants and one placebo-treated participant had serious infections which required hospitalization; however, none were treatment-related. One person treated with Nefecon had a serious case of pneumonia that was determined to be treatment-related. One person in the placebo group had a severe case of Campylobacter colitis that was determined to be treatment-related. There were two deaths in two Nefecon-treated participants, one during the treatment period and one during the 15-month follow-up, but neither was considered to be treatment related.[10] No new safety signals were identified in the OLE.[36] Patient-important side effects such as acne, peripheral and facial edema, fatigue, and weight increased were commonly reported although were often mild/moderate and resolved.[3]

A post-marketing study that used data from the US Food and Drug Administration Adverse event Reporting System (FAERS) reported on "positive" safety signals at both the system organ class and preferred terms levels.[35] Data from 1,515 people with IgAN were analyzed and four new safety signals that were not observed in the clinical trials were identified: asthenia, malaise, product dose omission issues, and anxiety. In addition, acne, hypertension, face swelling, and increased weight were classified as moderate clinical priority and none were classified as high clinical priority.

The FDA label highlights hypercorticism, adrenal axis suppression, risk of immunosuppression, and other corticosteroid effects as a warning/precaution.[3]

The safety profile observed in the NEFIGAN trial was similar. Additional safety data are detailed in Supplement Section D2 and Supplement Tables D3.34.

Systemic Glucocorticoids

Among both the full and reduced dose cohorts in the TESTING trial, there were 37 serious TEAEs reported by 28 (11%) of participants in the methylprednisolone group and eight serious TEAEs reported by seven (3%) in the placebo group, the majority of which were related to hospitalization or prolongation of hospitalization. Most of these serious events were in the full-dose group (30 events for methylprednisolone vs. five for placebo) rather than the reduced-dose group (seven events vs. three). Overall, there were 17 people who received methylprednisolone and three who received placebo who had serious infection requiring hospitalization (methylprednisolone full-dose: 12, reduced dose: 5). Serious adverse events were fatal for four individuals in the methylprednisolone group, all of which were infection related (three in full-dose, one in reduced-dose).[47,48]

There was one death due to kidney failure in the methylprednisolone group and zero in the placebo group. For deaths from any cause, there were six in the methylprednisolone group and three in the placebo group.[47,48] Table 3.5 below reports the safety profile for the reduced-dose cohort. Additional data on harms are presented in Supplement Section D2 and Supplement Tables D3.34.

Subgroup Analyses and Heterogeneity

Across the three interventions, effect modification was not observed for key outcomes by subpopulations defined by sociodemographic factors (e.g., sex, age, race, ethnicity) or risk of progression to ESKD (e.g., by baseline proteinuria levels). Where relevant, subgroup data is described among the outcomes above or in Supplement Section D2.

Table 3.5. Harms from Key Trials[10,24,29,48]

Trial	VISIONARY		ORIGIN 3		NefIgArd†		TESTING	
Arm	Sibe 400 mg	Placebo	Ata 150 mg	Placebo	Nefecon 16 mg	Placebo	Reduced Methyl-prednisolone	Placebo
N	259	251	214	214	182	182	121	120
Serious TEAE, n (%)	9 (3.5)	11 (4.4)	1 (0.5)	11 (5.1)	18 (10)	9 (5)	6 (5.0)	3 (2.5)
Treatment-related AE, n (%)	75 (29.0)	67 (26.7)	63 (29.4)	22 (10.3)	NR	NR	NR	NR

Trial	VISIONARY		ORIGIN 3		NefIgArd†		TESTING	
Arm	**Sibe 400 mg**	**Placebo**	**Ata 150 mg**	**Placebo**	**Nefecon 16 mg**	**Placebo**	**Reduced Methyl-prednisolone**	**Placebo**
N	259	251	214	214	182	182	121	120
Serious Treatment-related AE, n (%)	1 (0.4)	1 (0.4)	0	2 (0.9)*	4 (2)	4 (2)	NR	NR
Discontinuation due to AE, n (%)	1 (0.4)	4 (1.6)	2 (0.9)	8 (3.7)	17 (9)	3 (2)	NR	NR
All-Cause Deaths, n (%)	0	0	0	0	1 (1)‡	0	1 (0.8)§	0
Infections/ Infestations, n (%)	101 (39.0)	82 (32.7)	68 (31.8)	60 (28.0)	63 (35.0)	57(31.0)	NR	NR
Serious Infection/Infestation, n (%)	6 (1.2)		0	3 (1.4)	5 (3.0)#	2 (1.0)#	5 (4)*	2 (2)*

AE: adverse event, Ata: Atacicept, mg: milligram, n: number, N: total number, NR: not reported, Sibe: Sibeprenlimab, TEAE: treatment-emergent adverse event

*Severe events

†Data from 9-month treatment period.

‡Due to SARS-CoV-2 infection. To note, there was one additional death from cerebral hemorrhage during 15-month follow-up. Neither were determined to be treatment-related.

§Infection-related death.

#Three Nefecon-treated participants and one placebo-treated participants had severe infections leading to hospitalization.

Uncertainty and Controversies

General

- Given that peak incidence of IgAN is in the 30s and 40s, the management of IgAN in pregnant or potentially pregnant women is important. Current guidelines emphasize some risks of systemic glucocorticoids in pregnancy and recommend against the use of Nefecon in pregnancy.[23] Other drugs used in specific clinical scenarios such as cyclophosphamide are teratogenic and can cause ovarian failure in women not yet pregnant.[60] Pregnant women were not included in the key trials for atacicept and sibeprenlimab. Safe management strategies for women with IgAN of childbearing age are needed.
- The efficacy and safety of repeated and/or prolonged courses of Nefecon and systemic glucocorticoids are unclear. These medications have substantial side effects, particularly over time. The pivotal NefIgArd trial evaluated the comparative clinical efficacy of a nine-month treatment period for Nefecon. An open-label extension assessing additional time on Nefecon is ongoing.

- Many key trials of treatments for IgAN do not report data on quality of life. (An exception is the reporting of SF-36 in the NefIgArd trial.)
- Individuals with IgAN who have renal transplantation can have IgAN recur in the transplanted kidney and it is unclear how these therapies work in these circumstances.
- Trial inclusion criteria generally included individuals with baseline uPCR ranging from ≥0.75 to 1.0 g/g. Although clinical experts expressed concern that patients with lower levels of proteinuria still could have worsening kidney function, the efficacy of these medications in reducing IgAN progression when proteinuria is under these thresholds is unclear.
- Key trials focus on endpoints including kidney function as estimated by glomerular filtration rate (eGFR) as well as proteinuria (uPCR). For this review, we have prioritized eGFR over uPCR when both are available, given that the slope of decline in glomerular filtration rate is more directly linked to the timing of development of ESKD, the most patient-important endpoint. However, in general we lack data about the comparative effectiveness of interventions at delaying or avoiding ESKD directly.
- There is uncertainty about disease course if treatment with sibeprenlimab or atacicept is discontinued. Biomarker data (described in the Supplement Section D3) show that key biomarkers (e.g., APRIL, Gd-IgA1) begin to return to baseline after these therapies are stopped.
- In trials that report proteinuria remission, only about one third of patients achieve a uPCR response of ≤0.5 g/g. Many of these patients may need additional therapy or therapeutic alternatives.

Sibeprenlimab and Atacicept

- Although the safety profile of sibeprenlimab and atacicept seem similar to placebo from trial data, rarer and longer-term side effects are hard to detect until a drug enters widespread clinical practice. Given the immunosuppressive mechanisms of sibeprenlimab and atacicept, these types of effects are conceptually possible although speculative at this stage. Shorter-term pre-approval trials have neither the statistical power nor sufficient time on medication to rule out these types of potential adverse effects.

Nefecon

- Trial results reported treatment-emergent adverse events including peripheral edema and hypertension. Although budesonide formulations such as Nefecon are thought to have less systemic side effects given first-pass metabolism in the liver compared with systemic glucocorticoids, the differences in side effects between Nefecon and systemic glucocorticoids are unclear.

- The KDIGO guidelines recommend Nefecon over systemic glucocorticoids in settings where both are available. Clinical experts disagreed about this recommendation. For example, the UpToDate article on "IgA Nephropathy: Treatment and Prognosis" makes the opposite recommendation, favoring systemic glucocorticoids over Nefecon.[61] Direct comparisons of safety and efficacy for Nefecon versus systemic glucocorticoids have not been performed.

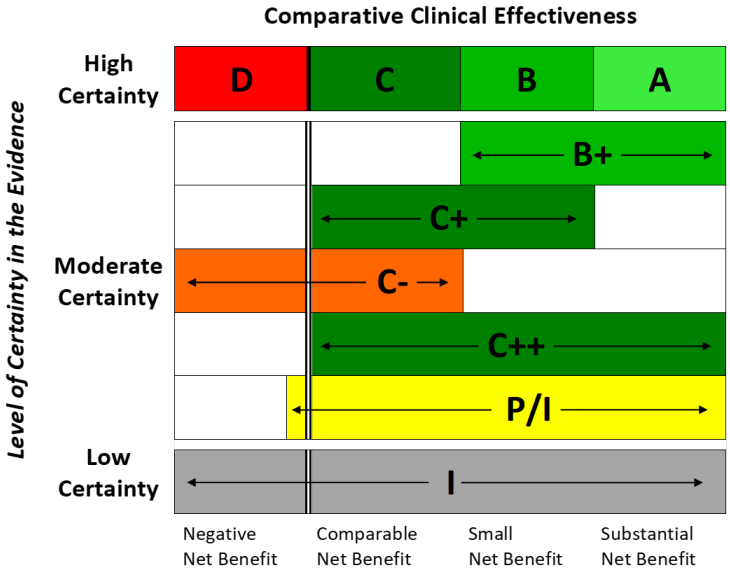
Systemic Glucocorticoids

- While our review focused on TESTING trial for the best available evidence, there are disagreements among clinical experts in reconciling discordant trial results. There have been multiple randomized trials of systemic glucocorticoids for IgAN, some of which included other immunosuppressive treatments such as cyclophosphamide or azathioprine.[50-54] The STOP-IgAN trial suggested no benefit of systemic glucocorticoids. However, the TESTING trial is larger (503 vs. 162 randomized participants), more recent, and is isolated to systemic glucocorticoids. By contrast, STOP-IgAN also involved concomitant adjunctive immunosuppressive agents including cyclophosphamide and azathioprine.
  Initially the TESTING trial used an initial dose of 0.6-0.8 mg/kg/d of methylprednisone but after an excess of serious infections were identified, a lower initial dose of 0.4 mg/kg/d along with antibiotic prophylaxis for *P. Jiroveci* pneumonia was used. Efficacy estimates excluding values from those receiving high exposure treatment are similar to those receiving low exposure treatment. Given better tolerability and similar efficacy, clinical experts typically use the lower doses in clinical practice. We therefore focused on the lower dose of methylprednisone to estimate both efficacy and safety for systemic glucocorticoids. However, if higher doses of methylprednisone are used in clinical practice, side effects of systemic glucocorticoids could be higher than we assumed.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" *– Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" *- Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" *– Any situation in which the level of certainty in the evidence is low*

Overall, our assessment of clinical comparative effectiveness is strongest in assessing sibeprenlimab, atacicept, and Nefecon versus no specific immunomodulatory therapy. In general, we have prioritized changes in glomerular filtration (eGFR) as more important than changes in proteinuria alone (uPCR), given that glomerular filtration directly estimates renal function.

For Nefecon, a large, well-executed Phase III trial demonstrated a meaningful decrease in eGFR relative to no specific immunomodulatory therapy although we lack data on progression to ESKD. At least for some patients, Nefecon's therapeutic efficacy is counterbalanced by some typical steroid side effects. We conclude that Nefecon provides net health benefits that are "incremental or better" (**B+**) compared with no specific immunomodulatory therapy.

For sibeprenlimab and atacicept, the published Phase III trials so far do not report differences in eGFR although they do demonstrate large improvements in uPCR relative to no specific immunomodulatory therapy. Accordingly, for sibeprenlimab and atacicept, we rely more heavily on the Phase II trials that report differences eGFR as well. Those Phase II trials are like the Phase III trials insofar as they demonstrate large, meaningful differences in uPCR. Importantly, they also demonstrate large, meaningful differences in eGFR. With these two new drugs, with a novel mechanism, there always remains the possibility of potential side effects that are too rare to detect in Phase II or Phase III clinical trials. That adds to our level of uncertainty about their level of benefit over no specific immunomodulatory therapy. We conclude that both sibeprenlimab and atacicept provide net health benefits that are "incremental or better" (**B+**) compared with no specific immunomodulatory therapy.

For the comparisons of sibeprenlimab, atacicept, and Nefecon relative to systemic glucocorticoids, we do not have direct randomized trial evidence. Clinical outcomes in the placebo arms of the key trials differ, emphasizing that different populations were included in the trials. We consider the multinational TESTING trial the best evidence of efficacy and safety for systemic glucocorticoids. The trial demonstrates that oral methylprednisolone is superior to no disease specific therapy at preserving glomerular filtration as measured by eGFR. However, that efficacy is counterbalanced by the relatively high proportion of side effects including serious side effects. These side effects appear to be substantially more limited at a lower methylprednisolone dose (0.4 mg/kg/d) with similar efficacy to the higher dose. Some clinical experts criticize the external validity of the TESTING trial given that so many enrolled individuals were in China. The TESTING trial was conducted in China, Australia, India, Canada, and Malaysia. In the US, although Asian individuals are relatively more affected by IgAN, the TESTING trial has underrepresentation or no representation of White (5%), Black, and Hispanic individuals relative to a US population. However, in TESTING, despite the low numbers of some race/ethnicity groups relative to a US population, there was no suggestion of different treatment effects among participants in China and other participants. Furthermore, STOP-IgAN also has potential limitations in terms of external validity, since the trial was conducted entirely in Germany and roughly one-third of patients also received cyclophosphamide and azathioprine. TESTING also enrolled a sicker population with more baseline proteinuria and higher rates of progression in the respective placebo arms, which could potentially make the benefit of systemic glucocorticoids easier to demonstrate in TESTING.[62] The other older, smaller trials also suggested benefit of systemic glucocorticoids in IgAN, directionally consistent with the results from TESTING.

The available evidence appears to show similar relative short-term efficacy of sibeprenlimab and atacicept to that of lower dose methylprednisolone, but without the glucocorticoid side effects. As noted above, however, there are uncertainties around longer-term and/or rare side effects with a new medication class. As such, we conclude that both sibeprenlimab and atacicept provide net health benefits that are "promising but inconclusive" (**P/I**) compared with lower dose methylprednisolone.

For the comparison between Nefecon and systemic glucocorticoids, separate trials show relatively similar efficacy in the short run. Trial results and mechanism of release suggest that Nefecon may have fewer steroid side effects than typical systemic glucocorticoids, which have substantial well-known side effects. However, it appears that Nefecon has steroid side effects in at least some patients and it is difficult to be certain about the relative rate of these side effects compared with lower dose methylprednisolone without a head-to-head trial. Unlike with sibeprenlimab and atacicept, however, we do not have significant concerns about unknown late or rare side effects as budesonide is a glucocorticoid that has been widely used. Overall, we conclude that Nefecon provides net health benefits that are "promising but inconclusive" (**P/I**) compared with lower dose methylprednisolone.

For the comparisons of sibeprenlimab, atacicept, and Nefecon relative to each other, direct randomized comparisons also do not exist. In the absence of such trials, we believe that available evidence for these comparisons is "insufficient" (**I**).

Table 3.6. Evidence Ratings

Treatment	Comparator	Evidence Rating
B-Cell Directed Therapies Compared with No Specific Immunomodulatory Therapy		
Sibeprenlimab	No specific immunomodulatory therapy	B+
Atacicept	No specific immunomodulatory therapy	B+
Nefecon	No specific immunomodulatory therapy	B+
B-Cell Directed Therapies Compared to Systemic Glucocorticoids		
Sibeprenlimab	Systemic Glucocorticoids	P/I
Atacicept	Systemic Glucocorticoids	P/I
Nefecon	Systemic Glucocorticoids	P/I
B-Cell Directed Therapies Compared to Each Other		
Sibeprenlimab	Atacicept	I
Sibeprenlimab	Nefecon	I
Atacicept	Nefecon	I

B+: 'Incremental or Better' – Moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit, I: 'Insufficient' – Any situation in which the level of certainty in the evidence is low, P/I: 'Promising but Inconclusive' – Moderate certainty of a small or substantial net health benefit with a small likelihood of a negative net health benefit

CTAF Votes

Table 3.7 CTAF Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
For patients with IgAN, is the current evidence adequate to demonstrate that the net health benefit of sibeprenlimab is greater than that of no specific immunomodulatory therapy? ***In deliberation, council members discussed the use of surrogate markers in clinical trials for the interventions.***	14	0
For patients with IgAN, is the current evidence adequate to demonstrate that the net health benefit of atacicept is greater than that of no specific immunomodulatory therapy?	13	1
For patients with IgAN, is the current evidence adequate to demonstrate that the net health benefit of Nefecon is greater than that of no specific immunomodulatory therapy?	14	0
For patients with IgAN, is the current evidence adequate to demonstrate that the net health benefit of sibeprenlimab is greater than that of systemic glucocorticoids? ***In deliberation, one council member expressed appreciation to the patient experts for sharing their experiences with systemic glucocorticoids; however, they shared that they voted 'no' because they believe without randomized data, the current evidence is not adequate to distinguish between the treatments. Another council member shared that despite the need for more long-term evidence, they voted 'yes' because the side effects of systemic glucocorticoids are so severe.***	9	5
For patients with IgAN, is the current evidence adequate to demonstrate that the net health benefit of atacicept is greater than that of systemic glucocorticoids?	9	5
For patients with IgAN, is the current evidence adequate to demonstrate that the net health benefit of Nefecon is greater than that of systemic glucocorticoids? ***Clinical experts shared their experiences in clinical practice using Nefecon with patients. One council member shared that he found this question challenging because while there are anecdotal data, he would like to see a comparative study of Nefecon to systemic glucocorticoids. One patient expert shared her experience with Nefecon explaining her intense side effects.***	5	9

Table 3.8. CTAF Votes on Comparative Clinical Effectiveness Questions – B-Cell Directed Therapies Compared to Each Other – Sibeprenlimab vs. Atacicept

Question	Sibeprenlimab	Atacicept	Can't Distinguish
For patients with IgAN, which intervention has the greater net health benefit?	0	14	0

Table 3.9. CTAF Votes on Comparative Clinical Effectiveness Questions – B-Cell Directed Therapies Compared to Each Other – Sibeprenlimab vs. Nefecon

Question	Sibeprenlimab	Nefecon	Can't Distinguish
For patients with IgAN, which intervention has the greater net health benefit?	4	0	10

Table 3.10. CTAF Votes on Comparative Clinical Effectiveness Questions – B-Cell Directed Therapies Compared to Each Other – Atacicept vs. Nefecon

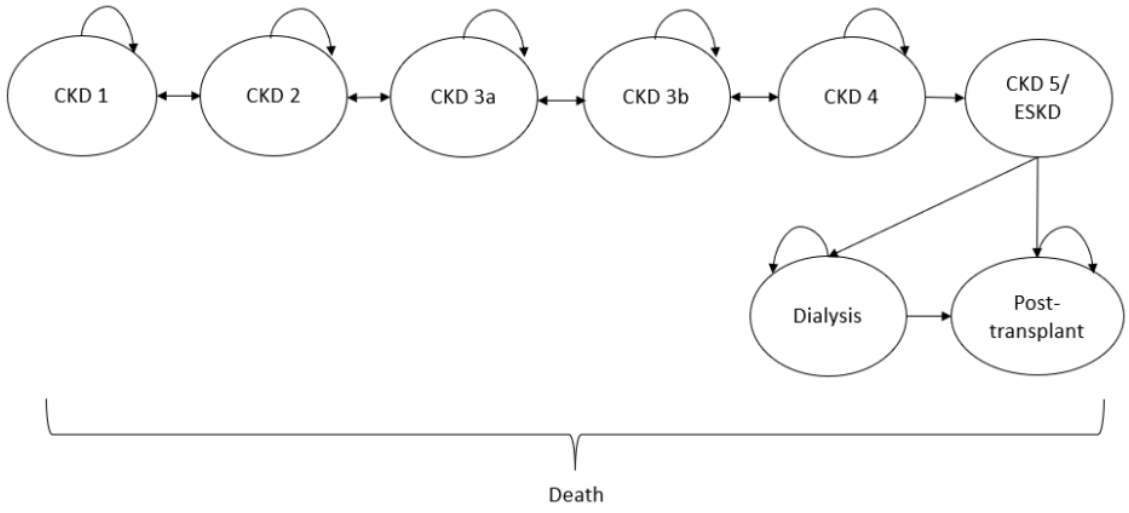
Question	Atacicept	Nefecon	Can't Distinguish
For patients with IgAN, which intervention has the greater net health benefit? ***One council member raised questions about some inconsistencies throughout the discussion about the use of systemic glucocorticoids and Nefecon. Another council member shared that it is unlikely that Nefecon will be a one-course treatment, so there needs to be comparative studies with long-term evidence.***	3	0	11

4. Long-Term Cost Effectiveness

4.1. Methods Overview

The aim of this analysis was to estimate the cost-effectiveness of atacicept, sibeprenlimab, and Nefecon for IgA nephropathy as compared to systemic glucocorticoids. We developed a *de novo* Markov model (Figure 4.1) with a cycle length of one month and informed by key clinical trials and prior relevant economic models.[8-10,11,12] The model included nine health states: chronic kidney disease (CKD) stages 1, 2, 3a, 3b, 4, and 5/end-stage kidney disease (ESKD); dialysis; post-transplant; and death. CKD stages reflect estimated glomerular filtration rate (eGFR): stage 1 (90 mL/min/1.73 m^2 or higher), stage 2 (60-89 mL/min/1.73 m^2), stage 3a (45-59 mL/min/1.73 m^2), stage 3b (30-44 mL/min/1.73 m^2), stage 4 (15-29 mL/min/1.73 m^2), and stage 5/ESKD (less than 15 mL/min/1.73 m^2). Patient transitions between CKD stages 1-4 reflected disease trajectory. CKD stage 5/ESKD was modeled as a tunnel state with all patients who reached this state transitioning to either dialysis or post-transplant after one cycle. Patients either remained on dialysis or transitioned to the post-transplant state. The post-transplant state included both successful and failed transplants. Patients remained in the model until they died.

Figure 4.1. Model Structure



CKD: chronic kidney disease; ESKD: end-stage kidney disease

The analysis was conducted over a lifetime horizon with costs and outcomes discounted at 3% per year. The base-case analysis adopted a health care sector perspective (i.e., focus on direct medical care costs only). Patient and caregiver productivity impacts were considered in a modified societal perspective analysis. Model outcomes included total life years (LYs) gained, quality-adjusted life

years (QALYs) gained, equal-value life years (evLYs) gained, time to ESKD, and total costs for each intervention. Additional information may be found in the Supplement.

Changes to the economic evaluation between the draft Evidence Report and the revised Evidence Report included:

- There was an error in the draft economic evaluation. We incorrectly applied on-treatment transitions for systemic glucocorticoids for the lifetime of the model. The updated model and results applied the systemic glucocorticoid treatment benefit and an excess risk of mortality for 24 months. The disutility and increased health care utilization costs associated with systemic glucocorticoid use were applied for four years in the base-case (with alternative specifications explored in scenario analyses). The change to 24 months aligns the treatment durability expectation for systemic glucocorticoids with that of Nefecon. Results across all arms of the model are impacted given systemic glucocorticoids are the reference comparator.
- Estimated net prices are used for sibeprenlimab and Nefecon, with a placeholder price for atacicept. Since the publication of the draft report, new estimates have become available and are used in the economic evaluation. Results for sibeprenlimab and atacicept are changed with the new prices.
- Removal of the scenario analysis that evaluated three courses of treatment with Nefecon.
- Additional information on model calibration in Supplement E2.

4.2. Key Model Assumptions and Inputs

Table 4.1 describes key model assumptions. Additional information regarding other model assumptions may be found in the Supplement.

Table 4.1. Key Model Assumptions

Assumption	Rationale
We assumed the same baseline patient characteristics for each treatment arm.	The clinical trials exhibited broad similarity in key demographic and clinical characteristics at baseline.[8-10]
In the base-case analysis, we modeled treatment duration and durability separately for each intervention. Treatment with Nefecon was applied for nine months, with treatment durability lasting 24 months. For atacicept and sibeprenlimab, patients remained on treatment until reaching ESKD.	Clinical trial evidence suggests treatment duration and durability vary by intervention.[8-10]
Treatment benefit and an increased risk of mortality for systemic glucocorticoids were assumed to last 24 months. A disutility and increased health care utilization costs reflecting other adverse effects associated with systemic glucocorticoids were assumed to last four years, with alternative specifications explored in scenario analyses.	The treatment benefit modeled for systemic glucocorticoids was matched to the durability of treatment benefit modeled for Nefecon. The disutility and increased health care utilization costs associated with systemic glucocorticoids is intended to reflect both short- and long-term adverse events.
Costs for dialysis were based on commercial insurance during the full coordination period or until the age of 65; subsequent costs assumed Medicare is the primary payer. A scenario analysis examined the impact of premature switching. The cost of dialysis for patients over the age of 65 was based on Medicare expenditures.	Once eligible for Medicare in the fourth month of dialysis, a 30-month coordination period is required before Medicare becomes the primary payer.[63] However, an analysis of US Renal Data System data found that 33% of dialysis patients prematurely switched to Medicare as a primary payer (e.g. due to unemployment) on average at the eleventh month of this coordination period, while 40% switched to Medicare late or never.[64]
We used slope differences between each intervention and the placebo arm observed in clinical trials to calibrate on-treatment transition probabilities based on transition probabilities derived from the best supportive care arm of the Phase III NefIgArd Part B trial and used in a previous cost-effectiveness model.[11]	Without long-term patient-level data, mean calibration was used to derive transitions between health states based on changes in eGFR.
Off-treatment transition probabilities derived from the best supportive care arm of the Phase III NefIgArd Part B trial and used in a previous cost-effectiveness model[11] were applied consistently across interventions during periods without treatment, unless data showed otherwise.	Key baseline characteristics such as age and eGFR were similar across Phase II and III studies of IgA nephropathy.[8-10] Only the Phase III study of Nefecon includes an off-treatment period during trial follow-up.

CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, ESKD: end-stage kidney disease, IgA: immunoglobulin A, US: United States

Table 4.2 summarizes key model inputs. Utility estimates for CKD stages were derived from a global survey of IgA nephropathy patients using the EQ-5D-5L instrument (including China, France, Germany, Italy, Spain, the United Kingdom, the US, and Japan).[65] While not specific to the US IgA nephropathy patient population, this study is the most recent to report utilities based on the EQ-5D instrument across each of the five CKD stages (for CKD stage 1, we assumed the utility for the average US adult).[66] Utilities for dialysis and the post-transplant health state (i.e. successful

transplant) were identified from a systematic review and meta-analysis of EQ-5D utilities estimated from patients who received a renal transplant.[67] For the systemic glucocorticoid comparator arm, we applied a disutility reflecting chronic use of these therapies that was used in prior ICER economic evaluations.[68] This disutility was applied to all patients for four years to reflect the fact that certain steroid-related adverse effects are short-term while others persist after cessation of steroid therapy (e.g. osteoporosis). Alternative specifications were explored in scenario analyses.

To estimate differences in outcomes between interventions and comparators, we applied forward and backward calibration factors to an evidence-based transition matrix representing no specific immunomodulatory therapy that was submitted by Calliditas Therapeutics AB during our data request period and used in a previous cost-effectiveness model.[11,69] We modeled a weighted average of eGFR across CKD health states to approximate changes in eGFR by treatment arm. Calibration focused on incremental comparisons to the no specific immunomodulatory therapy arm using the mean differences with uncertainty in published clinical trial evidence.[8-10] Additional information regarding model inputs may be found in the Supplement.

Table 4.2. Key Model Inputs

Parameter	Value	Source
Utility for CKD Stages, Mean	Stage 1: 0.85 (Average US adult) Stage 2: 0.82 Stage 3a: 0.77 Stage 3b: 0.71 Stage 4: 0.70 Stage 5: 0.70	Pickard et al.;[66] Tang et al.[65]
Utility for Dialysis, Mean (95% CI)	0.565 (0.49-0.62)	Liem et al.;[67] Authors' calculation
Post-Transplant Utility, Mean (95% CI)	0.81 (0.72-0.90)	Liem et al.[67]
Chronic Oral Corticosteroid Use Disutility	-0.023	Norman et al.[68]
Intervention Costs	Atacicept (annual): $292,500† Sibeprenlimab (annual): $292,500‡ Nefecon (9-month treatment course): $133,741‡	IPD Analytics; RedBook
Health Care Utilization Costs by CKD Stage (No Specific Immunomodulatory Therapy), PPPM (sd)	Stage 1: $1,201 ($2,274) Stage 2: $834 ($2,145) Stage 3: $1,929 ($3,193) Stage 4: $5,965 ($10,463) Stage 5: $11,882 ($18,383)	Lerma et al. ;[70] Pesce et al. ;[71] Authors' calculation
Health Care Utilization Costs by CKD Stage (Systemic Glucocorticoid Users), PPPM (sd)	Stage 1: $3,485 ($6,590) Stage 2: $2,419 ($6,223) Stage 3: $5,595 ($9,263) Stage 4: $5,965 ($10,463)	Lerma et al. ;[70] Pesce et al. ;[71] Authors' calculation

Parameter	Value	Source
	Stage 5: $11,882 ($18,383)	
Dialysis (Commercial), PPPM (sd)	$18,679 ($8,476)*	League et al.;[72] American Kidney Fund;[73] Authors' calculation
Dialysis (Medicare), PPPM	$8,430*	USRDS[74]
Transplant Episode, Mean	$446,800§	Ortner & Holzer[75]
Cost of Ongoing Care Following Transplant, PPPM	$4,617§	Ortner & Holzer[75]
Cost of Mortality, Mean (sd)	$36,245 ($79,803)	Pollock et al.[76]
Future Unrelated Medical Costs	Varies by age and gender	Jiao & Basu[77]

CKD: chronic kidney disease, CI: confidence interval, PPPM: per person per month, sd: standard deviation, US: United States

*Dialysis health state costs replaced CKD stage health care utilization costs

†Placeholder price

‡Estimated net price

§Charged amount

4.3. Results

Base-Case Results

The average per person total discounted costs, life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal value of life years (evLYs) gained, and time to ESKD are detailed in Table 4.3. Results regarding no specific immunomodulatory therapy are included as a scenario analysis.

Table 4.3. Results for the Base-Case

Treatment	Intervention Acquisition Costs*	Intervention-Related Costs†	Non-Intervention Costs‡	Total Costs*	Time to ESKD (Years)	QALYs	evLYs	LYs
Sibeprenlimab	$5,044,000	$0	$840,000	$5,884,000	17.26	14.18	14.78	18.76
Atacicept	$4,986,000	$0	$851,000	$5,837,000	17.06	14.08	14.67	18.64
Nefecon	$128,000	$0	$1,329,000	$1,458,000	7.11	9.59	9.65	13.17
Systemic Glucocorticoids	$0§	$0	$1,393,000	$1,393,000	6.82	9.16	9.16	12.68

ESKD: end-stage kidney disease, evLYs: equal value of life years gained, LYs: life years, QALYs: quality-adjusted life years

*For atacicept, results are based on placeholder price.

†Intervention-related costs include markup costs, administration costs, and costs of monitoring required for the intervention, as specified in clinical trials, guidelines, or package label.

‡Non-intervention costs include health state costs, dialysis and transplant charges, unrelated medical costs, and mortality costs associated with IgA nephropathy.

§Intervention acquisition costs for systemic glucocorticoids and no specific immunomodulatory therapy are captured in the non-intervention costs and are comparatively small.

Table 4.5 presents the discounted lifetime incremental results versus systemic glucocorticoids, including cost per QALY gained, cost per evLY gained, cost per life year gained, and cost per year of delayed ESKD onset. Incremental results versus no specific immunomodulatory therapy in terms of evLYs gained are presented below in the Scenario Analyses section. Incremental results versus no specific immunomodulatory therapy in terms of QALYs gained, LYs gained, and per year of delayed ESKD onset can be found in the Supplement.

Table 4.4. Incremental Cost-Effectiveness Ratios Compared to Systemic Glucocorticoids

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per Year of Delayed ESKD Onset
Sibeprenlimab	Systemic Glucocorticoids	$894,000	$799,000	$739,000	$430,000
Atacicept*	Systemic Glucocorticoids	$904,000	$806,000	$746,000	$434,000
Nefecon	Systemic Glucocorticoids	$151,000	$132,000	$131,000	$225,000

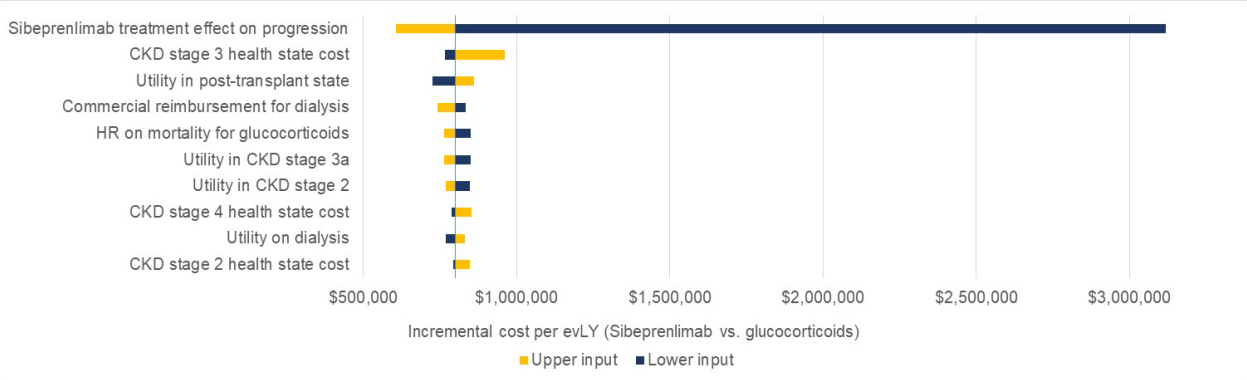
evLYs: equal value of life years, QALY: quality-adjusted life year, ESKD: end-stage kidney disease
*For atacicept, results are based on placeholder price.

Sensitivity Analyses

To demonstrate the effects of uncertainty on both costs and health outcomes, we varied input parameters using available estimates of parameter uncertainty (e.g., standard errors or plausible parameter ranges).

Figure 4.2 demonstrates the impact of varying individual inputs on the incremental cost effectiveness ratios with evLYs as the outcome. Given the parameters are similar across interventions against systemic glucocorticoids, we provide one example below (sibeprenlimab vs. systemic glucocorticoids) while the rest of the tornado diagrams are available in the Supplement. The key driver of the cost-effectiveness estimates is the effectiveness of each therapy in terms of movement through the CKD stages (we use a proxy of modeled eGFR changes). Other important drivers of the cost-effectiveness estimates include the increased risk of mortality related to glucocorticoid use, CKD health state costs for managing IgA nephropathy, CKD mortality, and health-related quality of life. For example, the sibeprenlimab treatment effect input parameter slows or speeds up progression through CKD health states compared with a fixed progression through CKD health states for glucocorticoids.

Figure 4.2. Tornado Diagram for Sibeprenlimab vs Systemic Glucocorticoids



CKD: chronic kidney disease, evLY: equal value of life years, HR: hazard ratio

Probabilistic sensitivity analyses were also performed by jointly varying multiple model parameters over at least 1,000 simulations. Tables 4.6 and 4.7 present the probability of reaching certain cost effectiveness thresholds for each intervention compared to systemic glucocorticoids.

Table 4.5. Probabilistic Sensitivity Analysis: Cost per QALY Gained Results versus Systemic Glucocorticoids

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Sibeprenlimab	0.0%	0.0%	0.0%	0.0%
Atacicept*	0.0%	0.0%	0.0%	0.0%
Nefecon	28%	31%	33%	36%

QALY: quality-adjusted life year

*For atacicept, results are based on placeholder price.

Table 4.6. Probabilistic Sensitivity Analysis: Cost Per evLY Gained Results versus Systemic Glucocorticoids

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Sibeprenlimab	0.0%	0.0%	0.0%	0.0%
Atacicept*	0.0%	0.0%	0.0%	0.0%
Nefecon	28%	31%	35%	39%

evLYs: equal value of life years gained

*For atacicept, results are based on placeholder price.

Scenario Analyses

Analysis 1: Modified societal perspective
Analysis 2: Premature switching to Medicare (at 0 months vs. 33 in the base case)
Analysis 3: Exclusion of unrelated medical costs
Analysis 4: No specific immunomodulatory therapy as the comparator
Analysis 5: Systemic glucocorticoid costs and disutilities applied for lower bound of 2 years and upper bound of lifetime

Table 4.7. Scenario Analysis Results: Cost per evLY Gained

Treatment	Base-Case Results†	Scenario Analysis 1†	Scenario Analysis 2†	Scenario Analysis 3†	Scenario Analysis 4	Scenario Analysis 5†
Sibeprenlimab	$799,000	$771,000	$851,000	$790,000	$799,000	$812,000 (lower) $779,000 (upper)
Atacicept*	$806,000	$779,000	$858,000	$797,000	$806,000	$820,000 (lower) $786,000(upper)
Nefecon	$132,000	$147,000	$104,000	$124,000	$176,000	$247,000 (lower) More effective, less costly (upper)

evLY: equal value life years, n/a: not applicable
*For atacicept, results are based on placeholder price.
†Base-case results and scenario analyses 1-3 and 5 are based on comparison to systemic glucocorticoids.

Threshold Analyses

Tables 4.8 and 4.9 present the annual price needed for each intervention to reach commonly cited cost effectiveness thresholds when compared to systemic glucocorticoids.

Table 4.8. QALY-Based Threshold Analysis Results compared to Systemic Glucocorticoids

	Annual Net/Placehol-der Price	Annual WAC/Plac-eholder Price	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY Gained
Sibeprenlimab	$292,500	$390,000	$46,200	$61,000	$75,600	$90,000
Atacicept	$292,500*	$390,000*	$45,600	$60,000	$74,500	$89,000
Nefecon†	$133,741	$165,113	$88,000	$110,900	$133,000	$155,500

n/a: not available, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Placeholder price

†The annual price for Nefecon represents the price of one 9-month treatment over the course of one year.

Table 4.9. evLY-Based Threshold Analysis Results compared to Systemic Glucocorticoids

	Annual Net/Placeholder Price	Annual WAC/Pla-ceholder Price	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Sibeprenlimab	$292,500	$390,000	$48,000	$64,500	$81,000	$97,200
Atacicept	$292,500*	$390,000*	$47,500	$64,000	$80,000	$96,500
Nefecon†	$133,741	$165,113	$91,500	$117,500	$143,000	$168,000

evLYs: equal value of life years gained, n/a: not available, WAC: wholesale acquisition cost

*Placeholder price

†The annual price for Nefecon represents the price of one 9-month treatment course over the course of one year.

Model Validation

Details regarding model validation can be found in the Supplement.

Uncertainty and Controversies

- Utilities for CKD stages, dialysis, and post-transplant reported in the literature vary widely. Previous cost-effectiveness analyses examining Nefecon for IgA nephropathy differed in their choice of utilities. In Ramjee et al., the utilities representing CKD stage 1 through ESKD with dialysis ranged from 1 to 0.77 and with 0.87 as the post-transplant utility.[12] In Yaghoubi et al., utilities representing these same health states ranged from 0.76 to 0.38 and with 0.71 as the post-transplant utility.[11] In general, systematic reviews report wide ranges of utilities for stages of CKD, dialysis, and post-transplant.[67,78] For instance, one review reports utilities for hemodialysis based on the EQ-5D-3L that range from 0.44 to 0.78.[78] In choosing utilities for this

model, we sought to balance study design considerations and clinical face validity. However, the literature indicates there is substantial uncertainty regarding quality of life in these health states. In sensitivity analyses, we explored the impact of a range of utilities to represent this diversity in the literature. Further research is needed to estimate utilities that appropriately reflect the quality of life for US patients with IgA nephropathy.

- Although a dialysis patient in the US becomes eligible for Medicare in the fourth month of dialysis, current policy requires a 30-month coordination period before Medicare may become the primary payer for dialysis.[63] We have incorporated this in the model by applying commercial dialysis costs for the first 33 months of dialysis (for patients under age 65). However, a recent study found that 33% of dialysis patients prematurely switched to Medicare as a primary payer (e.g. due to unemployment), while 40% switched to Medicare late or never.[64] While we have explored this variation in a scenario analysis, significant uncertainty remains regarding the true cost of dialysis over time within this patient population.

- We are uncertain about both treatment duration and treatment durability for the interventions assessed in this analysis. While Nefecon is FDA approved as a nine-month treatment, some patients may pursue multiple treatment courses. The effect of retreatment with this medication is currently unknown, as is treatment durability beyond two years of follow-up. Regarding atacicept and sibeprenlimab, both recommended treatment duration and treatment durability after stopping treatment are unknown.

- We derived treatment effects using calibrated parameters that altered the trajectory of simulated patients through the progression of CKD staging. While we approximated weighted averages of eGFR for each cohort, we did not have access to patient-level data which impacted our understanding of uncertainty in kidney functioning and its impact on survival and quality of life. Our sensitivity analyses demonstrate key parameters where future evidence and clinical trial follow-up will inform future understanding of the cost-effectiveness of these interventions.

- We used charged amounts for transplant episode costs and ongoing post-transplant care costs.[75] These cost estimates are unlikely to represent the actual amount paid. Because several components make up the total charged amount for transplants, it is difficult to estimate a single cost-to-charge ratio.

4.4 Summary and Comment

Our analysis has substantial uncertainties given that IgAN can progress over many years while data on new therapies only exist for the short term. Our best estimates find that at its current price, a single course of Nefecon is more expensive but more effective than systemic glucocorticoids with base-case findings meeting the upper bound of commonly cited cost-effectiveness thresholds. However, in probabilistic sensitivity analyses, there was uncertainty in whether Nefecon would meet commonly cited cost-effectiveness thresholds. For example, varying inputs related to adverse effects from systemic glucocorticoids led to either increases in the incremental cost-effectiveness ratios or decreases to a point where Nefecon may be more effective and less costly. We also estimate that sibeprenlimab compared to systemic glucocorticoids leads to life extensions and improvements in quality of life but, at the current estimated net price, far exceeds commonly used cost-effectiveness thresholds. The cost-effectiveness of atacicept will depend on its actual price, though would also far exceed commonly used cost-effectiveness thresholds if it is priced similarly to sibeprenlimab.

5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Table 5.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There are particular obligations to people with this condition because of disease severity and/or unmet need with currently available therapies.	Some currently available immunosuppressive treatments can have substantial toxicities and variable efficacy, resulting in difficult treatment decisions and unmet need for less toxic and more effective therapies. Many people with IgAN progress to ESKD, some because they are not diagnosed until late in the course of disease. To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported for the modeled population below. Individuals who manage IgAN with systemic glucocorticoids were used as a reference group. evLY shortfalls: Absolute shortfall: 18.7 Proportional shortfall: 59% QALY shortfalls: Absolute shortfall: 17.5 Proportional shortfall: 57.9% The absolute and proportional shortfalls represent the total and proportional health units of remaining quality adjusted life expectancy, respectively, that would be lost due to un- or under-treated illness. Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews.

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There are particular obligations to people with this condition because it disproportionately affects those from a racial/ethnic group that have not been equitably served by the health care system.	Prevalence estimates for IgAN differ among countries. In the US, Asian individuals have disproportionately high prevalence of IgAN. Conversely, Black individuals have disproportionately low prevalence of IgAN.[16]
The treatments are likely to improve caregivers' quality of life and/or ability to pursue their own education, work, and family life.	Once patients develop ESKD and require renal replacement therapy, caregiver needs increase. As such, new treatment options could allow caregivers more ability to pursue their own education, work, and family life.
If payment/cost were not an issue, the treatments are likely to improve access to treatment because of its method of delivery and/or treatment setting.	We do not anticipate that oral Nefecon, subcutaneous sibeprenlimab, or subcutaneous atacicept will improve access to treatment relative to current oral systemic glucocorticoids.

ICER did not calculate the Health Improvement Distribution Index (HIDI) given a lack of data on prevalence in different subpopulations. However, incidence estimates suggest that in the US, IgAN is more commonly diagnosed in Asian individuals and less commonly diagnosed in Black individuals (see table above).

CTAF Votes

At the public meeting, the CTAF deliberated and voted on the relevance of benefits beyond health and special ethical priorities to inform judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

To help inform judgments of overall long-term value for money, please indicate your level of agreement with the following statements:

Table 5.2. CTAF Votes on Benefits Beyond Health and Special Ethical Priorities – IgA Nephropathy

Special Ethical Priorities	Typical Obligations	Some Added Obligations	Substantial Added Obligations
Are there particular obligations to people with this condition because of disease severity and/or unmet need with currently available therapies? * ***Patient experts shared their experiences with this condition and their treatment. One patient expert called IgAN the 'silent killer,' because it can halt daily life and the ability to walk, critically think, and function. Another patient expert shared the difficulties of getting her diagnosis as a young woman, and the life-altering impact on her career and family plans. Both patients mentioned systemic glucocorticoids as one of only a few treatment options available at the time of their diagnosis.***	0	6	7
Are there particular obligations to people with this condition because it disproportionately affects those from a racial/ethnic group that have not been equitably served by the healthcare system?† ***It was shared that IgAN is more prevalent among Hispanic individuals and extremely prevalent among Asian individuals.***	2	10	2

Special Ethical Priorities	Typical Obligations	Some Added Obligations	Substantial Added Obligations
Apart from issues around disease severity/unmet need and race/ethnicity, are there other particular obligations to people with this condition?†	9	5	0

*There was one vote cast in error by a non-CTAF member and one CTAF member who did not vote on this question, so the votes have been updated to correct for these issues, totaling only 13 votes for this question compared to the public meeting recording.

†There are 15 votes cast in the public meeting recording, because one non-CTAF member voted. The reported votes have been updated to correct for this issue.

To help inform judgments of overall long-term value for money, please answer the following questions about sibeprenlimab, atacicept, and Nefecon when compared to systemic glucocorticoids:

Table 5.3. Midwest CEPAC Votes on Benefits Beyond Health and Special Ethical Priorities - Treatments

Benefits Beyond Health	No	Yes: Small Improvement	Yes: Substantial Improvement
Is sibeprenlimab likely to improve caregivers' quality of life and/or ability to pursue their own education, work, and family life? ***One clinical expert noted that patients have been willing to participate in clinical trials involving at home injectables because of the popularity of GLP-1s. One patient expert described injectables as freeing, compared to taking an oral medication every day. There was also discussion regarding the strain put on caregivers from dialysis; medications that can delay or alleviate dialysis would be seen as beneficial.***	2	3	9
Is atacicept likely to improve caregivers' quality of life and/or ability to pursue their own education, work, and family life?	2	3	9
Is Nefecon likely to improve caregivers' quality of life and/or ability to pursue their own education, work, and family life?	1	9	4

6. Health Benefit Price Benchmark

The threshold prices from the health care sector perspective, based on both evLYs and QALYs gained, are presented in Table 6.1 below. The Health Benefit Price Benchmark (HBPB) for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 per QALY and $150,000 per evLY gained. The annual HBPB is $61,000 to $81,000 for sibeprenlimab, $60,000 to $80,000 for atacicept, $110,900 to $143,000 for a single treatment course of Nefecon. To reach the HBPB, sibeprenlimab and atacicept would require discounts from WAC between 79% and 85%, and Nefecon would require a discount from WAC between 13% and 33%.

Table 6.1. Annual Cost-Effectiveness Threshold Prices Compared to Systemic Glucocorticoids

Annual Prices Using…	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Sibeprenlimab				
QALYs Gained	$390,000	$61,000	$75,600	81-84%
evLYs Gained	$390,000	$64,500	$81,000	79-83%
Atacicept				
QALYs Gained	$390,000*	$60,000	$74,500	81-85%
evLYs Gained	$390,000*	$64,000	$80,000	79-84%
Nefecon†				
QALYs Gained	$165,113	$110,900	$133,000	19-33%
evLYs Gained	$165,113	$117,500	$143,000	13-29%

evLY: equal value life year, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Placeholder price; The WAC price of atacicept was assumed to equal that of sibeprenlimab.

†The HBPB for Nefecon reflects the price for one 9-month treatment course over the course of one year.

CTAF Votes

Table 6.2. CTAF Votes on Long-Term Value for Money at Current Prices

Question	High Long-term Value for Money at Current Pricing	Intermediate Long-term Value for Money at Current Pricing	Low Long-term Value for Money at Current Pricing
Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering benefits beyond health and special ethical priorities, what is the long-term value for money of sibeprenlimab at current pricing?	0	2	12
Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering benefits beyond health and special ethical priorities, what is the long-term value for money of Nefecon at current pricing?	0	11	3

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the total potential budgetary impact of the interventions of interest (sibeprenlimab [Voyxact], atacicept, and Nefecon [Tarpeyo]) for the IgA nephropathy population. Potential budget impact is defined as the total differential cost of using the new therapy rather than a relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. For this analysis, we estimated the budget impact of each intervention compared to systemic glucocorticoids. All costs were undiscounted and estimated over a five-year time horizon. We used the net price for sibeprenlimab, the placeholder price for atacicept, and the net price for Nefecon in our estimates of budget impact. We also used the threshold prices (at $50,000, $100,000, $150,000, and $200,000) to estimate the percentage of the eligible patient population that could be treated before reaching the ICER potential budget impact threshold of $821 million. Further details on ICER's approach to the budget impact analysis are available in Section F of the Supplement.

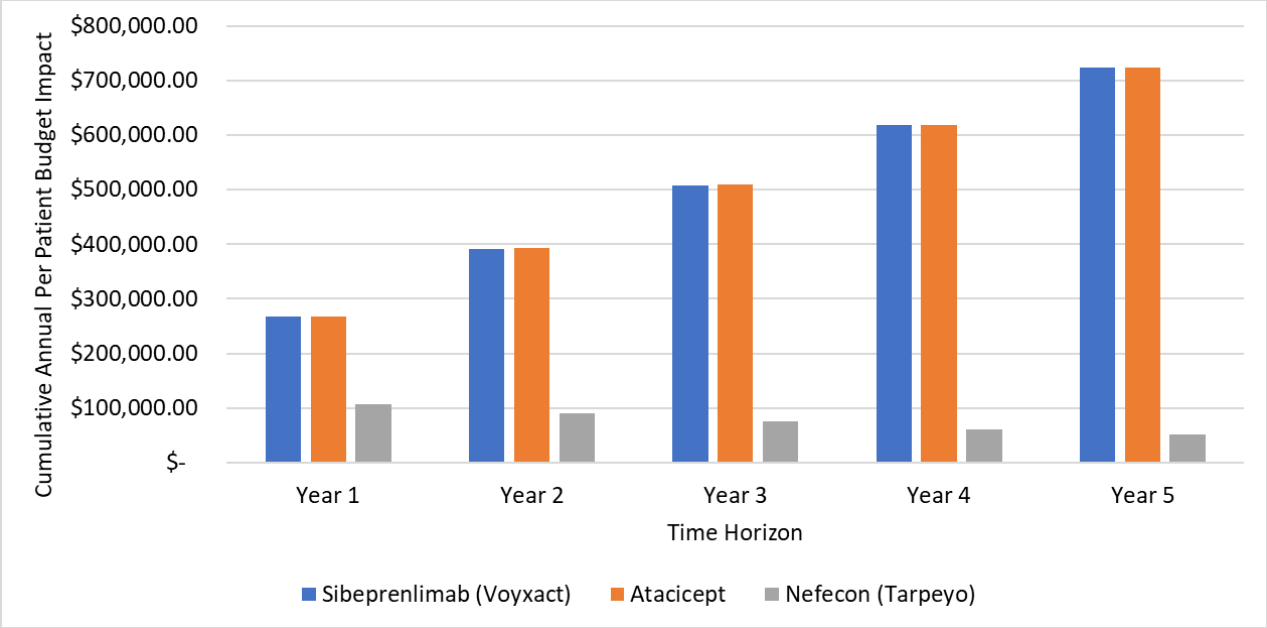
To estimate the size of the potential candidate population for treatment, we used the prevalence of IgA nephropathy in the US (approximately 40 per 100,000) multiplied by the total US population averaged over the next five years (approximately 341,000,000).[16,79] We then excluded the portion of the IgA nephropathy population that is already being treated with Nefecon, which is estimated to be approximately 20%,[80] as well as the portion of the IgA nephropathy population that is not in CKD stage 1 to 4, which is approximately 19.4%.[81] This results in an estimated 87,932 eligible patients in the US. For the purposes of this analysis, we assume that 20% of these patients would initiate treatment in each of the five years, or 17,586 patients per year.

7.2. Results

Figure 7.1 illustrates the cumulative annual per patient treated budget impact for sibeprenlimab, atacicept, and Nefecon compared to systemic glucocorticoids. The cumulative annual budget impact represents the incremental costs of each intervention compared to systemic glucocorticoids per patient across all patients treated within a time horizon (including those who initiated the treatment in previous years), assuming the intervention is used with 20% uptake each year over five years. At the annual net price of $292,500 for sibeprenlimab, the average annual budget impact per patient was $267,393 in year one and increased to $723,698 in year five. At the annual placeholder price of $292,500 for atacicept, the average annual budget impact per patient was $267,453 in year one and increased to $724,158 in year five. At the annual net price of $133,741 for Nefecon, the

average annual budget impact per patient was $107,618 in year one and decreased to $52,302 in year five. This is because the intervention costs of Nefecon are limited to year one.

Figure 7.1. Cumulative Annual Per Patient Treated Budget Impact for Each Intervention Compared to Systemic Glucocorticoids



Assuming a 20% uptake of sibeprenlimab per year, 6% of the eligible population could be treated at the annual net price of $292,500 before reaching the ICER potential budget impact threshold of $821 million. At the $200,000 per evLY and $150,000 per evLY threshold prices ($97,200 and $81,000 annually), 32% and 48% of the eligible population respectively could be treated before reaching the ICER potential budget impact threshold. 97% of the eligible population could be treated at the $100,000 per evLY threshold price ($64,500), and the entire eligible population could be treated at the $50,000 per evLY threshold price ($48,000) without reaching the ICER potential budget impact threshold.

Assuming a 20% uptake of atacicept per year, 6% of the eligible population could be treated at the annual placeholder price of $292,500 before reaching the ICER potential budget impact threshold of $821 million. At the $200,000 per evLY and $150,000 per evLY threshold prices ($96,500 and $80,000 annually), 33% and 49% of the eligible population respectively could be treated before reaching the ICER potential budget impact threshold. 99% of the eligible population could be treated at the $100,000 per evLY threshold price ($64,000), and the entire population could be treated at the $50,000 per evLY threshold price ($47,500) without reaching the ICER potential budget impact threshold.

Assuming a 20% uptake of Nefecon per year, 89% of the eligible population could be treated at the single course price of $133,741 before reaching the ICER potential budget impact threshold of $821 million. At the $200,000 per evLY and $150,000 per evLY threshold prices ($168,000 and $143,000), 55% and 76% of the eligible population could be treated before reaching the ICER potential budget impact threshold. The entire eligible population could be treated at the $100,000 per evLY and $50,000 per evLY threshold prices ($117,500, and $91,500) without reaching the ICER potential budget impact threshold.

Access and Affordability Alert

The goal of the Access and Affordability alert is to signal that the additional health care costs introduced by a new intervention may be difficult for the health care system to absorb over the short term. In this situation, other needed services may be displaced, or health care insurance costs may rapidly rise, which would threaten sustainable access to high-value care for all patients.

At the current net price of sibeprenlimab ($292,500 per year), 6% of the eligible population could be treated before reaching the ICER potential budget impact threshold of $821 million. Therefore, ICER is issuing an access and affordability alert for sibeprenlimab.

For atacicept, 6% of the eligible population could be treated before reaching the ICER potential budget impact threshold at a placeholder price of $292,500 per year; therefore, ICER is issuing an access and affordability alert under the assumed placeholder price. However, if priced within the ICER HBPB range ($100,000 per QALY to $150,000 per evLY), 49% to 100% could be treated and no access and affordability alert would be issued.

Nefecon has been on the market for almost five years and 89% of the eligible population could be treated before reaching the ICER potential budget impact threshold at the current net price ($133,741 for a single course of treatment). Therefore, ICER is not issuing an access an affordability alert for Nefecon.

8. Policy Recommendations

Following the CTAF's deliberation on the evidence, a policy roundtable discussion was moderated by Sarah Emond, President and Chief Executive Officer at ICER, around how to apply the evidence on the use of Nefecon, sibeprenlimab, and atacicept. The policy roundtable members included two patients, two clinical experts, one payer, and two representatives from the drug manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found here.

Health Equity

Recommendation 1

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with IgAN are introduced in a way that will help reduce health inequities.

For many years, systemic glucocorticoids were the only treatment available for IgAN. Systemic glucocorticoids have significant toxicities. As such, the introduction of newer agents has substantial promise to improve clinical outcomes in IgAN. There is not a price yet available for atacicept, but sibeprenlimab has been given a high price. High prices are often correlated with more aggressive utilization management and patient-facing cost-sharing, and therefore can exacerbate inequity. In addition, there are inequities in diagnosis and access to specialty care. Even in settings with universal access to health care, socioeconomic deprivation is associated with worse outcomes in IgAN.[82] At the Policy Roundtable, clinical and patient experts discussed the potential utility of routine screening with urinalysis in clinical practice as well as the need for equitable access to centers of excellence for glomerular diseases including IgAN. Finally, although IgAN is more common in men, women with IgAN have different treatment circumstances given that many are diagnosed at childbearing age. Better evidence is needed around the safety of IgAN treatments during pregnancy, and how clinical outcomes change when IgAN treatments are stopped, including during child-bearing years. Furthermore, since urinary tract infections are more common in women than men, women with IgAN are often misdiagnosed as having urinary tract infections. Awareness in clinical practice needs to be improved given that gross hematuria can be an initial manifestation of IgAN in both men and women.

To reduce inequity at a time of new awareness and new treatment options:

Manufacturers should take the following actions:

- Generate or collect safety and outcomes data about how new agents can be used in women of childbearing age including during pregnancy. Furthermore, there needs to be better understanding of how clinical outcomes change over the longer term when these medications are stopped, including for childbearing.
- As manufacturers promote public awareness as they introduce these new medications, they should be attentive to awareness in all communities.
- Manufacturers should align prices better with value, and payers should reduce friction in access for fairly-priced drugs, leading to improvements in equity.

Payers should take the following actions:

- Ensure that efforts at utilization management for medications for IgAN do not create requirements for large out-of-pocket spending that differentially affect vulnerable individuals.
- Ensure that efforts at utilization management for medications for IgAN are not overly complex or cumbersome.

Clinical specialty societies should take the following actions:

- Promote efforts to develop careers of nephrologists including through teaching and mentorship focused on the clinical care of glomerulonephritis, which will improve access to needed care.
- Promote laws that allow use of telemedicine across state lines when access to doctors with special expertise is limited.
- Promote efforts for early diagnosis of IgAN and other chronic kidney disorders in all communities at risk.

Payers

Recommendation 1

If the price of sibeprenlimab is reduced to a price aligned with value, and if the initial price of atacicept is aligned with value, payers should not require step therapy with systemic glucocorticoids or Nefecon before authorizing use of sibeprenlimab or atacicept for treatment of IgAN.

There is substantial unresolved uncertainty about the relative effectiveness of these treatment options. In terms of safety, there are no concerning safety signals for either sibeprenlimab or atacicept so far based on trial data alone. It is possible that with time, rarer side effects or longer-term side effects may become evident. Both types of steroids, however, show side effects from trial data. Many assume that these effects are not as severe for Nefecon than for systemic glucocorticoids although any difference has been difficult to demonstrate conclusively. In general, patients should not be required to take medicines with known serious side effects before gaining access to reasonably priced medications that do not have such side effects. As such, if prices of sibeprenlimab or atacicept are aligned with value in the future, step therapy should not require trials of systemic steroids or Nefecon before approval of sibeprenlimab or atacicept.

Recommendation 2

Payers should use the FDA labels and trial inclusion criteria as well as expert consensus to guide coverage policy for sibeprenlimab, Nefecon, and atacicept.

Although we know that individuals with IgAN and lower levels of proteinuria are likely to have some risk of deterioration of kidney function, individuals with less than 1 gram of proteinuria per day were not included in the key trials. As such, the efficacy and safety of these agents in individuals with low levels of proteinuria are unclear. However, clinical experts emphasized that treatment is also reasonable for individuals with low levels of proteinuria who still have deteriorating kidney function as measured by estimated GFR. Coverage policies should include patients represented in key trials (those with proteinuria of 1 gram per day or more) as well as patients with worsening kidney function despite lower levels of proteinuria.

Manufacturers

Recommendation 1

Manufacturers should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. In the case of IgAN, substantial new hope with the availability of these therapies is diminished by the extremely high price of sibeprenlimab. Nefecon is also priced slightly above a value-based price.

The manufacturer of sibeprenlimab should reduce the price by roughly 80% and the manufacturer of Nefecon should reduce the price of Nefecon by roughly 25% to align with value-based prices. The price for Nefecon has increased by more than one-third since initial pricing in 2022. Although there is not a price yet available for atacicept, the manufacturer of atacicept has an opportunity to enter the market at a more competitive price than sibeprenlimab, and one aligned with value. There is

very little information about the comparative effectiveness of sibeprenlimab and atacicept, so a price difference may be very influential in coverage decisions between those two options.

Recommendation 2

Manufacturers should create a cross-trial repository of blood and urine data and permit access by academic researchers to assist in better understanding how to identify patients with IgAN who are more or less likely to progress on and off various therapies.

Clinical experts noted that data from randomized trials potentially provide an extremely valuable source of information about risks in IgAN. The costs of generating these data were large, and the information generated from these data should be maximized.

Recommendation 3

Manufacturers should establish clinical registries to detect rarer side effects.

For sibeprenlimab and atacicept, there are no overtly concerning safety signals in relatively short-term trial data. Much of the current uncertainty about the balance between efficacy and safety with these newest medications is that rare or longer-term side effects might not yet be uncovered. Phase III clinical trials do not have duration or statistical power to detect some of these potential side effects. Assessing the potential of these types of side effects with larger and longer-term data sets may provide additional reassurance about the safety of long-term use.

Recommendation 4

Manufacturers should support studies to assess the efficacy of IgAN treatments in patients with IgAN and relatively lower levels of proteinuria (< 1 g/day), which is a key scientific unmet need.

Patients with relatively lower levels of proteinuria are thought to be at risk of disease progression, but were generally excluded from IgAN trials. As such, whether the treatments work to improve patient-meaningful outcomes is unclear. This evidence gap is important to resolve both for clinical practice as well as for coverage policy.

Clinicians and Clinical Societies

Recommendation 1

Clinicians and clinical societies should update treatment guidelines to provide specific guidance on the use of sibeprenlimab and atacicept.

Clinical societies should update their practice guidelines to include specific information about these newest options for IgAN. Nephrologists substantially disagree about the role of systemic steroids in treating IgAN, at least in comparison with Nefecon, and there are large practice variations across the world. Ideally, new guidelines should include the broadest possible range of international perspectives and minimize the influence of pharmaceutical manufacturers, to the extent possible, while including leading experts. In addition to the role of systemic steroids, key clinical guidance that would inform practice could include which patients to consider for which treatment options and how to monitor response to therapy and define treatment failure. Duration of therapy also remains an important uncertainty for all new treatments for IgAN. Payers and purchasers may be sources of information that could highlight evidence gaps that would inform coverage policy.

Patient Organizations

Recommendation 1

Patient organizations have a vital role to play to promote objective descriptions of the risks and benefits of new therapies to support shared decision-making for every patient. In addition, patient groups have a powerful voice and should apply that voice to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system.

Throughout this process, patients and patient organizations have emphasized the critical role of humanity, including access to care for novel IgAN therapies. Missed diagnoses and delayed diagnoses, as well as poor access to care even after diagnosis are often the source of anguish. When considering treatments, patients will have individualized priorities and concerns. As such, patient organizations have a powerful voice to advocate for fair access based on value-based prices. Initial prices in line with value combined with reduced utilization management and prior authorization would improve patient access, patient experience, and affordability.

Research Funding Organizations

Recommendation 1

Research funding organizations should support pragmatic analyses assessing the feasibility and the effectiveness of large-scale screening for IgAN and other kidney diseases including among children, which would inform public health practices like school-based screening programs.

Presently, some countries outside the United States in which prevalence of IgAN is relatively high perform school-based screening for kidney disease. This is conceptually compelling, because many individuals with IgAN and other chronic kidney disorders have irreversible deterioration of kidney function before recognition of the disease. As with any screening program, false positives can occur. Ideally, before any adoption of widespread screening, better understanding is needed of whether these programs improve clinical outcomes and how much they cost.

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

IgA Nephropathy: Immunoglobulin A Nephropathy (IgAN) is one of the most common forms of primary glomerulonephritis worldwide and a progressive autoimmune kidney disease. IgAN occurs when abnormal complexes of Immunoglobin A (IgA) build up in the glomeruli of kidneys and is diagnosed through a kidney biopsy. This can lead to a "cascade of inflammatory events", including inflammation of the glomeruli (glomerulonephritis), educed quality of life, end stage renal disease (ESRD), and the need for dialysis or transplantation.[1]

24-Hour Urine Protein to Creatinine Ratio (uPCR): A measurement used to evaluate proteinuria by assessing variation in urine protein concentration throughout the day. uPCR is recognized as the "gold standard" for evaluating proteinuria among patients with proteinuric kidney disease.[83]

Estimated Glomerular Filtration Rate (eGFR): A measurement of the "rate at which the glomerulus filters plasma to produce an ultrafiltrate" to assess the overall function of the kidney. A decline in eGFR can be correlated with the loss of other functions in the kidney and is crucial to the management of chronic kidney disease.[84]

End Stage Kidney Disease (ESKD): End stage kidney disease marks the final stage of chronic kidney disease and is indicated by a GFR of less than 15 mL/min/1.73 m^2. The condition reflects progressive loss of kidney function and requires patients to receive dialysis or kidney transplantation.[85]

Hematuria: Hematuria refers to the presence of blood in the urine and can take the form of gross hematuria or microscopic hematuria. Health care professionals diagnose hematuria using a urine test.[86]

Proteinuria: Proteinuria refers to the presence of protein in the urine and can be an indication of early renal disease or kidney damage. The extent of proteinuria corresponds with disease progression and can be used with eGFR to identify chronic kidney disease.[87]

SF-36: The 36-Item Short Form Health Survey (SF-36), developed by RAND corporation, is a generic questionnaire to measure an individual's self-reported quality of life.[88] The survey encompasses eight scales that touch on measures of physical and mental health. A high score indicates better health, and each item is scored based on a range of 0 to 100.

Urine Albumin-Creatinine Ratio (uACR): A measurement used to identify kidney damage by indicating the amount of albumin and creatinine is present in the urine. A uACR result of lower than 30 mg/g is considered normal and a result above 30 mg/g may suggest a higher risk of kidney failure.[89]

Urine Protein Excretion: The normal amount of urine protein excretion is less than 300 mg/day and anything above this is considered abnormal, necessitating further evaluation.[90] A 24-hour urinary protein excretion measurement can be used to assess the degree of one's proteinuria.[87]

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[91] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[92,93] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4%=2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above one

suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5). ICER did not calculator the Health Improvement Distribution Index (HIDI) given a lack of data on prevalence in different subpopulations. However, incidence estimates suggest that in the United States (US), IgAN is more commonly diagnosed in Asian individuals and less commonly diagnosed in Black individuals.[16]

A2. Potential Cost-Saving Measures in IgAN

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, please reference ICER's Value Assessment Framework). These services are ones that would not be directly affected by therapies for IgAN (e.g., need for dialysis and/or transplant), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of IgAN beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with IgAN that could be reduced, eliminated, or made more efficient.

One manufacturer commented on the carbon footprint of dialysis and emphasized the large use of energy, waste production, and production of carbon emissions that are associated with dialysis facilities and processes.

A3. Patient Input on Clinical Trial Design

Manufacturers were asked to submit a written explanation of how they engaged patients in the design of their clinical trials, including the methods used to gather patient experience data and how they determined the outcomes that matter most to patients. ICER did not receive any feedback on this inquiry.

B. Stakeholder Input: Supplemental Information

B1. Patient Community Insights: Methods

We spoke with five individuals living with IgAN who had various stages of disease progression, from early-stage kidney disease to individuals who had received a kidney transplant. We spoke with two patient advocacy groups. We also reviewed and described the 2020 Voice of a Patient report that highlighted topics such as disease symptoms, daily impacts, treatment goals, clinical trial experience, and challenges for treatment and care.[22] We did not receive any Share Your Story forms for this review.

B2. Clinical Expert Input: Methods

We spoke with clinical experts who are specialists in renal medicine including nephrologists and clinician scientists investigating glomerular diseases.

C. Clinical Guidelines

Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline 2025[23]

In part given the availability of new therapies for IgAN, KDIGO updated clinical practice guidelines in 2025. These clinical practice guidelines note that "the trials thus far have not shown how best to use and, in particular, how best to combine these new tools." As such, given the lack of head-to-head comparisons and lack of data on many combination therapies, the 2025 KDIGO guidelines integrate mechanistic conjecture as well as empirical data in formulating recommendations.

Diagnosis and Prognostication

The 2025 guidelines emphasized that the criterion standard for diagnosis of IgAN is a kidney biopsy. Recognizing the importance of proactive treatment as well as the emerging availability of treatment options, the 2025 guidelines now encourage biopsy to be considered in all adults with proteinuria greater than or equal to 0.5 g/day in whom IgAN is suspected. In any biopsy positive for IgAN, mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, and extent of crescents should be measured and integrated into the MEST-C score, which is correlated with IgAN prognosis.[94] The guidelines note that these findings on biopsy are important in part given the lack of validated prognostic biomarkers for IgAN, aside from eGFR and proteinuria.

Treatment

For individuals with confirmed IgAN at risk of progressive loss of kidney function, the 2025 guidelines emphasize the importance of simultaneously (1) reducing the production of IgA antibodies that eventually deposit in the kidneys as well as (2) protecting glomerular function in the kidneys once deposition of pathogenic IgA has already occurred. The 2025 version also has reduced the proteinuria goal to at least <0.5 g/day while on or off treatment (ideally <0.3 g/day). The guidelines acknowledge uncertainty about the duration of therapy for treatments that reduce the production of IgA antibodies but suggest that treatments to preserve glomerular function are likely to need indefinite treatment.

For treatment goal 1, treatment options include Nefecon for nine months. The guidelines raise the possibility of extended or additional treatment courses but note that efficacy and safety data are limited. The guidelines also include systemic glucocorticoids (methylprednisolone 0.4 mg/kg/d) for two months followed by a dose taper over six to nine months. The guidelines specify that systemic glucocorticoids should be used "in settings where Nefecon is not available." The guidelines do not

recommend routine use of other treatments, except in specific populations: cyclophosphamide (in rapidly progressive glomerulonephritis), hydroxychloroquine and mycophenolate mofetil (in China), or tonsillectomy (in Japan).

For treatment goal 2, the guidelines recommend renin-aldosterone inhibitors such as ACEi or ARB to lower blood pressure to below 120/70 in most patients. For patients who are at higher risk, replacing ACEi or ARB with sparsentan (a dual endothelin-angiotensin receptor antagonist) is recommended in settings where sparsentan is available. The guidelines also recommend SGLT2i for individuals at risk of progression.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of focus for the review is people with IgA nephropathy.

Data permitting, we will evaluate the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors (e.g., sex, age, race, ethnicity)
- Higher / lower risk of progression to ESKD (e.g., baseline proteinuria levels and eGFR)

Interventions

The intervention(s) of interest for this review are:

- Sibeprenlimab (Voyxact, Otsuka Holdings Co., Ltd.)
- Atacicept (Vera Therapeutics, Inc.)
- Delayed-release budesonide ("Nefecon", Tarpeyo, Calliditas Therapeutics AB)

Comparators

Data permitting, we intend to compare these agents to systemic steroids, to each other, and to no specific immunomodulatory therapy. All groups would be expected to receive renal protective therapies that may include renin-angiotensin system inhibitors (RASis), sodium-glucose cotransporter 2 (SGLT2) inhibitors, and/or endothelin receptor antagonists (ERAs), as well as lifestyle modification.

Outcomes

The outcomes of interest are described in the list below.

- Patient-important Outcomes
    - Development of ESKD
    - Symptomatic chronic kidney disease
    - Cardiovascular Disease
    - Mortality
    - Hospitalization
    - Fatigue
    - Quality of Life
- Other Outcomes
    - Kidney function (e.g., as measured by glomerular filtration rate)
    - Proteinuria
    - Hematuria
    - Changes in biomarkers (e.g., galactose-deficient IgA1)
- Adverse events (AEs) including but not limited to:
    - Serious AEs
    - Discontinuation due to AEs
    - Other AEs of interest
        - Infections
        - Injection site reactions
        - Other Corticosteroid adverse effects (e.g., weight gain, metabolic effects, bone loss)

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the US.

Table D1.1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).

Section and Topic	Item #	Checklist Item
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.

Section and Topic	Item #	Checklist Item
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new B-cell directed therapies for IgA Nephropathy followed established best research methods.[95,96] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[97] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews. Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data).

Table D1.2. Intervention Search: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews

#	Search Terms
1	exp Glomerulonephritis, IGA/
2	("Berger disease" OR "Berger nephropathy" OR "Berger's disease" OR "Berger's glomerulonephritis" OR "Berger's nephropathy" OR "glomerulonephritis, iga" OR "IgA glomerular nephritis" OR "IgA glomerulonephritis" OR "IgA glomerulo-nephritis" OR "IgA nephropathy" OR "IgA nephrotic syndrome" OR "IgA-associated glomerulonephritis" OR "IgA-associated nephropathy" OR "IgA-dominant glomeruloneph" OR "IgA-induced nephropathy" OR "IgAN (immunoglobulin A nephropathy)" OR "IgA-related nephropathy" OR "immunoglobulin A glomerulonephritis" OR "immunoglobulin A glomerulopathy" OR "immunoglobulin A nephropathy" OR "immunoglobulin A type nephropathy" OR "Bergers Disease" OR "Glomerulonephritides, IGA" OR "Iga Nephropathy 1" OR "IGA Type Nephritis" OR "Nephritis, IGA Type" OR "Nephropathy 1, Iga" OR "Nephropathy, IGA" OR "Nephropathy, Immunoglobulin A").ti,ab.
3	1 OR 2
4	("sibeprenlimab" OR " vis-649" OR " vis 649" OR "vis649").ti,ab.
5	("atacicept" OR "TACI Ig" OR "TACI-Fc5" OR "TACI-Ig" OR "TACI-Ig" OR "VT 001" OR "VT001" OR "VT-001").ti,ab.
6	("Budesonide" OR "Budesonide, (R)-Isomer" OR "Budesonide, (S)-Isomer" OR "PL 56" OR "PL56" OR "PL-56" OR "Targeted-release formulation of budesonide (TRF-budesonide)" OR "Tarpeyo" OR "VR 205" OR "VR205" OR "VR-205" OR "VR-205 (Japan)").ti,ab.
7	3 and (4 OR 5 OR 6)
8	7 NOT (animals not (humans and animals)).sh.
9	8 NOT (addresses OR autobiography OR bibliography OR biography OR comment OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR guideline OR interactive tutorial).pt
10	limit 9 to English language
11	Remove duplicates from 10

Updated search: 1/09/26

Table D.1.3. Intervention Search: EMBASE Search Strategy

#	Search Terms
1	'immunoglobulin A nephropathy'/exp
2	('Berger disease' OR 'Berger nephropathy' OR 'Berger's disease' OR 'Berger's glomerulonephritis' OR 'Berger's nephropathy' OR 'glomerulonephritis, iga' OR 'IgA glomerular nephritis' OR 'IgA glomerulonephritis' OR 'IgA glomerulo-nephritis' OR 'IgA nephropathy' OR 'IgA nephrotic syndrome' OR 'IgA-associated glomerulonephritis' OR 'IgA-associated nephropathy' OR 'IgA-dominant glomeruloneph' OR 'IgA-induced nephropathy' OR 'IgAN (immunoglobulin A nephropathy)' OR 'IgA-related nephropathy' OR 'immunoglobulin A glomerulonephritis' OR 'immunoglobulin A glomerulopathy' OR 'immunoglobulin A nephropathy' OR 'immunoglobulin A type nephropathy' OR 'Bergers Disease' OR 'Glomerulonephritides, IGA' OR 'Iga Nephropathy 1' OR 'IGA Type Nephritis' OR 'Nephritis, IGA Type' OR 'Nephropathy 1, Iga' OR 'Nephropathy, IGA' OR 'Nephropathy, Immunoglobulin A'):ti,ab
3	#1 OR #2
4	('sibeprenlimab' OR 'vis-649' OR 'vis 649' OR 'vis649'):ti,ab
5	('atacicept' OR 'TACI Ig' OR 'TACI-Fc5' OR 'TACI-Ig' OR 'TACI-Ig' OR 'VT 001' OR 'VT001' OR 'VT-001'):ti,ab
6	('Budesonide' OR 'Budesonide, (R)-Isomer' OR 'Budesonide, (S)-Isomer' OR 'PL 56' OR 'PL56' OR 'PL-56' OR 'Targeted-release formulation of budesonide (TRF-budesonide)' OR 'Tarpeyo' OR 'VR 205' OR 'VR205' OR 'VR-205' OR 'VR-205 (Japan)'):ti,ab
7	#3 and (#4 OR #5 OR #6)
8	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
9	#7 NOT #8
10	#9 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
11	#10 AND [english]/lim

Updated search: 1/09/26

Table D1.4. Comparator Search: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews

#	Search Terms
1	exp Glomerulonephritis, IGA/
2	("Berger disease" OR "Berger nephropathy" OR "Berger's disease" OR "Berger's glomerulonephritis" OR "Berger's nephropathy" OR "glomerulonephritis, iga" OR "IgA glomerular nephritis" OR "IgA glomerulonephritis" OR "IgA glomerulo-nephritis" OR "IgA nephropathy" OR "IgA nephrotic syndrome" OR "IgA-associated glomerulonephritis" OR "IgA-associated nephropathy" OR "IgA-dominant glomeruloneph" OR "IgA-induced nephropathy" OR "IgAN (immunoglobulin A nephropathy)" OR "IgA-related nephropathy" OR "immunoglobulin A glomerulonephritis" OR "immunoglobulin A glomerulopathy" OR "immunoglobulin A nephropathy" OR "immunoglobulin A type nephropathy" OR "Bergers Disease" OR "Glomerulonephritides, IGA" OR "Iga Nephropathy 1" OR "IGA Type Nephritis" OR "Nephritis, IGA Type" OR "Nephropathy 1, Iga" OR "Nephropathy, IGA" OR "Nephropathy, Immunoglobulin A").ti,ab.
3	1 OR 2
4	Exp steroids/ OR ("steroids" OR "corticosteroids" OR "systemic steroids" OR "systemic corticosteroids" OR "prednisone" OR "prednisolone" OR "methylprednisolone" OR "budesonide").ti,ab.
5	3 and 4
6	5 NOT (animals not (humans and animals)).sh.

#	Search Terms
7	6 AND ((exp randomized controlled trial/ OR exp systematic review/) OR (“randomized controlled trial” OR clinical trial OR controlled clinical trial).ti,ab.)
8	limit 7 to English language
9	Remove duplicates from 8

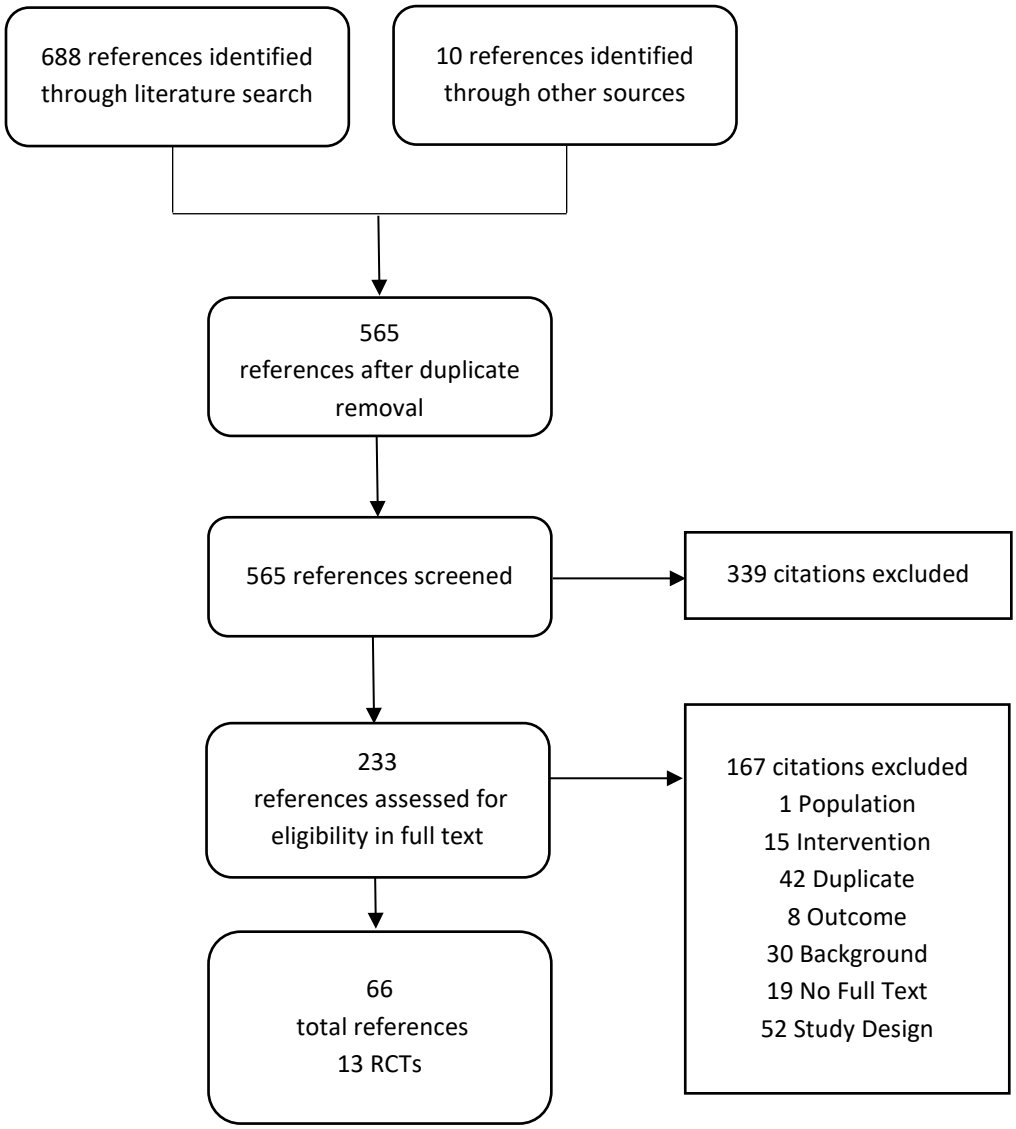
Updated search: 1/09/26

Table D1.5. Comparator Search: EMBASE Search Strategy

#	Search Terms
1	‘immunoglobulin A nephropathy’/exp
2	(‘Berger disease’ OR ‘Berger nephropathy’ OR ‘Berger's disease’ OR ‘Berger's glomerulonephritis’ OR ‘Berger's nephropathy’ OR ‘glomerulonephritis, iga’ OR ‘IgA glomerular nephritis’ OR ‘IgA glomerulonephritis’ OR ‘IgA glomerulo-nephritis’ OR ‘IgA nephropathy’ OR ‘IgA nephrotic syndrome’ OR ‘IgA-associated glomerulonephritis’ OR ‘IgA-associated nephropathy’ OR ‘IgA-dominant glomeruloneph’ OR ‘IgA-induced nephropathy’ OR ‘IgAN (immunoglobulin A nephropathy)’ OR ‘IgA-related nephropathy’ OR ‘immunoglobulin A glomerulonephritis’ OR ‘immunoglobulin A glomerulopathy’ OR ‘immunoglobulin A nephropathy’ OR ‘immunoglobulin A type nephropathy’ OR ‘Bergers Disease’ OR ‘Glomerulonephritides, IGA’ OR ‘Iga Nephropathy 1’ OR ‘IGA Type Nephritis’ OR ‘Nephritis, IGA Type’ OR ‘Nephropathy 1, Iga’ OR ‘Nephropathy, IGA’ OR ‘Nephropathy, Immunoglobulin A’):ti,ab
3	#1 OR #2
4	‘steroids’/exp OR ("steroids" OR “corticosteroids” OR "systemic steroids" OR “systemic corticosteroids” OR "prednisone” OR “prednisolone” OR “methylprednisolone” OR “budesonide”):ti,ab
5	#3 and #4
6	(‘animal’/exp OR ‘nonhuman’/exp OR ‘animal experiment’/exp) NOT ‘human’/exp
7	#5 NOT #6
8	#7 AND ((‘randomized controlled trial’/exp OR ‘systematic review’/exp) OR (“randomized controlled trial” OR clinical trial OR controlled clinical trial):ti,ab.)
9	#8 AND [english]/lim
10	#9 NOT [medline]/lim

Updated search: 1/09/26

Figure D1.1. PRISMA Flow Chart Showing Results of Literature Search for IgA Nephropathy



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, Minnesota); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

Data Extraction

Data were extracted into Microsoft Word and Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[96,98] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: “low risk of bias,” “some concerns,” or “high risk of bias.” Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias*: The study is judged to be at low risk of bias for all domains for this result.*

Some concerns*: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

High risk of bias*: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the following outcomes: 24-hour urinary protein-to-creatinine ratio (uPCR) and estimated glomerular filtration rate (eGFR). See Table D1.6.

Table D1.6. Risk of Bias Assessment

Studies*	Outcome	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Sibeprenlimab							
VISIONARY	**uPCR**	Low	Low	Low	Low	Low	Low
	eGFR	NA	NA	NA	NA	NA	NA
ENVISION	**uPCR**	Low	Low	Low	Low	Some Concern	Some Concern
	eGFR	Low	Low	Low	Low	Some Concern	Some Concern
Atacicept							
ORIGIN 3	**uPCR**	Low	Low	Low	Low	Low	Low
	eGFR	NA	NA	NA	NA	NA	NA
ORIGIN	**uPCR**	Low	Low	Low	Low	Low	Low
	eGFR	Low	Low	Low	Low	Low	Low
Nefecon							
NefIgArd	**uPCR**	Low	Low	Low	Low	Some Concern	Some Concern
	eGFR	Low	Low	Low	Low	Low	Low
NEFIGAN	**uPCR**	Low	Low	Some Concern	Low	Some Concern	Some Concern
	eGFR	Low	Low	Some Concern	Low	Some Concern	Some Concern
Systemic Glucocorticoids							
TESTING	**uPCR**	NA	NA	NA	NA	NA	NA
	eGFR	Low	High	Low	Low	Some Concern	High

eGFR: estimated glomerular filtration rate, NA: Not applicable, uPCR: Urinary protein-to-creatinine ratio

*At the time of this review, Phase III VISIONARY and Phase III ORIGIN 3 did not report on eGFR, and therefore RoB was not assessed for that outcome. The TESTING trial did not report on uPCR and therefore RoB was not assessed for that outcome.

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[55] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.7. Representation for each demographic category was evaluated by quantitatively comparing clinical trial participants with disease-specific incidence estimates (which were used to calculated prevalence estimates), using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR).[16] Next, a representation score between zero to three was assigned based on the PDRR estimate (See Table D1.8 for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.9.

Table D1.7. Demographic Characteristics and Categories

Demographic Characteristics	Categories
1. Race and Ethnicity*	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
2. Sex	• Female • Male
3. Age	• Older adults (≥65 years)

*Multinational trials: For multinational clinical trials, our approach is to evaluate only the subpopulation of patients enrolled from the US on racial and ethnic diversity

Table D1.8. Representation Score

PDRR	Score
0	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.9. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black or African American, White, and Hispanic or Latino	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

*American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

We identified incidence data for race/ethnicity and sex of adults with IgAN in the US from Sim et al. 2025.[16] We converted this data into prevalence estimates (adjusted to US census population) for use in our CDR tool. We did not identify any prevalence/incidence estimates for the age group of 65 years and older and the trials did not report this demographic data, and therefore we did not assess the trials on the representation of older adults.

Results

Table D1.10. Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)

Trial	Race and Ethnicity	Sex	Age (Older Adults)
VISIONARY	Fair	Good	NE
ENVISION	Poor	Good	NE
ORIGIN 3	Fair	Good	NE
ORIGIN	Fair	Good	NE
NEFIGARD	Poor	Good	NE
NEFIGAN	Poor	Good	NE
TESTING	Poor	Good	NE

NE: Not Estimated

Table D1.10 presents the clinical trial diversity ratings on race and ethnicity and sex for seven trials. Diversity ratings for age were not estimated due limited prevalence/incidence estimates for this age group and a lack of trial data. Given that these are multinational clinical trials and US-specific enrollment data were not publicly available, each trial was rated using the full sample.

Table D1.11. Race and Ethnicity

	White	Black/ African American	Asian	Hispanic/ Latino	Total Score	Diversity Rating	AIAN	NHPI
Prevalence*	64.71%	5.83%	20.25%	23.19%	-	-	NR	NR
VISIONARY	36.70%	0.80%	59.00%	11.40%	-	-	0.20%	NR
PDRR	0.57	0.14	2.91	0.49	-	-	NC	NC
Score	2	1	3	1	7	Fair	NC	NC
ENVISION	23.00%	0.60%	74.00%	5.80%	-	-	0.60%	0.00%
PDRR	0.36	0.10	3.65	0.25	-	-	NC	NC
Score	1	1	3	1	6	Poor	NC	NC
ORIGIN 3	43.30%	0.49%	54.70%	9.90%	-	-	0	0.49%
PDRR	0.67	0.08	2.70	0.43	-	-	NC	NC
Score	2	1	3	1	7	Fair	NC	NC
ORIGIN	53.00%	0.00%	44.00%	3.00%	-	-	NR	NR
PDRR	0.82	0.00	2.17	0.13	-	-	NC	NC
Score	3	0	3	1	7	Fair	NC	NC
NefIgArd	75.50%	0.00%	22.80%	NR	-	-	NR	NR
PDRR	1.17	0.00	1.13	NC	-	-	NC	NC
Score	3	0	3	0	6	Poor	NC	NC
NEFIGAN	97.00%	NR	1.00%	14.00%	-	-	NR	NR
PDRR	1.50	NC	0.05	0.60	-	-	NC	NC
Score	3	0	1	2	6	Poor	NC	NC
TESTING	4.90%	0.00%	94.80%	0.00%	-	-	NR	NR
PDRR	0.08	0.00	4.68	0.00	-	-	NC	NC
Score	1	0	3	0	4	Poor	NC	NC

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

*Estimated prevalence estimates from incidence data for IgAN population from Sim et al. 2025[16]

Table D1.12. Sex and Age

	Sex				Age		
	Male	Female	Score	Rating	Older Adults (≥65 Years)	Score	Rating
Prevalence*	63.00%	36.00%	-	-	NR	-	-
VISIONARY	58.80%	41.20%	-	-	NR	-	-
PDRR	0.93	1.14	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC
ENVISION	56.80%	43.20%	-	-	NR	-	-
PDRR	0.90	1.20	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC
ORIGIN 3	56.70%	43.30%	-	-	NR	-	-
PDRR	0.90	1.20	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC
ORIGIN	59.00%	41.00%	-	-	NR	-	-
PDRR	0.94	1.14	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC
NefIgArd	65.90%	34.10%	-	-	NR	-	-
PDRR	1.05	0.95	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC
NEFIGAN	71.00%	29.00%	-	-	NR	-	-
PDRR	1.13	0.81	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC
TESTING	61.00%	39.00%	-	-	NR	-	-
PDRR	0.97	1.08	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC

NC: not calculated, NR: not reported PDRR: Participant to Disease-prevalence Representation Ratio
*Estimated prevalence estimates from incidence data for IgAN population from Sim et al. 2025[16]

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[99,100]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include: “Glomerulonephritis, IGA”, “immunoglobulin A nephropathy”, “Sibeprenlimab”, “Atacicept”, and “Tarpeyo”. We selected studies which would have met our inclusion criteria, and for which no findings have been published. We provided a qualitative analysis of the objectives and

methods of these studies to ascertain whether there may be a biased representation of study results in the published literature

Data Synthesis and Statistical Analyses

Relevant data on key outcomes of the main studies were summarized qualitatively in the body of the evidence report and in the evidence tables below in Supplement Section D3.

Feasibility of Conducting Indirect Comparison / Network Meta-Analysis (NMA)

We examined the feasibility of conducting indirect comparisons or an NMA because direct evidence for the comparative efficacy of the interventions (sibeprenlimab, atacicept, and Nefecon) and the comparator (systemic glucocorticoids) for IgA Nephropathy was not available. We examined whether there were notable differences in study populations, study design, intervention type, outcome definition and measurement, and analytic methods, as well as quality of these studies.

After thorough review of the trials, indirect comparison/NMA was not feasible for this review because the outcome measures and timepoints differed across the trials. In addition, not all trials reported outcomes of interest, leading to a disconnected network. Instead, evidence was reported qualitatively.

D2. Additional Clinical Evidence

Additional Methods

Sibeprenlimab

For VISIONARY, of the enrolled participants at the time of the interim analysis, the median age was 42 years old, 63% were male, and 59% were Asian. Approximately 39% were taking SGLT2 inhibitors. Enrolled participants had biopsy confirmed IgAN with a uPCR ≥ to 0.75 g/g or a 24-hour urine protein ≥1 gram per day, an eGFR ≥ to 30 mL/min/1.73m^2, and on a stable course of maximally-tolerated ACEi or ARB for three months prior to randomization.[24]

For ENVISION, enrolled participants had a median age of 39 (range: 18-73), 57% were male, and 74% were Asian. The median time since diagnostic kidney biopsy was 565 days. Approximately one quarter (23.2%) of participants had previously used systemic immunosuppressive therapy. The median range of baseline eGFR levels was between 56 and 68.5 mL/min/1.73m^2, reflecting early stage kidney disease. Eligible participants were adults with biopsy-confirmed IgAN, a uPCR ≥0.75 g/g, eGFR ≥45 mL/min/min per 1.73m^2, and on stable and maximally tolerated dose of either ACEi or ARB for three months prior to screening. The primary outcome was change from baseline in the log-transformed 24-hour uPCR at month 12. Secondary endpoints include the change in uPCR at months 9 and 16, change from baseline in eGFR, and number of participants who achieve clinical remission (i.e. urinary protein excretion <300 mg per day).[8]

Key exclusion criteria for both trials include forms of chronic kidney disease (CKD) other than IgAN, nephrotic syndrome, serum IgG levels <600 mg/dL at screening, individuals who received systemic immunosuppression, including glucocorticoids, within 16 weeks of screening.[8,24]

Atacicept

For ORIGIN, enrolled participants had a median age of 39 years, 59% were male, 44% were Asian, and the mean baseline eGFR was 63 (SD: 27), reflecting early stage kidney disease. One third of participants were taking angiotensin-converting enzyme inhibitors (ACEi) only and two thirds were taking angiotensin receptor blockers (ARB) alone. The primary outcome was the change from baseline in 24-hour uPCR at week 24. Key secondary endpoints include change in 24-hour uPCR at week 36, change in eGFR across three timepoints, and Gd-IgA1 levels.

Eligible participants for both trials were adults with biopsy-confirmed IgAN, 24-hour uPCR >0.75 g/g for ORIGIN and >1.0 g/g for ORIGIN 3, and eGFR ≥30 mL/min/min per 1.73m^2. Key exclusion criteria included rapidly progressing glomerulonephritis (i.e., loss of ≥50% of eGFR within three months prior to screening), nephrotic syndrome, and treatment with systemic glucocorticoids or immunosuppressives within three months of screening.[9]

Nefecon

For NefIgArd, enrolled participants had a median age of 43 for Nefecon and 42 for placebo, were predominantly male (~66%) and White (75.5%). The median eGFR at baseline was 56.1 (IQR 45.5 – 70.9) for Nefecon-treated participants and 55.1 (IQR: 45.9 – 67.7) for placebo-treated participants, with 60% having a median eGFR less than 60 mL/min/1.73m2. Prior to randomization, there were 41.2% of participants who were using ACE inhibitors and 52.7% who were using ARBs, and 4% using both. Across both groups, 9% of participants had been treated with systemic glucocorticoids or immunosuppressant more than 12 months prior to randomization.[10]

The primary outcome of the trial was the time-weighted mean eGFR over two years with the two-year eGFR slope being a supportive endpoint. Key secondary endpoints included a composite endpoint of time to confirmed 30% or more reduction in eGFR or kidney failure, uPCR across various timepoints, proportion of participants with microhematuria, need for rescue medication, and quality of life (as measured by the short-form 36 [SF-36]).[10]

Eligible participants were adults with biopsy-proven IgAN with persistent proteinuria (uPCR greater than 0.8 g/g or daily excretion of 1 g) despite stable dose of RASi treatment and an eGFR of 35-90 mL/min/1.73m2. Key exclusion criteria included people who have undergone kidney transplant, have secondary forms of IgAN or non-IgAN glomerulonephritis, and have blood pressure greater than 140/90 mmHg.[10]

Systemic Glucocorticoids

Enrolled participants in the TESTING trial were predominantly Chinese (75.5%), had a median age of 36, and 60% were men. The median eGFR at baseline was 56.2 and 59.0 mL/min/1.73m^2 for the methylprednisolone and placebo groups, respectively. Nearly half of the participants were receiving ACEi or ARB medication at baseline, and no participants were receiving SGLT2 inhibitors as they were not considered as a part of standard of care until just before the end of trial period.[47]

The primary endpoint of the trial was a composite outcome of the first occurrence of a sustained 40% eGFR decrease, kidney failure, or death due to kidney disease. Key secondary endpoints include composite endpoints with different eGFR thresholds (e.g., 30%, 50%), proteinuria reduction, and eGFR slope.[47]

Eligible participants were adults with biopsy-confirmed primary IgAN, an eGFR between 20 and 120 mL/min/1.73m^2, and a 24-hour urine protein excretion ≥ 1 g/day. Key exclusion criteria included secondary IgAN, a contraindication to glucocorticoids, and use of systemic immunosuppression treatments in past year.[47]

Additional Results

If a sub-header for a specific intervention/comparator is not listed for an outcome below, then additional data were not available or not reported in the respective trials.

Estimated Glomerular Filtration Rate (eGFR)

Systemic Glucocorticoids

In reduced dose cohort of TESTING, there were significantly fewer participants who received methylprednisolone that had an eGFR reduction of 30%, 40%, and 50%, compared to placebo (30% reduction HR: 0.29, 95% CI: 0.13 to 0.66, p=0.003; 40% reduction HR: 0.22, 95% CI: 0.08 to 0.56, p=0.002; 50% reduction HR: 0.30, 95% CI: 0.10 to 0.88, p=0.029).[48]

In the full-dose cohort, the slope was lower for both groups (methylprednisolone: -1.79, placebo: -6.95; p=0.03) leading to a combined annualized eGFR slope of -2.5 mL/min/1.73m^2/year for methylprednisolone and -4.97 for placebo (p=0.002) (See Supplement Table D3.13).

A post-hoc analysis of the TESTING trial reports that while methylprednisolone improved kidney outcomes in both men and women, men experience worse kidney outcomes than women (44% high risk of primary outcome in men, p=0.03).[101]

24-Hour Urinary Protein-to-Creatinine Ratio (uPCR)

Sibeprenlimab

In the ENVISION trial, the baseline 24-hour uPCR was 1.5 g/g for sibeprenlimab 4 mg/kg and 1.7 g/g for placebo. There was a dose-dependent reduction observed across the sibeprenlimab groups with a change of -56.7% observed in the sibeprenlimab 4 mg/kg group compared to a change of -12.7% in the placebo group at month nine. This translates to an absolute change of -0.85 g/g for sibeprenlimab 4 mg/kg and -0.17 g/g for placebo. At month 12, 58.5% of the sibeprenlimab group achieved a ≥30% reduction in uPCR greater compared to 28.9% of the placebo group. At month 16, four months after the last dose, this changed to 51.2% and 21.2% in the sibeprenlimab and placebo groups, respectively.[8]

Atacicept

In the Phase II ORIGIN trial, participants who received atacicept 150 mg had a change of -33% in 24-hour uPCR compared to a change of -7% in participants who received placebo at week 24. A similar reduction was observed in the atacicept 150 mg group at week 36 whereas there was a 3% increase in participants who received placebo (difference vs. placebo: 35; 95% CI: 9.1 to 53.1; p=0.012).[9]

At month 18 in the OLE, there were similar reductions (~46%) in uPCR in the pooled atacicept group and those who switched from placebo to atacicept.[31]

Nefecon

Changes in uPCR were consistent among subgroups defined by time since diagnosis.[102]

Among people who received Nefecon, 53% achieved a uPCR reduction of 30% for at least nine months compared to 16% of people who received placebo. This reduced to 13% of Nefecon-treated participants and 5% of placebo-treated participants achieving a 30% uPCR reduction for at least 18 months.[103]

Spot UPCR

Sibeprenlimab

In the VISIONARY trial, there was a 45.6% reduction in spot uPCR at month nine in participants who received sibeprenlimab compared to an 14.4% increase in the placebo group.[24]

Urine Protein Excretion (UPE)

Sibeprenlimab

In ENVISION, participants in the sibeprenlimab 4 mg/kg group had a change of -0.86 g/day compared to a change of -0.21 g/day in the placebo group at month 12. There were 41.5% of participants in the sibeprenlimab 4 mg/kg group and 18.4% in the placebo group whose UPE reduced below one gram per day. In the sibeprenlimab 4 mg/kg group, 29.3% and 41.5% of participants had a UPE reduction below 500 mg and 1 gram per day, respectively. In comparison, 2.6% and 18.4% of participants in the placebo group had a UPE reduction below 500 mg and 1 gram per day, respectively.[8]

Clinical remission was defined as a reduction in 24-hour UPE to less than 300 mg per day for three consecutive months. At month 16, seven participants in the sibeprenlimab 4 mg/kg group (17.1%) reached clinical remission compared to one person in the placebo group (2.6%).[8]

Atacicept

In the Phase IIa JANUS trial, there was one patient in the atacicept 25 mg group and two participants in the 75 mg group that experienced increases in proteinuria during the 24-week treatment period.[30]

Nefecon

In NEFIGAN, there were greater reductions in UPE in Nefecon-treated participants compared to placebo, with a difference of 31% between the Nefecon 16 mg group and placebo (p=0.004) at month nine and 38% at month 12 (p<0.0001).[33]

Systemic Glucocorticoids

In TESTING, the time-averaged 24-hour urine protein excretion was 1.70 g/day (95% CI: 1.5 to 1.9) in the methylprednisolone group and 2.39 g/day (95% CI: 2.2 to 2.6) in the placebo group. There was a significant difference between the two groups (difference: -0.69 g/day; 95% CI: -0.98 to -0.41; p<0.001) but this was mostly observed early in the trial and not after three years of follow-up. Similar results were observed for both the full-dose and reduced-dose cohorts. There was no significant difference in the reduction of urine protein between men and women (p=0.28).[47]

Urinary Albumin-to-Creatinine Ratio (uACR)

Sibeprenlimab

In VISIONARY, participants who received sibeprenlimab had a mean reduction in uACR of 58.3% and participants who received placebo had a reduction of 11.9% at month nine. Reductions in both groups continued at month 12 (sibeprenlimab: 64.5%, placebo: 17.8%).[24]

Atacicept

In ORIGIN 3, participants who received atacicept had a mean reduction in natural-log transformed uACR of 47.3% and participants who received placebo had an 8.8% reduction (difference: 42.2%; 95% CI: 27.3 to 54.1) at week 36.[29]

Nefecon

In NefIgArd, the time-averaged percent reduction in uACR between month 12 and 24 was 48.2% in Nefecon group and 3.7% in the placebo group (difference: 46.3; 95% CI: 36.5 to 54.5; p<0.0001).[10] Similar reductions were observed in the NEFIGAN trial and a publication that evaluated a cohort of Chinese participants in the NefIgArd trial.[33,34]

Rescue Medication

Nefecon

By month 24 in the NefIgArd trial, there were fewer Nefecon-treated participants who received rescue medication compared to placebo, although this difference was not statistically significant. (8.2% vs. 11%; HR: 0.68; 95% CI: 0.34 to 1.33; p=0.26)[10] In the OLE, there was one person being retreated with Nefecon that received rescue medication at month 12.[104]

Composite Endpoints

Nefecon

Among the 45 participants who were retreated with Nefecon in the NefIgArd OLE, two (4.4%) met the composite endpoint of patients on dialysis, undergoing kidney transplant, or an eGFR <15 mL/min/1.73m^2 compared to no participants in the group with delayed Nefecon treatment (received placebo in NefIgArd RCT).[105]

Systemic Glucocorticoids: Combined Reduced and Full Dose

The primary endpoint of the TESTING trial was a composite endpoint of the first occurrence of a sustained 40% eGFR decrease, kidney failure, or death due to kidney disease. The annual event rate of this endpoint was significantly lower in the methylprednisolone group compared to placebo. (annual event rate %: 7.3 vs. 12.1; HR: 0.53; 95% CI: 0.39 to 0.72; p<0.001). There was a greater risk of reaching the composite endpoint in Chinese participants (HR: 0.61; 95% CI: 0.44 to 0.84) compared to non-Chinese participants (HR: 0.24; 95% CI: 0.1 to 0.56; p=0.048) and in men compared to women (HR: 1.44; 95% CI: 1.05 to 1.97; p=0.03). There was no difference between the full-dose and reduced-dose (full-dose HR: 0.58; 95% CI: 0.41 to 0.81; reduced-dose HR: 0.27; 95% CI: 0.11 to 0.65; p for heterogeneity=0.11) or other key subgroups.[47,101]

There were significantly fewer participants in the methylprednisolone group who had kidney failure that required dialysis or a transplant compared to the placebo group (annual event rate %: 4.9 vs. 7.8; HR: 0.59; 95% CI: 0.4 to 0.87; p=0.008).[47]

There were significantly less patients who received methylprednisolone that reached key secondary composite endpoints that looked at kidney failure, all-cause death, or a 30% eGFR reduction (HR: 0.56; 95% CI: 0.42 to 0.75; p<0.001), 40% eGFR reduction (HR: 0.56; 95% CI: 0.42 to 0.76; p<0.001), and 50% eGFR reduction (HR: 0.62; 95% CI: 0.46 to 0.85; p=0.003) compared to participants who received placebo.[47]

Hematuria

Sibeprenlimab

A conference abstract presents data on hematuria resolution in the ENVISION trial. Remission in hematuria was defined as a reduction in red blood cell count to less than five red blood cell/high power field (RBC/HPF) There were nine participants who received any sibeprenlimab dose and one participant who received placebo that had hematuria remission during the trial.[106]

Atacicept

In the double-blind portion of ORIGIN, 45% (15 of 33) of participants in the atacicept 150 mg group and 56% (19 of 34) in the placebo group had hematuria at baseline. At week 36, there were significantly more participants who received atacicept 150 mg that had one grade improvement or greater in hematuria (87% vs. 32%; p=0.002) and who had resolution to negative/trace levels (80% vs. 5%; p<0.001) compared to placebo.[9] In the OLE, among the participants who had hematuria present at baseline (63/113), there was a 75% reduction in hematuria at week 96.[31]

Biomarkers

Sibeprenlimab

In VISIONARY, there were reductions in serum galactose-deficient IgA1 (Gd-IgA1) in participants who received sibeprenlimab throughout week 48 whereas there was an increase in the placebo group. Similar results were observed for serum IgA, IgG, and IgM. The APRIL levels of participants who received sibeprenlimab were 95.8% lower than baseline at week 48 whereas APRIL levels increased from baseline for the placebo group.[24]

In ENVISION, there was a reduction in the serum level of APRIL during treatment with sibeprenlimab. However, levels became to return toward baseline levels after treatment ended at month 12. Across the 12 month treatment period, the mean percentage of the baseline level of Gd-IgA1 for sibeprenlimab-treated participants was lower than the baseline level whereas it was greater than baseline levels for the placebo group. Between months 12 and 16, Gd-IgA1 levels for the sibeprenlimab group began to return to baseline levels. Similar trends were observed for IgA, IgG, and IgM levels.[8] This data can be found in Supplement Table D3.27.

Atacicept

In ORIGIN 3, there was a -68.3% change in Gd-IgA1 in the atacicept group and -2.9% in the placebo group at week 36. These reductions were observed as early as week four and remained relatively stable.[29]

In the ORIGIN trial, levels of serum IgG, IgA, IgM, and Gd-IgA1 decreased from baseline up to week 36 in the atacicept group while levels remained stable in the placebo group.[9] In the OLE, in the 26 weeks of follow-up after the last atacicept dose at week 96, the Gd-IgA1 increased by 117%.[56] Similar trends were observed in the Phase IIa JANUS trial.[30,31] This data can be found in Supplement Table D3.29.

Nefecon

In NefIgArd, there were reductions in Gd-IgA1, IgG anti-IgA antibodies, and IgA-IC levels while participants were receiving treatment. After participants stopped treatment at month nine, these levels began to return to baseline levels (see Supplement Table D3.36).[107]

Nefecon: Real-World Evidence

We identified six abstracts and one publication that describe Nefecon benefits in real-world settings.

Ngai 2024 reported on a retrospective analysis of 30 patients with IgAN who received Tarpeyo for greater than nine months at a single center in New York City. Before Tarpeyo initiation, the average eGFR was 68.4 mL/min/1.73m^2. At month nine, eGFR among the 30 patients increased by an average of 3.6 mL/min/1.73m^2. There were two mild adverse events which resolved, one of which led to a dose reduction.[43]

Zhang 2025 reported on a retrospective study of 12 patients with IgAN and 36 propensity-matched controls on convention therapy, including corticosteroids and immunosuppressants. At month 12, treatment with Nefecon led to reductions in proteinuria and preserved renal function and no serious infections. Adverse effects reported included bowel habit changes, sleep disturbance, and menstrual irregularities.[40]

Zhang 2025 reported on three pediatric patients with IgAN treated with Nefecon and during the three-month follow-up, reductions in proteinuria and hematuria were observed.[42]

Ren 2025 reported on a retrospective analysis of 26 Chinese patients with IgAN. At month nine, there was proteinuria reduction, increased eGFR, and hematuria resolution.[41]

Chen 2025 reported on a retrospective cohort study of 25 patients with IgAN. At month six, patients treated with Nefecon had reduced proteinuria and improved renal function as measured by eGFR. Adverse events were mild and gastrointestinal issues and infections were most commonly reported.[39]

Gu 2025 reported on a single-center observation study of 16 patients with IgAN. At month six, modest proteinuria reduction was observed.[38]

Ouyang 2025 was a real-world study that evaluated the efficacy and safety of Nefecon in patients with IgAN who have severe renal impairment, defined by an eGFR between 25 to 35 mL/min/1.73m^2. Treatment with Nefecon was well tolerated among the 11 patients, no new safety signals were identified, and there was a decrease in proteinuria. The study concludes that more data are needed to confirm the efficacy and safety of Nefecon in this population.[44]

Additional Harms

Sibeprenlimab

In VISIONARY, the most commonly reported TEAEs in the sibeprenlimab group were upper respiratory tract infection (18%), injection site pain (13%), Covid-19 (13%), nasopharyngitis (12%), and influenza (9%).[24]

In the ENVISION trial, treatment-related AEs were reported by 15.4% of participants treated with any sibeprenlimab dose and 13.2% treated with placebo. There were similar reporting of serious TEAEs (~ 4 to 5%) between groups, although none were deemed related to sibeprenlimab or placebo. There was no increased risk of infection with sibeprenlimab treatment (49.6% vs. 55.3% for placebo). There was one death in the placebo group related to respiratory failure due to underlying COPD. The most commonly reported adverse events (≥5% in pooled sibeprenlimab group) were Covid-19, pyrexia, nasopharyngitis, upper respiratory tract infection, headache, hypertension, diarrhea, and muscle spasm.[8]

Atacicept

In ORIGIN, treatment-related AEs were reported by 55% of participants in the combined atacicept 75 mg and 150 mg group and by 41% of participants in the placebo group. These were most commonly injection site reactions and one participant discontinued treatment due to the reaction. None of these events were deemed serious. Infections were reported by 44% of the atacicept 75 or 150 mg group and 32% of the placebo group. All were mild to moderate aside from one severe case of norovirus gastroenteritis which was resolved and was deemed not related to atacicept.[9]

Of the 111 participants in the OLE between weeks 36 and 96, 52 (47%) had a treatment-related AE, 43 (39%) reported infection or infestation, 12 (11%) had serious TEAEs, and 2 (2%) discontinued treatment due to AEs. There were no deaths in ORIGIN or the OLE. The most commonly reported adverse events (≥5% in pooled atacicept group) were Covid-19, upper respiratory tract infection, and nasopharyngitis. In the OLE, Covid-19, upper respiratory tract infection, and nasopharyngitis were commonly reported during the extension period.[31]

In the Phase IIa JANUS trial, no deaths, cardiac failure, demyelination or other cardiovascular conditions were reported. The most commonly reported treatment-related adverse events were injection-site reactions (erythema, pruritus, bruising). One participant who received atacicept 25 mg reported one grade three event of cervical spinal stenosis during the safety follow-up period. One participant who received atacicept 25 mg of had viral gastroenteritis, which was an AE of special interest.[30]

An integrated safety analysis of atacicept across various indications (e.g. multiple sclerosis, lupus nephritis, rheumatoid arthritis). Across the included trials, treatment with atacicept led to higher rates of treatment-emergent AEs and more treatment discontinuation compared to placebo. Rates of infection were similar between atacicept and placebo groups. There were a total of 11 deaths during treatment, none of which occurred in patients who received atacicept 75 mg or placebo.[32]

Nefecon

In the NefIgArd trial, TEAEs were reported by 87% of participants who received Nefecon 16mg and by 69% of participants who received placebo during the nine-month treatment period. During the 15-month observational follow-up period, the percentage of participants reported TEAEs reduced in the Nefecon group to 73% and increased to 71% in the placebo group.[10]

There were five cases of new-onset diabetes in participants who received Nefecon (four during treatment period, one during follow-up), and two cases in participants who received placebo (during follow-up). All these participants were pre-diabetic at baseline. By two years, Hemoglobin A1c (HbA1c) levels returned back to baseline levels. The most commonly reported TEAEs were peripheral edema, hypertension, muscle spasms, and headache (see Supplement Table D3.33).[10]

Some of the most commonly reported TEAEs (≥5% in Nefecon 16 mg group) were peripheral edema, hypertension, muscle spasms, acne, headache, weight gain. A detailed list of TEAEs can be found in Supplement Table D3.33.[10]

In the post-marketing study, there were nine deaths reported, none of which were related to Nefecon treatment. A subgroup analysis reported that men had a higher risk of face swelling compared to women and women had a higher risk of swelling, muscle spasm, and hypertension than men. Both women and men had similar risks of weight gain. In addition, patients between the ages of 18 and 64 had a higher relative risk of muscle spasms and hypertension compared to patients 65+.[35]

Similar results were observed in NEFIGAN (see Supplement Table D3.34).[33]

Subgroup Analyses and Heterogeneity

For sibeprenlimab, uPCR results were consistent among key subgroups for VISIONARY (sex, ethnicity, region, race, age, screening uPCR, eGFR, SGLT2i use, baseline histopathologic activity, medication history, and prior use of immunosuppressants) and ENVISION (baseline uPCR) (see Supplement Table D3.19).[8,24]

For atacicept, uPCR results were consistent among key subgroups for ORIGIN 3 (age, sex, region, race, baseline uPCR, baseline eGFR, and SGLT2i use) (see Supplement Table D3.20).[29] No subgroup data were reported in the ORIGIN trial.

For Nefecon, changes in the time-weighted eGFR over two years were not dependent on baseline uPCR or proteinuria levels, baseline eGFR, baseline hematuria, baseline dose of RASi age, sex, region, or race (all p-values >0.1) in the NefIgArd trial. Similarly, the mean change in eGFR across various timepoints was not dependent on baseline uPCR values.[10] A publication evaluating a cohort of Chinese participants in the NefIgArd trial reports consistent results with the global study population (see Supplement Tables D3.21-23).[34]

In the TESTING trial for systemic glucocorticoids, there was no difference in the magnitude of benefit observed between the full and reduced dose cohorts although there were fewer side effects. Within the reduced-dose cohort, there were no differences in the primary composite endpoint among subgroups of interest (baseline proteinuria, eGFR, histological scoring, race, sex, age, and time between biopsy and randomization).[47,48] Additional subgroup data for TESTING are reported in Supplement Section D2 and Supplement Tables D3.25-26.

D3. Evidence Tables

Table D3.1. Study Design

Trial Information	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
Sibeprenlimab				
VISIONARY **NCT05248646** **Perkovic. NEJM. 2025.**[24]	Phase III, Multicenter, Randomized, Placebo-Controlled, Parallel Assignment, Double Blind N=530 Duration: 24 Months	Arms: 1) Sibeprenlimab 400 mg SC Q4W 2) Placebo SC Q4W	**Inclusion:** • Male and female patients ≥18 years of age with biopsy-confirmed IgAN • Stable and maximally tolerated dose of ACEI and/or ARB for at least 3 months prior to screening. • Screening uPCR ≥0.75 g/g or urine protein ≥1.0 g/day • eGFR ≥30 mL/min/1.73 m^2, (for the exploratory cohort only: eGFR 20- <30 mL/min/1.73 m^2), calculated using the CKD-EPI equation.) **Exclusion:** • Secondary forms of IgAN or IgA vasculitis. • Coexisting chronic kidney disease other than IgAN. • Kidney biopsy findings in addition to IgAN including those of diabetic nephropathy, membranous nephropathy, or lupus nephritis. Hypertensive vascular changes are acceptable.	• Urinary protein to creatinine ratio (uPCR) in a 24-hour collection (At 9 months) • Annualized rate of change from baseline (slope) of eGFR (Over 24 months) • Proportion of subjects achieving urine total protein <1.0 g/day and ≥25% reduction from baseline. (At 12 months) • Annualized slope of eGFR (Over 12 months)

Trial Information	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
			• Kidney biopsy MEST or MEST-C score of T2 or C2 (Oxford IgAN classification). If MEST-scoring was not performed, the presence of > 50% tubulo-interstitial fibrosis, or crescents in > 25% of glomeruli is exclusionary. This does not apply to the exploratory cohort. • Nephrotic syndrome • Serum IgG < 600 mg/dL at screening. • Chronic systemic immunosuppression, including glucocorticoids, within 16 weeks of randomization	
ENVISION **NCT04287985** **Mathur. NEJM. 2024.**[8]	Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled N=155 Duration: 16 Months	Arms: 1) VIS649 2 mg/kg Q4W IV 2) VIS649 4 mg/kg Q4W IV 3) VIS649 8 mg/kg Q4W IV 4) Placebo	**Inclusion:** • Male and female patients ≥ 18 years of age with biopsy-confirmed IgAN • Stable and maximally tolerated dose of ACEI and/or ARB for at least 3 months prior to screening. • Screening uPCR ≥0.75 g/g or 24-hr urine protein ≥1.0 g/day • eGFR ≥30 mL/min/1.73 m2, calculated using the CKD-EPI formula. **Exclusion:** • Secondary forms of IgAN as defined by the treating physician. Co-existing CKD, other than IgAN. • Evidence of additional pathological findings in the kidney biopsy (e.g.,	• Number of Participants With Adverse Events Graded by Severity (Baseline to 16 months) • Changes From Baseline in Clinical Laboratory Tests (Baseline to 16 months) • Clinically Meaningful Changes From Baseline in Vital Signs (Baseline to 16 months) • Clinically Significant Physical Examinations (Baseline to 16 months) • Change From Baseline in uPCR: Month 12 (12 months)

Trial Information	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
			diabetic kidney disease, membranous nephropathy, or lupus nephritis • Kidney biopsy MEST or MEST-C score as defined in the protocol. • Nephrotic syndrome. • Received a solid organ transplant, including kidney, bone marrow or hematologic stem cell transplantation. • Currently receiving systemic immunosuppression (excluding topical, ophthalmic, per rectum, or inhaled corticosteroids); or received treatment with systemic corticosteroid therapy/systemic immunosuppressive agents within 16 weeks of initial screening. • Any chronic infectious disease/acute infectious disease at the time of screening. • Type 1 diabetes; uncontrolled Type 2 diabetes, as evidenced by a screening hemoglobin A1c value >8%. • Uncontrolled BP (>140 mm Hg systolic or >90 mm Hg diastolic) • History of chronic autoimmune neurodegenerative disorder such as multiple sclerosis. • Poorly compensated or controlled ischemic heart disease or	

Trial Information	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
			cardiomyopathy, as judged by the Investigator. • Chronic obstructive pulmonary disease (COPD) or asthma that has required systemic steroid therapy during the prior year. • Known cirrhosis or liver dysfunction, defined as presence of coagulopathy, platelet count <100,000/µL or alanine aminotransferase >3× upper limit of normal.	
Atacicept				
ORIGIN 3 **NCT04716231** **Lafayette. NEJM. 2025.**[29]	Phase III, Multi-part, Randomized, Double-Blind, Placebo-Controlled N=376 Duration: 104 Weeks	Arms: 1) Atacicept 150 mg Q1W SC injection 2) Placebo	**Inclusion Criteria:** • Male and female patients ≥18 years of age with biopsy-confirmed IgAN • Screening urine protein excretion ≥1.0 per 24-hr or 24-hr urine protein ≥1.0 g/day • eGFR ≥30 mL/min/1.73 m^2, calculated using the CKD-EPI formula. • Stable and maximally tolerated dose of ACEI and/or ARB for at least 3 months prior to screening. • Systolic blood pressure ≤150 mmHg and diastolic blood pressure ≤90 mmHg **Exclusion Criteria:** • IgAN secondary to another condition (e.g., liver cirrhosis), or other causes of	• Change from baseline in urine protein to creatinine ratio (uPCR) [36 weeks] • Annualized rate of change in estimated glomerular filtration rate (eGFR) [52 and 104 weeks]

Trial Information	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
			mesangial IgA deposition including IgA vasculitis (i.e., Henoch- Schönlein purpura), systemic lupus erythematosus (SLE), dermatitis herpetiformis, ankylosing spondylitis • Total urine protein excretion ≥5g per 24-hour or urine protein to creatinine ratio (uPCR) ≥5 mg/mg based on a 24-hour urine sample during the Screening Period • Evidence of rapidly progressive glomerulonephritis (loss of ≥50% of eGFR within 3 months of screening) • Evidence of nephrotic syndrome within 6 months of screening (serum albumin <30g/L in association with uPCR >3.5 mg/mg • Renal or other organ transplantation prior to, or expected during the study • Concomitant chronic renal disease in addition to IgAN • Uncontrolled diabetes, defined as hemoglobin-A1c (HbA1c) >7.5% at screening	
ORIGIN **NCT04716231**	Phase IIb, Randomized, International, Multicenter, Double-	Arms: 1) Atacicept 150 mg Q1W SC injection 2) Atacicept 75 mg Q1W SC injection	**Inclusion:** Male and female patients ≥18 years of age with biopsy-confirmed IgAN Screening urine protein excretion >0.75 per 24-hr or 24 hr uPCR >0.75 g/g	• Change from baseline in 24-hr uPCR in the combined 150 & 75 mg group vs. placebo [Week 24]

Trial Information	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
Lafayette. Kidney International. 2024.[9]	Blind, Placebo-Controlled N=116 Duration: 5/2021-6/2022	3) Atacicept 25 mg Q1W SC injection 4) Placebo	• eGFR ≥30 mL/min/1.73 m^2, calculated using the CKD-EPI formula. • Stable and maximally tolerated dose of ACEI and/or ARB for at least 3 months prior to screening. • Systolic blood pressure ≤150 mmHg and diastolic blood pressure ≤90 mmHg **Exclusion**: •Secondary causes of IgAN •Evidence of rapidly progressive glomerulonephritis (loss of ≥50% of eGFR within 3 months of screening) or nephrotic syndrome (serum albumin 3.5 mg/mg) •Total urine protein excretion ≥5 g per 24-hour or UPCR ≥5 mg/mg based on a 24-hour urine sample during the Screening Period. 5. •Renal or other organ transplantation prior to, or expected during, the study with the exception of corneal transplants.	
ORIGIN EXTEND **NCT06674577** **Barratt. JASN. 2025.**[31]	Phase IIb, Multicenter, Rollover N=476 Duration: 156 Weeks	Arms: 1) Atacicept 150 mg Q1W SC injection	**Inclusion Criteria:** • For Atacicept Drug Holiday Group only: Systolic blood pressure ≤150 mmHg and diastolic blood pressure ≤90 mmHg at screening and Day 1	• Incidence of adverse events observed during the dosing period [Baseline until 156 weeks] • Changes in proteinuria based on UPCR (Urine Protein Creatinine Ratio) and UACR (Urine Albumin-

Trial Information	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
			Exclusion Criteria: • Evidence of rapidly progressive glomerulonephritis (loss of ≥50% of eGFR within 3 months of screening) • Known hypersensitivity to atacicept or any component of the formulated atacicept • For Atacicept Drug Holiday Group only: History of splenectomy, major surgery within 6 weeks prior to screening or planned/expected major surgery during the study period (including the safety follow-up period), and treatment with other investigational agents within the last 4 weeks • Evidence of nephrotic syndrome (serum albumin <30g/L in association with UPCR >3.5 mg/mg) within 6 months of screening • Currently on chronic dialysis, or expected to initiate dialysis within 12 weeks of screening • Renal or other organ transplantation prior to, or expected during, the study, with the exception of corneal transplants **Prohibited medications:** • Use of systemic corticosteroids (including oral budesonide) or	Creatinine Ratio) on spot urine. [Baseline until 156 weeks] • Hematuria level based on blood on urine dipstick [Baseline until 156 weeks] • Changes in serum Gd-IgA1 levels [Baseline until 156 weeks]

Trial Information	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
			immunosuppressive medications (e.g., MMF, azathioprine, cyclophosphamide, hydroxychloroquine) for the treatment of IgAN within 2 months prior to Screening • For glucocorticosteroids (GCS), "Systemic" is defined as oral, rectal or injectable (intravenous or intramuscular) routes of administration, Other routes of administration are allowed, including intra-articular, inhaled, topical, ophthalmic, optic and intranasal • Use of B-cell-directed biologic therapies including belimumab, rituximab, ocrelizumab within 12 months of screening • Use of other biologics (e.g., anti-TNF, abatacept, anti-IL-6) and investigational biologics for the treatment of IgAN within 6 months of screening	
JANUS **NCT04716231** **Barratt. ISN. 2022.**[30]	Phase IIa, Double Blind, Placebo Controlled N=16	Arms: 1) Atacicept 25 mg Q1W SC injection 2) Atacicept 75 mg Q1W SC injection 3) Placebo	**Inclusion Criteria:** • Male and female patients ≥18 years of age with biopsy-confirmed IgAN • Screening uPCR ≥0.75 and ≤6 mg/mg • Stable and optimal dose of ACEI and/or ARB for at least 8 weeks prior to screening.	• Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs), Adverse Event of Special Interest (AESIs), Serious TEAEs, TEAEs Leading to Discontinuation and TEAEs Leading to Death [Baseline up to 96 Weeks]

Trial Information	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
			Exclusion Criteria: • Concomitant significant renal disease other than IgA nephropathy • IgA nephropathy with significant glomerulosclerosis or cortical scarring • Diagnosis of Henoch- Schönlein purpura • Failure to meet estimated glomerular filtration rate (eGFR) and biopsy requirement criteria • Serum IgG below 6 grams per liter (g/L) • Use of cyclophosphamide ever or use of other immunosuppressants or systemic corticosteroids within 4 months • Active infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks • History, or current diagnosis, of active tuberculosis (TB), or untreated latent TB infection • History of or positive HIV and/or positive for hepatitis B or Hepatitis C at screening	
Tarpeyo				
NefIgArd **NCT03643965** **Lafayette. Lancet. 2023.**[10]	Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled N=365	Arms: 1.) Nefecon 16 mg once daily for 9 months 2.) Placebo oral capsule	**Inclusion Criteria:** • Male and female patients ≥18 years of age with biopsy-confirmed IgAN • Stable and maximally tolerated dose of ACEI and/or ARB	•Ratio of Urine Protein to Creatinine Ratio (UPCR) at 9 Months Compared to Baseline •Time-weighted Average of Estimated Glomerular Filtration Rate (eGFR) [Up to 2 years and 1 month]

Trial Information	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
	Duration: 9/5/2018-7/10/2023 Part A: 9-month treatment, 3 month follow up Part B: Additional 12 months follow up. 2 year data		• Screening uPCR ≥0.75 g/g or 24-hr urine protein ≥1.0 g/day **Exclusion Criteria:** •Systemic diseases that may cause mesangial IgA deposition. •Patients who have undergone a kidney transplant. •Patients with acute or chronic infectious disease including hepatitis, tuberculosis, human immunodeficiency virus (HIV), and chronic urinary tract infections. •Patients with liver cirrhosis, as assessed by the Investigator. •Patients with a diagnosis of type 1 or type 2 diabetes mellitus which is poorly controlled. •Patients with history of unstable angina, class III or IV congestive heart failure, and/or clinically significant arrhythmia, as judged by the Investigator; •Patients with unacceptable blood pressure control defined as a blood pressure consistently above national guidelines for proteinuric renal disease, as assessed by the Investigator •Patients with diagnosed malignancy within the past 5 years.	

Trial Information	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
NEFIGAN **NCT01738035** **Fellstrom. Lancet. 2017.**[33]	Multicenter, Randomized, Double-Blind, Placebo Controlled N=150 Duration: 12/2012-09/2015	Arms: 1) Nefecon 8mg/day (2 active + 2 placebo capsules daily) for 9 months 2) Nefecon 16 mg/day (4 active capsules daily) for 9 months 3) Placebo (4 capsules daily) for 9 months	**Inclusion Criteria:** • Male and female patients ≥18 years of age with biopsy-confirmed IgAN • Urine protein creatinine ratio ≥0.5 g/g OR urine protein ≥0.75 g/24hr • Estimated GFR (using the CKD-EPI formula) OR measured GFR ≥50 mL/min per 1.73 m^2 OR ≥45 mL/min per 1.73m^2 for patients on a maximum recommended or maximum tolerated dose of an ACEI and/or ARB • Willing to change antihypertensive medication regimen if applicable Willing and able to give informed consent **Exclusion Criteria:** • Secondary forms of IgA nephropathy as defined by the treating physician (for example, Henoch-Schönlein purpura patients and those with associated alcoholic cirrhosis) • Presence of crescent formation in ≥50% of glomeruli assessed on renal biopsy • Kidney transplanted patients • Severe gastrointestinal disorders • Patients currently treated with systemic immunosuppressive or systemic corticosteroid drugs (excluding topical or nasal steroids) or have been previously	•Mean change from baseline in UPCR at 9 Months •Mean changes from baseline in uPCR, eGFR, 24-h urine protein excretion, UACR, 24-h urine albumin excretion at 12 months

Trial Information	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
			treated for more than one week within the last 24 months. • Patients currently treated chronically (daily dosing) with inhaled corticosteroid drugs or have previously been treated chronically for more than one month within the last 12 months • Patients previously treated with immunosuppressive or systemic corticosteroids for the treatment of IgA nephropathy • Patients with known allergy or intolerance to ACEI, ARB or to any component of the trial drug formulation • Patients with acute or chronic infectious disease incl. hepatitis, HIV positive patients and patients with chronic urinary tract infections • Severe liver disease according to the discretion of the Investigator • Patients with Type 1 or 2 diabetes • Patients with uncontrolled cardiovascular disease as judged by the Investigator • Patients with current malignancy or history of malignancy during the last three years	
Systemic Glucocorticoids				

Trial Information	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
TESTING **NCT01560052** **Lv. JAMA. 2022.**[47]	Randomized, Double-Blind, Placebo-Controlled, Multicenter N=503 Duration: 5/2012-7/2021	Arms: 1) Oral methylprednisolone 0.4 mg/kg per day (maximum, 32 mg/d) for 2 months followed by dose tapering by 4 mg per day each month, or matching placebo, for a total of 6 to 9 months ** Antibiotic prophylaxis for *Pneumocystis jirovecii pneumonia* was administered during the initial 12 weeks of therapy 2) Placebo	**Inclusion:** • Male and female patients ≥18 years of age with biopsy-confirmed IgAN • Proteinuria: ≥1.0 g/day while receiving maximum tolerated dose of RAS blockade • eGFR: 30 to 120 ml/min per 1.73m^2(inclusive) while receiving maximum tolerated RAS blockade **Exclusion:** • Indication for immunosuppressive therapy with corticosteroids • Contraindication to immunosuppressive therapy with corticosteroids •Systemic immunosuppressive therapy in the previous year. •Malignant /uncontrolled hypertension (>160mm systolic or 110mmHg diastolic) •Current unstable kidney function for other reasons	•Progressive kidney failure, which is a composite of a 40% decrease in eGFR, the development of end stage kidney disease defined as a need for maintenance dialysis or kidney transplantation, and death due to kidney disease. [1-6 years] •For reduced dose: Change in proteinuria from baseline at 6 and 12 months Mean change in eGFR at 6 and 12 months [1 year]
STOP-IgAN **NCT00554502** **Rauen. NEJM. 2015.**[50]	Randomized, Open-Label, Multicenter, Controlled N=162 Duration: 2/2008-2/2015	Arms: 1) Supportive care alone 2) Supportive care + immunosuppressive therapy	**Inclusion:** •Male or female patients from 18-70 years with histologically proven primary IgAN with typical mesangioproliferative feature •Proteinuria above 0.75 g/day within 12 weeks prior to or at the first visit in the run-in phase (month -6) and presence of	•Ful clinical remission [By end of 3 year study period] •Decrease in eGFR of ≥15 ml/min from baseline [By end of 3 year study period]

Trial Information	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
			at least one further risk factor for the development of end stage renal disease **Exclusion:** • Any prior immunosuppressive therapy • Variants of primary IgAN or secondary IgAN • Significant liver dysfunction • Contraindication for immunosuppressive therapy Creatinine clearance below 30 ml/min	

ACEi: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, CKD: Chronic Kidney Disease, eGFR: estimated glomerular filtration rate, g: gram, IgAN: Immunoglobulin A Nephropathy, mg/dL: milligrams per deciliter, ml/min per 1.73m^2: milliliter per min per 1.73 squared meters, n: number, N: total number, Q4W: Every 4 weeks, SC: subcutaneous, TEAE: Treatment-emergent adverse event, uPCR: Urinary protein-to-creatinine ratio

Table D3.2. Sibeprenlimab Baseline Characteristics [8,24-26,108,109]

Intervention		Sibeprenlimab						
Trial		VISIONARY		ENVISION				
Arm		Sib 400 mg	Placebo	Sib 2 mg/kg	Sib 4 mg/kg	Sib 8 mg/kg	Pooled Sib	Placebo
N		152	168	38	41	38	117	38
Demographic Characteristics								
Age, Years	Median (Range)	42 (18, 75)	43 (18, 83)	41 (25, 71)	39 (20, 73)	42 (23, 72)	40 (20, 73)	36 (18, 52)
Sex, n (%)	Female	52 (34.2)	68 (40.5)	16 (42.1)	15 (36.6)	12 (31.6)	43 (36.8)	24 (63.2)
	Male	100 (65.8)	100 (59.5)	22 (57.9)	26 (63.4)	26 (68.4)	74 (63.2)	14 (36.8)
Race/Ethnicity, n (%)	American Indian/ Alaska Native	NR	NR	0	0	1 (2.6)	1 (0.9)	0
	Asian	94 (61.8)	95 (56.5)	28 (73.7)	31 (75.6)	28 (73.7)	87 (74.4)	28 (73.7)
	Black/African American	0	1 (0.6)	0	1 (2.4)	0	1 (0.9)	0
	Hispanic/Latino	NR	NR	2 (5.3)	3 (7.3)	2 (5.3)	7 (5.9)	2 (5.3)
	Native Hawaiian/ Pacific Islander	NR	NR	0	0	0	0	0
	White	55 (36.2)	66 (39.3)	9 (23.7)	9 (22)	8 (21.2)	26 (22.2)	10 (26.3)
	Unknown/NR/Other	3 (2)	7 (4.2)	1 (2.6)	0	1 (2.6)	2 (1.7)	0
Region, n (%)	North America	22 (14.5)	21 (12.5)	NR	NR	NR	NR	NR
	South America	11 (7.2)	15 (8.9)	NR	NR	NR	NR	NR
	Europe	30 (19.7)	36 (21.4)	NR	NR	NR	NR	NR
	East Asia	43 (28.3)	48 (28.6)	NR	NR	NR	NR	NR
	South/Southeast Asia	46 (30.3)	48 (28.6)	NR	NR	NR	NR	NR
	Japan	NR	NR	5 (13.2)	5 (12.2)	5 (13.2)	15 (12.8)	4 (10.5)
	Rest of World	NR	NR	33 (86.8)	36 (87.8)	33 (86.8)	102 (87.2)	34 (89.5)
BMI (kg/m^2)	Mean (SD)	28 (6.1)	26.7 (4.9)	27.2 (4.5)	28.1 (6.4)	27.6 (5.8)	27.6 (5.6)	27.4 (6.7)
Blood Pressure, mm HG, Mean	Systolic	124.5 (11.3)	123.1 (11.4)	NR	NR	NR	NR	NR

Intervention		Sibeprenlimab						
Trial		VISIONARY		ENVISION				
Arm		Sib 400 mg	Placebo	Sib 2 mg/kg	Sib 4 mg/kg	Sib 8 mg/kg	Pooled Sib	Placebo
N		152	168	38	41	38	117	38
	Diastolic	77.8 (8.1)	78.7 (8)	NR	NR	NR	NR	NR
History of Hypertension, n (%)		NR	NR	29 (76.3)	31 (75.6)	28 (73.7)	88 (75.2)	24 (63.2)
IgAN Disease Characteristics								
Urinary Protein Excretion (g/day)	Median (Range)	NR	NR	1470 (668-6922)*	1927 (331-8600)*	1900 (764-12435)*	NR	2133.5 (761-8479)*
uPCR-24h (g/g)	Mean (SD)	1.3 (1.7)	1.3 (1.6)	1.5 (0.12)†	1.5(0.12)†	1.4 (0.14)†	1.5 (0.07)†	1.7 (0.17)†
	Median (IQR)	1.2 (0.5, 6.7)	1.3 (0.5, 5.5)	NR	NR	NR	NR	NR
	≤2.0 g/g	123 (80.9)	137 (81.5)	24 (63.2)	26 (63.4)	24 (63.2)	74 (63.2)	25 (65.8)
	>2.0 g/g	29 (19.1)	31 (18.5)	9 (23.7)	10 (24.4)	9 (23.7)	28 (23.9)	9 (23.7)
	Data Missing	NR	NR	5 (13.2)	5 (12.2)	5 (13.2)	15 (12.8)	4 (10.5)
Proteinuria, g/24 hr	Median (IQR)	NR	NR	1.5 (0.67, 6.9)	1.9 (0.33, 8.6)	1.9 (0.76, 12.4)	1.8 (0.33, 12.4)	2.1 (0.76-8.5)
eGFR (mL/min/1.73m^2)	Mean (SD)	63.5 (24.4)	63.4 (25.3)	NR	NR	NR	NR	NR
	Median (Range)	57.5 (25, 131)	60 (27, 129)	58 (35, 154)	64 (35, 133)	56 (34, 109)	58 (34, 154)	68.5 (33, 116)
	≥30 to <45 ml/min	37 (24.3)	43 (25.6)	NR	NR	NR	NR	NR
	≥45 ml/min	115 (75.7)	125 (74.4)	NR	NR	NR	NR	NR
Median Time from Biopsy to Randomization, Years (range)		1.3 (0.1, 23.7)	1.9 (0, 34.0)	781 (2, 5657)‡	288 (12, 6263)‡	364 (10, 5776)‡	490 (NR)‡	933 (10, 6431)‡
Hematuria, n (%)	Negative	33 (21.7)	49 (29.2)	NR	NR	NR	NR	NR
	Positive	119 (78.3)	119 (70.8)	NR	NR	NR	NR	NR
Baseline Treatment Use, n (%)								
ACEi and/or ARB		149 (98)	163 (97)	NR	NR	NR	NR	NR
ACEi or ARB		NR	NR	37 (97.4)	40 (97.6)	37 (97.4)	114 (97.4)	38 (100)
SGLT2i		56 (36.8)	72 (42.9)	3 (7.9)	2 (4.9)	1 (2.6)	6 (5.1)	3 (7.9)

Intervention	Sibeprenlimab						
Trial	VISIONARY		ENVISION				
Arm	Sib 400 mg	Placebo	Sib 2 mg/kg	Sib 4 mg/kg	Sib 8 mg/kg	Pooled Sib	Placebo
N	152	168	38	41	38	117	38
Previous Use of Systemic Glucocorticoids or Immunosuppressants	6 (3.9)	6 (3.6)	14 (36.8)	7 (17.1)	8 (21.1)	29 (24.8)	7 (18.4)

ACEi: Angiotensin-Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Blockers, n: number, N: total number, NA: not applicable, NR: not reported, eGFR: Estimated Glomerular Filtration Rate, SD: standard deviation, SGLT2i: Sodium-Glucose Cotransporter 2 inhibitor, Sib: Sibeprenlimab, uPCR: Urine Protein-To-Creatinine Ratio

*mg/day

†Geometric mean (geometric standard error)

‡Days

Table D3.3. ORIGIN 3 & ORIGIN Baseline Characteristics [9,29]

Intervention		Atacicept						
Trial		ORIGIN 3		ORIGIN				
Arm		Ata 150 mg	Placebo	Ata 25 mg	Ata 75 mg	Ata 150 mg	Combined[§]	Placebo
N		106	97	16	33	33	66	34
Demographic Characteristics								
Age, Years	Mean (SD)	40.1 (11.1)	40.9 (11.6)	40 (15)	41 (13)	38 (11)	40 (12)	39 (13)
	<40	48 (45.3)	49 (50.5)	NR	NR	NR	NR	NR
	≥40	58 (54.7)	48 (49.5)	NR	NR	NR	NR	NR
Sex, n (%)	Female	49 (46.2)	39 (40.2)	7 (44)	14 (42)	11 (33)	25 (38)	15 (44)
	Male	57 (53.8)	58 (59.8)	9 (56)	19 (58)	22 (67)	41 (62)	19 (56)
Race/Ethnicity, n (%)	American Indian/ Alaska Native	0	0	0	0	0	0	0
	Asian	59 (55.7)	52 (53.6)	7 (44)	20 (61)	16 (48)	36 (55)	8 (24)
	Black/African American	0	1 (1)	0	0	0	0	0
	Hispanic/Latino	14 (32)	6 (6.2)	1 (6)	2 (6)	1 (3)	3 (5)	0
	Native Hawaiian/ Pacific Islander	0	1 (1)	0	1 (3)	0	1 (2)	0

Intervention		Atacicept						
Trial		ORIGIN 3		ORIGIN				
Arm		Ata 150 mg	Placebo	Ata 25 mg	Ata 75 mg	Ata 150 mg	Combined[§]	Placebo
N		106	97	16	33	33	66	34
	White	46 (43.4)	42 (43.3)	7 (44)	12 (36)	17 (52)	29 (44)	26 (76)
	Not Hispanic or Latino	92 (86.8)	91 (93.8)	NR	NR	NR	NR	NR
	Unknown/NR/Other	1 (0.9)	1 (1)	2 (12.5)	0	0	0	0
Blood Pressure, mm Hg, Median (IQR)	Systolic	NR	NR	127 (8)	127 (13)	127 (12)	127 (13)	127 (13)
	Diastolic	NR	NR	81 (8)	80 (9)	80 (9)	80 (9)	77 (8)
IgAN Disease Characteristics								
Urinary Protein Excretion (g/day)	Median (Range)	NR	NR	2.3 (1.0)	2.1 (1.0)	2.3 (1.2)	2.2 (1.1)	2.0 (0.9)
uPCR-24h (g/g)	Mean (SD)	1.7 (0.9)	1.8 (1.2)	1.6 (0.8)	1.7 (0.9)	1.7 (1.0)	1.7 (0.9)	1.6 (0.8)
	Median (IQR)	NR	NR	1.4 (1.1, 1.9)	1.4 (1.2, 1.9)	1.4 (1.0, 2.2)	1.4 (1.1, 2.2)	1.5 (0.9, 2.1)
eGFR (mL/min/1.73m^2)	Mean (SD)	65.3 (27.7)	64.9 (29)	71 (29)	64 (25)	56 (23)	60 (24)	66 (32)
	Median (Range)	NR	NR	65 (51, 90)[*]	63 (43, 79)[*]	49 (41, 63)[*]	53 (41, 72)[*]	57 (42, 87)[*]
	<30 ml/min	NR	NR	0 (0)	1 (3)	1 (3)	2 (3)	2 (6)
	≥30 to <45 ml/min	NR	NR	3 (19)	8 (24)	11 (33)	19 (29)	8 (24)
	≥45 ml/min	NR	NR	13 (81)	24 (73)	21 (64)	45 (68)	24 (71)
uACR, g/g	Mean (SD)	1.3 (0.7)	1.3 (0.9)	1.2 (0.7)	1.3 (0.7)	1.4 (0.8)	1.3 (0.8)	1.2 (0.7)
Proteinuria, g/day	Mean (SD)	2.2 (1)	2.3 (1.4)	NR	NR	NR	NR	NR
Median Time from Biopsy to Randomization, Years (Range)		NR	NR	1.7 (1.6)[†]	3.4 (2.8)[†]	3.3 (3.4)[†]	3.4 (3.1)[†]	2.1 (2.4)[†]
Time Since Diagnosis (Years), Median (Q1, Q3)		2.5 (2.6)	2.5 (2.4)	NR	NR	NR	NR	NR
Hematuria, n (%)	Negative/Trace	42 (39.6)	39 (40.2)	NR	NR	NR	NR	NR
	1+ or Higher	21 (19.8)	16 (16.5)	NR	NR	NR	NR	NR
	2+	25 (23.6)	20 (20.6)	NR	NR	NR	NR	NR
	3+	18 (17)	22 (22.7)	NR	NR	NR	NR	NR
Baseline Treatment Use, n (%)								
ACEi and ARB		NR	NR	1 (6)[‡]	3 (9)[‡]	3 (9)[‡]	6 (9)[‡]	2 (6)[‡]

Intervention		Atacicept						
Trial		ORIGIN 3		ORIGIN				
Arm		Ata 150 mg	Placebo	Ata 25 mg	Ata 75 mg	Ata 150 mg	Combined§	Placebo
N		106	97	16	33	33	66	34
ACEi Alone		NR	NR	10 (63)	6 (18)	6 (18)	12 (18)	11 (32)
ARB Alone		NR	NR	4 (25)	21 (64)	23 (70)	44 (67)	19 (56)
RASi Use		105 (99.1)	97 (100)	NR	NR	NR	NR	NR
SGLT2i		59 (55.7)	49 (50.5)	3 (19)	3 (9)	4 (12)	7 (11)	6 (18)
Immunoglobulin Characteristics								
Gd-IgA1, ug/L	Mean (SD)	5248.2 (4192.5)	4671.8 (2411.7)	6292 (4572)	5813 (3573)	5646 (2697)	5731 (3149)	6340 (3697)
IgA, mg/dL	Mean (SD)	336.7 (119.1)	332.5 (109.8)	315 (143)	313 (131)	320 (100)	317 (115)	337 (154)
IgG, mg/dL	Mean (SD)	1165.9 (278.7)	1150.1 (277)	1018 (217)	1159 (289)	1059 (206)	1109 (254)	1153 (305)
IgM, mg/dL	Mean (SD)	111.8 (57.1)	99.1 (54.8)	98 (44)	121 (100)	94 (56)	107 (82)	102 (50)

ACEi: Angiotensin-Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Blockers, Ata: Atacicept, eGFR: estimated glomerular filtration rate, n: number, N: total number, mL/min/1.73m^2: milliliter per minute per 1.73 meters squared, NA: not applicable, NR: not reported, SD: Standard Deviation, SGLT2i: Sodium-Glucose Cotransporter 2 inhibitor, UARC: Urine Albumin-Creatinine Ratio, UPCR: Urine Protein-To-Creatinine Ratio

*Median (IQR)

†Median time from biopsy to screening, years (range)

‡Included participants using a stable regimen of ACEi þ ARB, ACEi þ mineralocorticoid receptor antagonist (MRA), or ARB þ MRAc

§Combined atacicept dose of 75mg and 150mg

Table D3.4. ORIGIN OLE & JANUS Baseline Characteristics[30,31]

Intervention		Atacicept			
Trial		ORIGIN OLE	JANUS		
Arm		Ata 150 mg	Ata 25 mg	Ata 75 mg	Placebo
N		113	6	5	5
Demographic Characteristics					
Age, Years	Mean (SD)	NR	41 (16.9)	43 (8.9)	46 (3.1)
	Median (range)	37 (18-67)	NR	NR	NR
	<40	NR	NR	NR	NR
	≥40	NR	NR	NR	NR
Sex, n (%)	Female	46 (41)	5 (83)	2 (40)	1 (20)
	Male	67 (59)	1 (17)	3 (60)	4 (80)
Race/Ethnicity, n (%)	American Indian/ Alaska Native	0	0	0	0
	Asian	51 (45)	1 (17)	1 (20)	1 (20)
	Black/African American	0	0	0	0
	Hispanic/Latino	4 (4)	1 (17)	3 (60)	0
	Native Hawaiian/ Pacific Islander	1 (1)	0	0	0
	White	59 (52)	5 (83)	2 (40)	4 (80)
	Not Hispanic or Latino	108 (96)	NR	NR	NR
	Unknown/NR/Other	2 (2)	0	0	2 (40)
History of Tonsillectomy, n (%)		NR	0	2 (40)	0
Blood Pressure, mm Hg, median (IQR)	Systolic	127 (14)	NR	NR	NR
	Diastolic	80 (10)	NR	NR	NR
IgAN Disease Characteristics					
Urinary Protein Excretion (g/day)	Median (Range)	NR	2.1 (1.9, 2.9)[*]	1.7 (1.6, 2.3)[*]	3.2 (2.3, 3.3)[*]
uPCR-24h (g/g)	Mean (SD)	1.8 (1.3)	NR	NR	NR
	Median (IQR)	1.4 (1, 2.2)	1.8 (0.8, 2.2)[†]	1.4 (1.3, 1.7)[†]	1.6 (1.5, 1.6)[†]
eGFR (mL/min/1.73m^2)	Mean (SD)	62 (28)	NR	NR	NR
	Median (Range)	56 (41, 73)[*]	57 (53, 85)[‡]	55 (52, 92)[‡]	49 (48, 54)[‡]
	<30 ml/min	6 (5)	NR	NR	NR
	≥30 to <45 ml/min	31 (27)	NR	NR	NR
	≥45 ml/min	75 (66)	NR	NR	NR
uACR, g/g	Mean (SD)	1.3 (0.9)	NR	NR	NR

Intervention		Atacicept			
Trial		ORIGIN OLE	JANUS		
Arm		Ata 150 mg	Ata 25 mg	Ata 75 mg	Placebo
N		113	6	5	5
Median Time from Biopsy to Randomization, Years (Range)		NR	1.8 (0.12, 2.96) §	0.97 (0.33, 2,52) §	0.5 (0.31, 1.05) §
Time Since Diagnosis (Years), Median (Q1, Q3)		NR	2.17 (0.12, 2.99)	2.55 (2.52, 4.62)	1.26 (1.05, 12.42)
Hematuria, n (%)	Negative/Trace	49 (43)	NR	NR	NR
	1+ or Higher	63 (56)	NR	NR	NR
	Missing	1 (1)	NR	NR	NR
Baseline Treatment Use, n (%)					
ACEi and/or ARB		NR	6 (100)	5 (100)	5 (100)
ACEi and ARB		9 (8)	NR	NR	NR
ACEi Alone		31 (27)	3 (50)	1 (20)	3 (60)
ARB Alone		66 (58)	3 (50)	4 (80)	2 (40)
Diuretics		NR	3 (50)	2 (40)	0
SGLT2i		15 (12)	NR	NR	NR
Previous use of Systemic Glucocorticoids or immunosuppressants		NR	2 (33)	1 (20)	1 (20)
Immunoglobulin Characteristics					
Gd-IgA1, ug/L	Mean (SD)	5785 (3221)	6258 (3211)#	6052 (2773) #	7690 (3642) #
IgA, mg/dL	Mean (SD)	311 (115)	3.6 (1.2) ¤	3.02 (0.85) ¤	3.97 (1.7) ¤
IgG, mg/dL	Mean (SD)	1099 (247)	9.5 (1.8) ¤	10.9 (1.10) ¤	10.51 (2.6) ¤
IgM, mg/dL	Mean (SD)	104 (69)	0.9 (0.6) ¤	1.09 (0.3) ¤	1.3 (0.5) ¤
Complement (mg/l)					
Serum C3	Median (Q1, Q3)	NR	1625 (1410, 1700)	1260 (1230, 1300)	1330 (1180, 1520)
Serum C4	Median (Q1, Q3)	NR	332 (305, 370)	379 (233, 408)	287 (282, 310)

ACEi: Angiotensin-Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Blockers, Ata: Atacicept, eGFR: Estimated Glomerular Filtration Rate, mL/min/1.73m^2: milliliter per minute per 1.73 meters squared, n: number, N: Total number, NA: Not Applicable, NR: Not Reported SD: Standard Deviation, SGLT2: Sodium-Glucose Cotransporter 2 inhibitors, UARC: Urine Albumin-Creatinine Ratio, UPCR: Urine Protein-To-Creatinine Ratio

*Total protein by 24-hr urine collection (g/d), median (Q1, Q3)

†uPCR by 24-h urine collection (mg/mg), median (Q1, Q3)

‡eGFR by CKD-EPI (ml/min per 1.73m2), median (Q1, Q3)
§Time since most recent kidney biopsy (years), median (Q1, Q3)
#ng/ml
¤g/l

Table D3.5. Nefigard Part B & OLE Baseline Characteristics [10,31,105]

Intervention		**Nefecon**			
Trial		**NefIgArd (Lafayette 2023)**		**NefIgArd OLE**	
Arm		**Nefecon 16 mg**	**Placebo**	**2nd Course of Nefecon**	**1st Course of Nefecon**
N		**182**	**182**	**45**	**74**
Demographic Characteristics					
Age, Years	**Mean (SD)**	43.8 (10.78)	41.6 (10.65)	NR	NR
	Median (Range)	43 (36, 50)	42 (34, 49)	46 (29, 70)	47 (25, 76)
	<45 Years Old, n (%)	98 (54)	104 (57)	NR	NR
Sex, n (%)	**Female**	65 (36)	59 (32)	6 (13.3)	19 (25.7)
	Male	117 (64)	123 (68)	39 (86.7)	55 (74.3)
Race/Ethnicity, n (%)	**American Indian/ Alaska Native**	0	0	0	0
	Asian	43 (24)	40 (22)	9 (20)	7 (9.5)
	Black/African American	0	0	0	0
	Hispanic/Latino	NR	NR	NR	NR
	Native Hawaiian/ Pacific Islander	0	0	0	0
	White	138 (76)	137 (75)	36 (80)	64 (86.5)
	Unknown/NR/Other	1 (1)	5 (3)	0	3 (4.1)
Weight (kg)		NR	NR	NR	NR
Diabetic at Baseline, n (%)		16 (9)	8 (4)	NR	NR
Prediabetic at Baseline, n (%)		71 (39)	50 (27)	NR	NR
Blood Pressure, mm Hg, Median (IQR)	**Systolic**	126 (121 - 132)	124 (117 - 130)	NR	NR
	Diastolic	79 (76 - 84)	79 (74 - 84)	NR	NR

Intervention		Nefecon			
Trial		NefIgArd (Lafayette 2023)		NefIgArd OLE	
Arm		Nefecon 16 mg	Placebo	2nd Course of Nefecon	1st Course of Nefecon
N		182	182	45	74
IgAN Disease Characteristics					
uPCR g/g	Mean (SD)	1.48 (0.85)	1.48 (1.15)	1.25 (0.86, 1.8)‡	1.3 (1.0, 1.8) ‡
	Median (IQR)	1.28 (0.90, 1.76)	1.25 (0.88, 1.74)	NR	NR
Proteinuria, g/24 hr	Mean (SD)	2.71 (1.73)	2.71 (2.20)	NR	NR
	Median (IQR)	2.29 (1.61–3.14)	2.17 (1.53–3.39)	NR	NR
	<2.0 g/24h, n (%)	78 (43)	79 (43)	NR	NR
	≥2.0 g/24h, n (%)	104 (57)	103 (57)	NR	NR
eGFR (mL/min/1.73m^2)	Mean (SD)	NR	NR	51.0 (42, 62)‡	49.9 (39.9, 64.9) ‡
	Median (Range)	56.14 (45.50–70.97)	55.11 (45.96–67.74)	NR	NR
	<60 mL/min	109 (60)	109 (60)	NR	NR
	≥60 mL/min	73 (40)	73 (40)	NR	NR
uACR, g/g	Mean (SD)	1.16 (0.68)	1.16 (0.84)	NR	NR
	Median (IQR)	0.99 (0.68, 1.40)	0.98 (0.66, 1.42)	NR	NR
Total Urine Albumin, g/24h	Mean (SD)	2.12 (1.34)	2.11 (1.58)	NR	NR
	Median (IQR)	1.77 (1.24–2.49)	1.70 (1.12–2.54)	NR	NR
Microhematuria at Randomization, n (%)	Yes	123 (68)	127 (70)	NR	NR
	No	59 (32)	55 (30)	NR	NR
Median Time from Biopsy to Randomization, Years (Range)		2.4 (0.6, 6.9)*	2.6 (0.6, 6.5) *	NR	NR
Baseline Treatment Use, n (%)					
ACEi and ARB		8 (4)	8 (4)	NR	NR
ACEi Alone		81 (45)	69 (38)	NR	NR
ARB Alone		90 (49)	102 (56)	NR	NR
Previous Use of Systemic Glucocorticoids or Immunosuppressants		15 (8)†	19 (10) †	NR	NR

ACEi: Angiotensin-Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Blockers, eGFR: Estimated Glomerular Filtration Rate, IQR: Interquartile Range, mL/min/1.73m^2: milliliter per minute per 1.73 meters squared, n: number, N: total number, NA: not applicable, NR: not reported, SD: standard deviation, UARC: Urine Albumin-Creatinine Ratio, uPCR: Urine Protein-To-Creatinine Ratio

*At time of informed consent

†In the 12 months before randomization

‡ Mean (IQR)

Table D3.6. Nefigard Part A, China Cohort, NEFIGAN Baseline Characteristics[33,34,45]

Intervention		TR- Budesonide						
Trial		NeflgArd - Part A FAS		NeflgArd - China Cohort		NEFIGAN		
Arm		Nefecon 16 mg	Placebo	Nefecon 16 mg	Placebo	Nefecon 8 mg	Nefecon 16 mg	Placebo
N		97	102	32	30	51	48	50
Demographic Characteristics								
Age, Years	Mean (SD)	NR	NR	NR	NR	40.6 (13.0)	37.5 (11.9)	38.9 (12.0)
	Median (Range)	44 (25, 69)	43 (23, 73)	38 (31, 42)	39 (31, 47)	NR	NR	NR
	<45 Years Old, n (%)	52 (53.6)	56 (54.9)	27 (84.4)	20 (66.7)	NR	NR	NR
Sex, n (%)	Female	29 (29.9)	35 (34.3)	15 (46.9)	14 (46.7)	14 (27)	15 (31)	15 (30)
	Male	68 (70.1)	67 (65.7)	17 (53.1)	16 (53.3)	37 (73)	33 (69)	35 (70)
Race/Ethnicity, n (%)	Asian	11 (11.3)	13 (12.7)	32 (100)	30 (100)	0	1 (2)	1 (2)
	Hispanic/Latino	9 (9.3)	7 (6.9)	NR	NR	11 (22)	7 (15)	3 (6)
	White	85 (87.6)	86 (84.3)	NR	NR	49 (96)	47 (98)	48 (96)
	Not Hispanic or Latino	88 (90.7)	94 (92.2)	NR	NR	40 (78.4)	41 (85.4)	47 (94)
	Unknown/NR/Other	1 (1.0)	3 (2.9)	NR	NR	2 (4)	0 (0)	1 (2)
BMI (kg/m^2)	Mean (SD)	29 (26, 32)	28 (24, 31)	25 (23, 26)‡	24 (21, 27) ‡	26.5 (4.4)	27.8 (5.2)	27.5 (5.4)
Weight (kg)		NR	NR	NR	NR	80.9 (14.5)	86.7 (16.9)	85.2 (18.9)
Diabetic at Baseline, n (%)		9 (9.3)	1 (1.0)	3 (9.4)	0 (0)	NR	NR	NR
Prediabetic at Baseline, n (%)		44 (45.4)	30 (29.4)	10 (31.3)	10 (33.3)	NR	NR	NR
Neither Diabetic nor Prediabetic, n (%)		NR	NR	19 (59.4)	20 (66.7)	NR	NR	NR

Intervention		TR- Budesonide						
Trial		NefIgArd - Part A FAS		NefIgArd - China Cohort		NEFIGAN		
Arm		Nefecon 16 mg	Placebo	Nefecon 16 mg	Placebo	Nefecon 8 mg	Nefecon 16 mg	Placebo
N		97	102	32	30	51	48	50
Blood Pressure, mm Hg, median (IQR)	Systolic	128 (122, 134)	124 (117, 131)	120 (116, 125)	120 (111, 125)	127.7 (13.6)[#]	126.7 (11.6)[#]	128.1 (11.9)[#]
	Diastolic	79 (76, 84)	78 (73, 83)	81 (73, 85)	81 (77, 86)	80.3 (9.7)	78.1 (9.6)	80.2 (10.1)
IgAN Disease Characteristics								
Urinary Protein Excretion (g/day)	Median (Range)	NR	NR	NR	NR	1.1 (0.9, 1.8)[¤]	1.3 (0.9, 2.1)[¤]	1.2 (1.0, 3.2)[¤]
uPCR g/g	Median (IQR)	1.27 (0.95, 1.75)	1.21 (0.87, 1.79)	1.38 (0.84, 1.94)	1.18 (0.92, 1.55)	0.8 (0.5, 1.2)	0.8 (0.5, 1.3)	0.8 (0.5, 1.6)
Proteinuria, g/24 hr	Median (IQR)	2.33 (1.71, 3.25)	2.25 (1.51, 3.57)	1.98 (1.49, 2.77)	1.62 (1.3, 2.43)	NR	NR	NR
	<2.0 g/24h, n (%)	39 (40.2)	43 (42.2)	17 (53.1)	17 (56.7)	NR	NR	NR
	≥2.0 g/24h, n (%)	36 (37.1)[*]	31 (30.4)[*]	15 (46.9)	13 (43.3)	NR	NR	NR
	≥3.0 g/24h, n (%)	22 (22.7)	28 (27.5)	NR	NR	NR	NR	NR
eGFR (mL/min/1.73m^2)	Mean (SD)	NR	NR	NR	NR	74.1 (25.8)	83.8 (25.9)	76.5 (23.2)
	Median (Range)	54.9 (46.4, 68.9)	55.5 (45.5, 67.7)	65.1 (39.6, 78.5)	61.5 (48.4, 77)	NR	NR	NR
	<60 mL/min	63 (64.9)	61 (59.8)	14 (43.8)	13 (43.3)	NR	NR	NR
	≥60 mL/min	NR	NR	18 (56.3)	17 (56.7)	NR	NR	NR
uACR, g/g	Median (IQR)	0.98 (0.75, 1.35)	0.98 (0.66, 1.55)	1.11 (0.66, 1.6)	0.9 (0.66, 1.22)	0.7 (0.5, 1.0)	0.7 (0.4, 1.2)	0.7 (0.4, 1.3)
Total Urine Albumin, g/24h	Median (IQR)	NR	NR	NR	NR	1.0 (0.7, 1.6)	1.1 (0.8, 1.8)	1.1 (0.8, 2.2)
Microhematuria at Randomization, n (%)	Yes	60 (61.9)	70 (68.6)	25 (78.1)	26 (86.7)	32 (63)	42 (88)	40 (80)
	No	NR	NR	7 (21.9)	4 (13.3)	NR	NR	NR
Median Time from Biopsy to Randomization, Years (Range)		2.0 (0.8, 6.1)[†]	2.8 (0.5, 7.1)[†]	1.8 (0.4, 3.8)[§]	2.1 (0.7, 4.1)[§]	NR	NR	NR

Intervention	TR- Budesonide						
Trial	**NefIgArd - Part A FAS**		**NefIgArd - China Cohort**		**NEFIGAN**		
Arm	**Nefecon 16 mg**	**Placebo**	**Nefecon 16 mg**	**Placebo**	**Nefecon 8 mg**	**Nefecon 16 mg**	**Placebo**
N	**97**	**102**	**32**	**30**	**51**	**48**	**50**
Time Since Diagnosis (Years), median (Q1, Q3)	NR	NR	NR	NR	1972 (623, 4188)**	1219 (498, 2573) **	1101 (294, 2870) **
Baseline Treatment Use, n (%)							
ACEi and ARB	3 (3.1)	7 (6.9)	2 (6.3)	1 (3.3)	12 (24)	8 (17)	13 (26)
ACEi Alone	54 (55.7)	44 (43.1)	3 (9.4)	3 (10.0)	25 (49)	26 (52)	21 (42)
ARB Alone	38 (39.2)	48 (47.1)	26 (81.3)	25 (83.3)	14 (28)	14 (29)	16 (32)
Missing/Not Recorded	NR	NR	1 (3.1)	1 (3.3)	NR	NR	NR
Previous Use of Systemic Glucocorticoids or immunosuppressants	9 (9.3)	7 (6.9)	2 (6.3)	0 (0)	14 (28)	6 (13)	7 (14)

ACEi: Angiotensin-Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Blockers, eGFR: Estimated Glomerular Filtration Rate, IQR: Interquartile Range, n: number, N: total number, NA: not applicable, NR: not reported, SD: standard deviation, SGLT2: Sodium-Glucose Cotransporter 2, UARC: Urine Albumin-Creatinine Ratio, uPCR: Urine Protein-To-Creatinine Ratio

*>2 to <3.5 g/24 h

†Time from diagnosis to start of treatment

‡Median (IQR)

§Median (IQR), time from biopsy to informed consent

#Mean (SD)

¤24-hr protein excretion

**Time since diagnosis (days)

Table D3.7. Systemic Glucocorticoids Baseline Characteristics[47,48,50]

Comparator		Oral Methylprednisolone				STOP-IgAN		
Trial		TESTING: Overall Cohort		TESTING: Reduced Dose				
Arm		Methylpredni-solone	Placebo	Methylpredni-solone	Placebo	Run-In Phase[†]	Supportive Care	Supportive Care + Immunosupp-resion
N		257	246	121	120	337	80	82
Demographic Characteristics								
Age, Years	Mean (SD)	NR	NR	36.7 (10.74)	36.6 (10.81)	43.7 (12.8)	45.8 (12.5)	42.8 (13.1)
	Median (IQR)	35.6 (29.4, 46.3)	36.6 (29.0, 45.9)	NR	NR	NR	NR	NR
Sex, n (%)	Male	155 (60)	150 (61)	69 (57)	70 (58.3)	NR	NR	NR
	Female	102 (40)	96 (39)	52 (43)	50 (41.7)	*81* (24)	*15* (19)	*20* (24)
Race/Ethnicity, n (%)	White	13 (5)	12 (5)	6 (6.6)	9 (7.5)	NR	NR	NR
	Chinese	195 (76)	184 (75)	65 (53.7)	63 (52.5)	NR	NR	NR
	Japanese	0	1 (0.4)	0 (0)	1 (0.8)	NR	NR	NR
	Mixed	0	1 (0.4)	0 (0)	1 (0.8)	NR	NR	NR
	Other Eastern Asian	1 (0.4)	0	1 (0.8)	0 (0)	NR	NR	NR
	South Asian	30 (12)	33 (13)	30 924.8)	33 (27.5)	NR	NR	NR
	Southeast Asian	18 (7)	15 (6)	17 (14)	13 (10.8)	NR	NR	NR
Current Smoker, %		19 (7)	23 (9)	9 (7.4)	12 (10)	18	16	17
BMI	Mean (SD)	NR	NR	25.4 (4.8)	26.1 (5)	27.9 (5.3)	28.6 (5.3)	27.0 (5.0)
	Median (IQR)	24.2 (21.6, 26.7)	24.7 (22.0, 28.0)	NR	NR	NR	NR	NR
IgAN Disease Characteristics								
Serum Creatinine, mg/dl	Mean (SD)	NR	NR	NR	NR	1.5 (0.6)	1.6 (0.6)	1.6 (0.7)
eGFR, ml/min/1.73m2	Mean (SD)	56.1 (43.2, 75)[*]	59 (42, 77.6)[*]	63.4 (22.1)	66.6 (24.9)	61.5 (27.3)	57.4 (24.9)	61.1 (29.0)
Urine Protein, g/d	Median (IQR)	1.99 (1.4, 3.1)	1.93 (1.4, 2.9)	NR	NR	2.2 (1.8)	1.6 (0.7)	1.8 (0.8)

Comparator		Oral Methylprednisolone				STOP-IgAN		
Trial		TESTING: Overall Cohort		TESTING: Reduced Dose				
Arm		Methylpredni-solone	Placebo	Methylpredni-solone	Placebo	Run-In Phase[†]	Supportive Care	Supportive Care + Immunosupp-resion
N		257	246	121	120	337	80	82
Creatinine Clearance, ml/min	Mean (SD)	NR	NR	NR	NR	76.0 (34.7)	76.2 (31.0)	76.3 (36.4)
Proteinuria, g/24h	Mean (SD)	NR	NR	2.38 (1.41)	2.58 (2.09)	NR	NR	NR
Protein-to-Creatinine Ratio	Mean (SD)	NR	NR	NR	NR	1.4 (1.4)	1.0 (0.5)	1.1 (0.6)
Cholesterol, mg/dl	Mean (SD)	NR	NR	NR	NR	210.1 (48.3)	191.6 (40.7)	193.6 (45.7)
Blood Pressure, mm Hg, mean (SD)	Systolic	123.8 (115, 132.5) [*]	125 (116, 131) [*]	NR	NR	131 (14)	127 (8.5)	124 (9.7)
	Diastolic	80 (73.5, 85) [*]	80 (74, 86) [*]	NR	NR	81 (9.9)	78 (7)	77 (7)
Time Since Kidney Biopsy, Months	Median (IQR)	5 (4, 11)	5 (3, 14)	5 (3, 18)	6 (4, 27)	NR	NR	NR
Baseline Treatment Use, n (%)								
Antihypertensive Drugs, No./Patient	Mean (SD)	NR	NR	NR	NR	2.3 (1.4)	3.0 (1.6)	2.8 (1.3)
RAS-Blocking Agents, %	RAS-Blocking Agents	NR	NR	NR	NR	321 (95)	77 (96)	82 (100)
	ACEi without ARB	140 (54.5)	128 (52)	NR	NR	172 (51)	27 (34)	40 (49)
	ARB without ACEi	119 (46.3)	120 (48.8)	NR	NR	64 (19)	24 (30)	12 (15)
	ACEi + ARB	NR	NR	NR	NR	84 (25)	26 (32)	30 (36)
	Max Daily ACEi Dose	NR	NR	NR	NR	108 (32)	30 (37)	39 (48)
	Max Daily ARB Dose	NR	NR	NR	NR	61 (18)	26 (33)	14 (17)
	Max ACEi + ARB Dose	NR	NR	NR	NR	47 (14)	5 (6)	5 (6)
Dose of ACE Inhibitor or ARB	No ACE or ARB Received	0	1 (0.4)	NR	NR	NR	NR	NR

Comparator		Oral Methylprednisolone				STOP-IgAN		
Trial		TESTING: Overall Cohort		TESTING: Reduced Dose				
Arm		Methylpredni-solone	Placebo	Methylpredni-solone	Placebo	Run-In Phase†	Supportive Care	Supportive Care + Immunosupp-resion
N		257	246	121	120	337	80	82
	<50% of Maximum Labeled Dose	30 (11.7)	35 (14.2)	NR	NR	NR	NR	NR
	≥50% of Maximum Labeled Dose	222 (86.4)	201 (81.7)	NR	NR	NR	NR	NR
	Received but Dose Unknown	5 (1.9)	9 (3.7)	NR	NR	NR	NR	NR
Aldosterone Antagonist Therapy, %		NR	NR	NR	NR	1	0	4
Statin Therapy, %		NR	NR	NR	NR	57	73	81
Hypertension, n (%)		128 (50)	113 (46)	57 (47.1)	61 (50.8)	NR	NR	NR
Macrohematuria, n (%)		42 (16)	38 (15)	15 (12.4)	14 (11.7)	NR	NR	NR
Previous Corticosteroids, n (%)		18 (7)	10 (4)	13 (10.7)	7 (5.8)	NR	NR	NR
Previous other Immunosuppressant, n (%)		17 (7)	12 (5)	9 (7.4)	6 (5)	NR	NR	NR
Diabetes, n (%)		7 (3)	10 (4)	6 (5)	7 (5.8)	NR	NR	NR
Family History of IgA Nephropathy, n (%)		3 (1)	9 (4)	1 (0.80	4 (3.3)	NR	NR	NR
Tonsillectomy, n (%)		2 (0.8)	1 (0.4)	1 (0.8)	0 (0)	NR	NR	NR
Stroke, n (%)		NR	NR	1 (0.8)	1 (0.8)	NR	NR	NR
Coronary Heart Disease, n (%)		NR	NR	2 (1.7)	0 (0)	NR	NR	NR

ACEi: Angiotensin-Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Blockers, CI: Confidence Interval, eGFR: Estimated Glomerular Filtration Rate, n: number, N: total number, NA: not applicable, NR: not reported SD: standard deviation, SGLT2: Sodium-Glucose Cotransporter 2, RAS: Renin-angiotensin system, uPCR: Urine Protein-To-Creatinine Ratio

*Median (IQR)

†This phase includes patients receiving intensive supportive care. After this phase, only the patients who were still considered to be at high risk were randomly assigned to continue supportive care alone or to receive supportive care with the addition of immunosuppressive therapy.

Table D3.7. Note: Data italicized was calculated

Table D3.8. Sibeprenlimab Key Efficacy[8,24,109]

Intervention			Sibeprenlimab					
Trial			VISIONARY		ENVISION*			
Arm			Sib 400 mg	Placebo	Sib 2 mg/kg	Sib 4 mg/kg	Sib 8 mg/kg	Placebo
N			152	168	38	41	38	38
24-Hour Urinary Protein to Creatinine Ratio (uPCR)								
Mean 24-HR uPCR g/g	Baseline	Mean (SD)	1.3 (1.7)	1.3 (1.6)	1.46 (0.12)	1.53 (0.12)	1.44 (0.14)	1.68 (0.17)
	Month 9	CFB, LS Mean (SE)	NR	NR	-0.7 (0.2)	-0.85 (0.1)	-0.99 (0.1)	-0.17 (0.2)
		CFB, % (SD)	-50.2 (44.0, 55.6) ‡	2.1 (-13.8, 8.5) ‡	-49.6 (7.7)	-56.7 (6.2)	-62.8 (5.5)	-12.7 (13.4)
		Difference vs. Placebo, % (96.5% CI); p-Value	51.2 (42.9, 58.2); <0.0001		NR	NR	NR	NR
		Ratio of Geometric LS Mean (96%CI)	0.49 (0.44, 0.56)	1.02 (0.92, 1.14)	NR	NR	NR	NR
		Ratio of v. Placebo (96.5% CI); p-Value	0.49 (0.42, 0.52); <0.0001		NR	NR	NR	NR
	Month 12	CFB, LS Mean (SE)	NR	NR	-0.64 (0.2)	-0.89 (0.1)	-0.97 (0.2)	-0.22 (0.2)
		CFB, Mean % (SD)	56.6 (50.8, 61.7)‡	5.1 (-6.7, 15.7)‡	-47.2 (8.2)	-58.8 (6.1)	-62 (5.7)	-20 (12.6)
		Difference vs. Placebo, % (95% CI);	54.3 (46.4, 60.9)		33.96 (0.4, 56.2)	48.45 (23.2, 65.4)	52.52 (28.8, 68.4)	REF
	Month 16	CFB, LS Mean (SE)	NR	NR	-0.45 (0.2)	-0.87 (0.2)	-1.04 (0.2)	-0.11 (0.2)
		CFB, Mean (SE)	NR	NR	-36.5 (10.6)	-58.0 (6.6)	-64.6 (5.7)	-10.6 (15.0)
Participants Achieving ≥30% Decline From Baseline in uPCR	Month 9	n (%)	NR	NR	19 (50)	20 (48.8)	21 (55.3)	7 (18.4)
	Month 12	n (%)	NR	NR	19 (50)	24 (58.5)	23 (60.5)	11 (28.9)
	Month 16	n (%)	NR	NR	18 (47.4)	21 (51.2)	24 (63.2)	8 (21.2)

Intervention			Sibeprenlimab					
Trial			VISIONARY		ENVISION*			
Arm			Sib 400 mg	Placebo	Sib 2 mg/kg	Sib 4 mg/kg	Sib 8 mg/kg	Placebo
N			152	168	38	41	38	38
Spot uPCR								
Mean Change, g/g	Month 9	LS Geometric Mean Percent Change (95% CI)	45.6 (37.2, 52.9)	14.4 (0.1, 30.7)	NR	NR	NR	NR
		Difference v. placebo (95% CI)	52.4 (42.7, 60.5)		NR	NR	NR	NR
	Month 12	LS Geometric Mean Percent Change (95% CI)	*-52.1 (-58.3, -43.0)*	*8.04 (-5.9, 25.4)*	NR	NR	NR	NR
Urine Protein Excretion								
Change from Baseline in 24-hour Urine Protein Excretion, mg/day	Month 12	Mean (95% CI)	NR	NR	49.5 (30.6, 63.2)	57.8 (43, 68.8)	65.5 (53.1, 74.6)	18.7 (-11.5, 40.8)
		CFB, LS Mean (SE) - g/day	NR	NR	-0.68 (0.2)	-0.86 (0.2)	-1.06 (0.2)	-0.21 (0.2)
		n (%) Whose UPE Level Decreased below 500 Mg per day	NR	NR	5 (13.2)	12 (29.3)	11 (28.9)	1 (2.6)
		n (%) Whose UPE level Decreased Below 1 g per Day	NR	NR	16 (42.1)	17 (41.5)	21 (55.3)	7 (18.4)
	Month 16	Mean (95% CI)	NR	NR	36.2 (10.7, 54.5)	55.2 (38.5, 67.4)	68.5 (56.3, 77.2)	8.3 (-28.1, 34.4)
estimated Glomerular Filtration Rate (eGFR)								
Mean Change From Baseline, ml/min per 1.73 m^2	Baseline	Mean (SD)	63.5 (24.4)	63.4 (25.3)	NR	NR	NR	NR
		Median (Range)	NR	NR	58 (35-154)	64 (35-133)	56 (34-109)	68.5 (33-116)
	Month 12	CFB, LS Mean (SE)	NR	NR	-2.7 (1.8)	0.2 (1.7)	-1.5 (1.8)	-7.4 (1.8)
		CFB, Difference vs. Placebo (95% CI)	NR	NR	4.6 (-0.3, 9.5) †	7.6 (2.8, 12.3) †	5.8 (0.9, 10.7) †	REF†
		Mean Change (SE)	NR	NR	-4.1 (1.7)	0.1 (1.6)	-0.8 (1.6)	-5.9 (1.7)

Intervention		Sibeprenlimab					
Trial		**VISIONARY**		**ENVISION***			
Arm		**Sib 400 mg**	**Placebo**	**Sib 2 mg/kg**	**Sib 4 mg/kg**	**Sib 8 mg/kg**	**Placebo**
N		**152**	**168**	**38**	**41**	**38**	**38**
Annualized eGFR slope From baseline, ml/min/1.73 m^2/year	**Difference vs. Placebo (95% CI); p-Value**	NR	NR	1.81 (-2.8, 6.4)	5.96 (1.5, 10.4)	5.08 (0.5, 9.6)	REF
Clinical Remission#							
Month 9	**n (%)**	NR	NR	4 (10.5)	5 (12.2)	7 (18.4)	1 (2.6)
Month 12	**n (%)**	NR	NR	3 (7.9)	5 (12.2)	10 (26.3)	1 (2.6)
Month 16	**n (%)**	NR	NR	3 (7.9)	7 (17.1)	9 (23.7)	1 (2.6)

CFB: change from baseline, CI: confidence interval, eGFR: Estimated Glomerular Filtration Rate, mL/min/1.73m^2: milliliter per minute per 1.73 meters squared, n: number, N: total number, NA: not applicable, NR: not reported, SD: standard deviation, SE: standard error, Sib: Sibeprenlimab, UPE: Urine Protein Excretion, uPCR: Urine Protein-To-Creatinine Ratio

*ENVISION trial calculated geometric mean

†LS mean difference in eGFR relative to placebo from baseline to month 12

‡95% CI

§g/day

#Defined as a decrease in the level of urinary protein excretion to <300mg per day

Table D3.8 Note: Italicized data has been digitized or calculated

Table D3.9. ORIGIN 3, ORIGIN, ORIGIN OLE Key Efficacy [9,29,31,56]

Intervention			Atacicept								
Trial			ORIGIN 3		ORIGIN					ORIGIN OLE	
Arm			Ata	Placebo	Ata 25	Ata 75	Ata 150	Combined Ata**	Placebo	Ata 150	Placebo-Switched
N			106	97	16	33	33	66	34	80	31
24-Hour Urinary Protein to Creatinine Ratio (uPCR)											
Mean 24-HR uPCR g/g	Baseline	Mean (SD)	NR	NR	1.6 (0.8)	1.7 (0.9)	1.7 (1.0)	1.7 (0.9)	1.6 (0.8)	1.8 (1.3)	
	Month 6	Mean % CFB (SD)	NR	NR	-37	-28 (8.72)	-33 (7.97)	-31.01 (5.75)	-7 (11)	NR	NR
		Difference vs. Placebo, % (95% CI); p-value	NR	NR	32 (-2.2, 55.0); NR	22 (-7.61, 44.1); 0.13	28 (0.43, 48.5); 0.047	25 (1.74, 43.01); 0.037	REF	NR	NR
	Month 9	CFB, LS Mean (SE)	NR	NR	NR	NR	NR	-0.42 (0.11)*	-0.07 (0.16)*	NR	NR
		Mean % CFB (SD)	-45.7	-6.8	-38	-34 (7.9)	-33 (8.02)	-34.31 (7.3)	3.24 (NR)	-34 (NR)	3 (NR)
		Difference vs. Placebo, % (95% CI); p-value	41.8 (28.9, 52.3); p<0.0001		40 (9.4, 60.1); NR	36 (10.9, 53.8); 0.0085	35 (9.13, 53.1); 0.012	35 (13.03, 51.53); 0.0042	REF	NR	NR
	Month 18	Mean % CFB, (SD)	NR	NR	NA	NA	NA	NA	NA	-45 (NR)	-47 (NR)

Intervention			Atacicept								
Trial			ORIGIN 3		ORIGIN					ORIGIN OLE	
Arm			Ata	Placebo	Ata 25	Ata 75	Ata 150	Combined Ata**	Placebo	Ata 150	Placebo-Switched
N			106	97	16	33	33	66	34	80	31
	Week 96	Mean % CFB, (SD)	NR	NR	NA	NA	NA	NA	NA	*-52.23 (5)*	
Estimated Glomerular Filtration Rate (eGFR)											
Mean Change From Baseline, ml/min per 1.73 m^2	Baseline	Mean (SD)	NR	NR	71 (29)	64 (25)	56 (23)	60 (24)	66 (32)	62 (28)	
		Median (Range)	NR	NR	65 (51, 90)†	63 (43, 79) †	49 (41, 63) †	53 (41, 72)†	57 (42, 87)	56 (41, 73)	
		CFB, Mean (SE)	NR	NR	NR	*2.5 (1.3)*	*2.9 (1.2)*	*2.7 (1.0)*	*-0.8 (1.1)*	*2.3 (NR)*	
	Month 9	CFB, Mean (SE)	NR	NR	NR	0.67 (-3.2, 4.8)	0.92 (-3.2, 5.2)	0.83 (-2.01, 3.82)§	-4.9 (-8.5, -1.1)	*1.1 (NR)*	
		Difference vs. Placebo (95% CI)	NR	NR	NR	5.6	5.8	5.7	REF	NR	NR
		CFB, Mean (95% CI)	NR	NR	NR	1.2 (-5.4, 8.2) ‡	1.59 (-5.2, 8.9) ‡	1.4 (-3.5, 6.6) ‡	-8.5 (-14.6, -1.9) ‡	NR	NR
		Difference vs. Placebo (95% CI)	NR	NR	NR	10.5 (0.32, 21.7)	11 (0.61, 22.4)	10.7 (1.5, 20.7); 0.022	REF	NR	NR
		Geometric LS Mean CFB (95% CI)	NR	NR	NR	NR	NR	NR	NR	0.97 (0.94, 1.01)	0.97 (0.94, 1)
	Week 48	Mean CFB	NR	NR	NA	NA	NA	NA	NA	*0.05*	
	Week 60	Mean CFB	NR	NR	NA	NA	NA	NA	NA	*0.33*	
	Week 72	Mean CFB	NR	NR	NA	NA	NA	NA	NA	*0.25*	
	Week 96	Mean CFB	NR	NR	NA	NA	NA	NA	NA	*-2.02*	

Intervention			Atacicept								
Trial			ORIGIN 3		ORIGIN					ORIGIN OLE	
Arm			Ata	Placebo	Ata 25	Ata 75	Ata 150	Combined Ata**	Placebo	Ata 150	Placebo-Switched
N			106	97	16	33	33	66	34	80	31
	Week 96 + 26	CFB, Mean (SE)	NR	NR	NR	NR	NR	NR	NR	-3.9	
Annualized eGFR slope From Baseline, ml/min/1.73 m^2/year	Week 36	Mean Change (SE)	NR	NR	4 (3.4) #	1.7 (2.3) #	2.6 (2.4) #	NR	-3.2 (2.4) #	NR	
		Difference vs. Placebo (95% CI); p-Value	NR	NR	7.2 (-1.02, 15.5) #	4.3 (-1.6, 11.5) #	5.9 (-0.75, 12.5) #	NR	REF#	NR	
	Between Weeks 36 And 96	Mean Change (SE)	NA	NA	NA	NA	NA	NA	NA	-0.4 (0.9) ¤	
	All 96 Weeks		NA	NA	NA	NA	NA	NA	NA	-0.6 (0.5)	

Ata: Atacicept, CFB: Change from Baseline, CI: Confidence Interval, eGFR: Estimated Glomerular Filtration Rate, mL/min/1.73m^2: milliliter per minute per 1.73 meters squared, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, SD: Standard Deviation, SE: Standard Error, uPCR: Urine Protein-To-Creatinine Ratio

*LSM Estimates on Natural Log Scale

† Median (IQR)

‡Geometric

§ Adjusted geometric mean change

Used 9 months of data (trial length)

¤ From week 39 to 96

** Combined atacicept dose of 75mg and 150mg

Table D3.9 Note: Italicized data has been digitized or calculated

Table D3.10. JANUS Key Efficacy [30,110]

Intervention			Atacicept		
Trial			JANUS		
Arm			Ata 25 mg	Ata 75 mg	Placebo
N			6	5	5
24-Hour Urinary Protein to Creatinine Ratio (uPCR)*					
Mean 24-HR uPCR mg/mg	Baseline	Absolute Levels at Baseline (mg/mg)	1.8 (0.8, 2.2)	1.4 (1.3, 1.7)	1.6 (1.5, 1.6)
	Week 24	Absolute Levels (mg/mg)	2.2 (1.0, 2.9)	0.9 (0.7, 1.6)	2 (1.2, 2.7)
		% CFB	-23.6 (-60.5, 16.9)	-25.3 (-40.8, -14.5)	24.5 (-24.3, 64.2)
	Week 48	Absolute Levels (mg/mg)	2 (1.2, 2.7)	1.3 (1, 2.3)	1.1 (1, 2.2)
		% CFB	-37.6 (-44.1, -31)	6.9 (-35.5, 40)	-37.6 (-44.6, 37.7)
	Week 72	Absolute Levels (mg/mg)	1.1 (0.2, 3.6)	1.6 (1.2, 2.2)	2.5 (0.9, 2.8)
		% CFB	-50.1 (-73.6, -8.2)	-3.2 (-30.2, 73.3)	27.8 (-40.7, 73.5)
Urine Protein Excretion*					
Change from Baseline in 24-Hour Urine Protein Excretion, g/day	Baseline	Mean (95% CI), g/day	2.1 (1.9, 2.9)	1.7 (1.6, 2.3)	3.2 (2.3, 3.3)
	Week 24	Absolute Levels (g/day)	3.5 (1.8, 3.7)	1.5 (0.6, 3.2)	4.5 (3.4, 5)
		% CFB	-8.5 (-63.4, 36.7)	-29 (-49.4, 19.1)	14.9 (3.7, 61.9)
	Week 48	Absolute Levels (g/day)	2.4 (1.2, 3.7)	2.1 (0.9, 4)	2.4 (1.5, 4.5)
		% CFB	-44.2 (-49.8, -38.6)	27 (-30.7, 75.2)	-27.7 (-51.2, 13.5)
	Week 72	Absolute Levels (g/day)	1 (0.2, 5.9)	2.6 (1.8, 2.8)	2.9 (2.7, 6)
		% CFB	-57.2 (-84.3, -1.7)	10.7 (-2.4, 56.2)	-8.7 (-19, 53.1)
Estimated Glomerular Filtration Rate (eGFR) *					
Mean Change from Baseline, ml/min per 1.73 m^2	Baseline	Absolute Levels at baseline	57 (53, 85)	55 (52, 92)	49 (48, 54)
	Week 24	Absolute Levels	52 (47, 60)	50 (38, 74)	40 (38, 47)
		% CFB	-7.1 (-11.3, -2.4)	-3.8 (-20.4, 13)	-7.4 (-20.8, -4.1)
	Week 48	Absolute Levels	56 (47, 60)	65.5 (43.5, 98)	39 (37, 46)
		% CFB	3.4 (-7.8, 5.7)	9.1 (-8.8, 27.5)	-8.3 (-22.0, -6.1)
	Week 72	Absolute Levels	59 (57, 79)	50 (38, 89)	34 (27, 52)
		% CFB	11.8 (11.3, 36.2)	-3.3 (-3.8, 31)	-25 (-29.2, -3.7)

Ata: Atacicept, CFB: Change from Baseline, CI: Confidence Interval, eGFR: Estimated Glomerular Filtration Rate, mL/min/1.73m^2: milliliter per minute per 1.73 meters squared, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, SD: Standard Deviation, SE: Standard Error, uPCR: Urine Protein-To-Creatinine Ratio

*All values presented as median (Q1, Q3)

Table D3.11. NefIgArd & NefIgArd OLE Key Efficacy[10,31,36,103,104]

Intervention			**Nefecon**			
Trial			**NefIgArd (Lafayette 2023)**		**NefIgArd OLE**	
Arm			**Nefecon 16 mg**	**Placebo**	**2nd Course of Nefecon**	**1st Course of Nefecon**
N			**182**	**182**	**45**	**74**
24-Hour Urinary Protein to Creatinine Ratio (uPCR)						
Mean 24-HR uPCR, g/g	**Month 6**	**% CFB, Mean (95% CI)**	-23.1 (-29.5, -16.1)	-7.3 (-15, 1.2)	NA	NA
		Difference vs. Placebo, % (95% CI)	17.1 (6.1, 26.7)		NA	NA
	Month 9	**% CFB, Mean (95% CI)**	-33.6 (-39.6, -27)	-5.2 (-13.8, 4.3)	-33 (NR)	-31 (NR)
		Difference vs. Placebo, % (95% CI)	30.0 (19.9, 38.8)		NR	NR
		Ratio of Geometric LS Mean (96% CI)	NR	NR	0.67 (0.56, 0.8)	0.69 (0.6, 0.8)
	Month 12	**Mean (95% CI), mg/mg**	NA	NA	NA	NA
		% CFB, Mean (95% CI)	-51.3 (-56.2, -45.9)	-3.2 (-12.8, 7.5)	NA	NA
		Difference vs. Placebo, (95% CI); p-Value	49.7 (41.6, 56.6)		NA	NA
	Month 18	**% CFB, Mean (95% CI)**	-43.1 (-49, -36.6)	-2.9 (-13, 8.3)	NA	NA

Intervention			Nefecon			
Trial			NefIgArd (Lafayette 2023)		NefIgArd OLE	
Arm			Nefecon 16 mg	Placebo	2nd Course of Nefecon	1st Course of Nefecon
N			182	182	45	74
		Difference vs. Placebo, (95% CI); p-Value	41.4 (31.7, 49.8)		NA	NA
	Month 24	% CFB, Mean (95% CI)	-30.7 (-38.9, 21.5)	-1 (-12.8, 12.4)	NA	NA
		Difference vs. Placebo, % (95% CI)	30.1 (41.5, 16.4)		NA	NA
Time-Averaged UPCR	Between 12 and 24 Months	% CFB, Mean (95% CI)	-40.3 (-46, -34)	1 (-9, 12)	NA	NA
		Difference vs. Placebo, % (95% CI); p-Value	40.9 (31.9, 48.7); p <0.0001		NA	NA
		Ratio of Geometric LS Mean (95% CI)	0.6 (0.54, 0.66)	1.01 (0.91, 1.12)	NA	NA
		Difference vs. Placebo (95% CI); p-Value	0.59 (0.51, 0.68); <0.0001		NA	NA
Participants Achieving ≥30% Decline from Baseline in uPCR	At Least 6 Months	N (%)	111 (61)	41 (23)	NA	NA
	At Least 9 Months	N (%)	96 (53)	29 (16)	NA	NA
	At Least 12 Months	N (%)	93 (51)	25 (14)	NA	NA
	At Least 18 Months	N (%)	23 (13)	9 (5)	NA	NA
Estimated Glomerular Filtration Rate (eGFR)						
Mean Change from Baseline, ml/min per 1.73 m^2	Baseline	Mean (IQR)	NR	NR	51 (42, 62)	49.9 (39.9, 64.9)

Intervention			Nefecon			
Trial			NefIgArd (Lafayette 2023)		NefIgArd OLE	
Arm			Nefecon 16 mg	Placebo	2nd Course of Nefecon	1st Course of Nefecon
N			182	182	45	74
		Median (Range)	56.14 (45.5, 71.0)	55.1 (46.0, 67.7)	NR	NR
	Month 6	CFB, Mean (95% CI)	1.2 (-0.1, 2.5)	-3.3 (-4.5, -2.0)	NR	NR
		Difference vs. Placebo, (95% CI)	4.5 (2.8, 6.6)		NR	NR
	Month 9	CFB, Mean (95% CI)	0.66 (-0.8, 2.2)	-4.6 (-5.9, -3.2)	-1.28 (NR)	-1.53 (NR)
		Difference vs. Placebo (95% CI)	5.2 (3.4, 7.6)		NA	NA
	Month 12	CFB, LS Mean (95% CI)	-1.52 (-2.96, -0.03)	-5.85 (-7.2, -4.5)	NA	NA
		Difference vs. Placebo (95% CI)	4.3 (2.4, 6.7)		NA	NA
	Month 18	CFB, Mean (SE)	-4.6 (-6.5, -2.7)	-9.5 (-11.2, -7.7)	NA	NA
		Difference vs. Placebo (95% CI)	4.9 (2.43, 7.96)		NA	NA
	Month 24	CFB, Mean (95% CI)	-6.11 (-8.04, -4.1)	-12 (-13.8, -10.2)	NA	NA
		Difference vs. Placebo (95% CI)	5.89 (3.35, 9.15)		NA	NA
		CFB, Mean (95% CI)	-11 (NR)	-21.5 (NR)	NA	NA
Annualized eGFR Slope from Baseline, ml/min/1.73 m^2/year		Mean Change (SE)	-3.06 (NR)*	-6 (NR)*	NA	NA
		Difference vs. Placebo (95% CI); p-Value	2.95 (1.67, 4.58); p<0.0001		NA	NA
Time-Weighted Average of eGFR	Over 24 Months	CFB, Mean (95% CI)	-2.47 (-3.9, -1.02)	-7.52 (-8.8, -6.2)	NA	NA

Intervention			Nefecon			
Trial			NefIgArd (Lafayette 2023)		NefIgArd OLE	
Arm			Nefecon 16 mg	Placebo	2nd Course of Nefecon	1st Course of Nefecon
N			182	182	45	74
		Difference vs. Placebo (95% CI); p-Value	5.1 (3.2, 7.4); p<0.0001		NA	NA
	Between Month 12 and 24	CFB, Mean (95% CI)	-4.1 (-5.7, -2.4)	-9.1 (-10.6, -7.6)	NA	NA
		Difference vs. Placebo (95% CI); p-Value	5 (2.9, 7.7); p<0.0001		NA	NA
		Ratio of Geometric LS Mean (95% CI)	0.93 (0.9, 0.96)	0.84 (0.81, 0.86)	NA	NA
		Difference vs. Placebo (95% CI); p-Value	1.11 (1.06, 1.16); p<0.0001		NA	NA

CFB: Change from Baseline, CI: Confidence Interval, n: number, N: Total number, eGFR: Estimated Glomerular Filtration Rate, ml/min/1.73 m^2: millimeter per minute per 1.73 meters squared, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, SD: Standard Deviation, SE: Standard Error, uPCR: Urine Protein-To-Creatinine Ratio

*Analysis based on multiply imputed log-transformed eGFR values at two years. Mean changes were annualized (i.e., divided by 2) to provide the change from baseline per year in each treatment arm and the difference between Nefecon and placebo in two-year eGFR slope per year.

Table D3.12. NefIgArd Part A, NefIgArd China Cohort, NEFIGAN Key Efficacy [33,34,45,104]

Intervention	Nefecon						
Trial	NefIgArd - Part A FAS		NefIgArd - China Cohort		NEFIGAN		
Arm	Nefecon 16 mg	Placebo	Nefecon 16 mg	Placebo	Nefecon 8 mg	Nefecon 16mg	Placebo
N	97	102	32	30	51	48	50
24-Hour Urinary Protein to Creatinine Ratio (uPCR)							

Intervention			Nefecon						
Trial			NefIgArd - Part A FAS		NefIgArd - China Cohort		NEFIGAN		
Arm			Nefecon 16 mg	Placebo	Nefecon 16 mg	Placebo	Nefecon 8 mg	Nefecon 16mg	Placebo
N			97	102	32	30	51	48	50
Mean 24-HR uPCR g/g	Month 6	CFB, % (95% CI)	NA	NA	-26 (-41.5, -6.4)	-5.8 (-25.7, 19.4)	NR	NR	NR
		Difference vs. Placebo, % (95% CI)	NA		21.4 (-9.9, 43.8)		NR	NR	NR
	Month 9	CFB, Mean (SEM)	-0.41 (NR)	-0.07 (NR)	NR	NR	-0.13 (0.09)	-0.22 (0.09)	0.036 (0.09)
		CFB Difference vs. Placebo (SEM)	NR	NR	NR	NR	-0.17 (0.12)	-0.26 (0.13)	REF
		CFB, % (SD)	31 *(4.5)*	-5 *(3.5)*	-37.6 (-52.2, 18.6)	-9.1 (-30.6, 19)	NR	NR	NR
		Difference vs. Placebo, % (95% CI); p-Value	27 (13, 39); p=0.0003		31.4 (-0.3, 53.1); NR		NR	NR	NR
		Ratio of Geometric LS Mean (96%CI)	0.69 (0.61, 0.79)	0.95 (0.83, 1.08)	NR	NR	0.81 (0.64, 1.04) *	0.72 (0.56, 0.92) *	REF
		Ratio of Int. vs. Placebo (96.5% CI); p-Value	0.73 (0.61, 0.88); p=0.0003		NR	NR	NR	NR	NR
	Month 12	CFB, Mean (SEM)	-0.68 (NR)	-0.09 (NR)	NR	NR	-0.196 (0.08)	-0.277 (0.09)	0.004 (0.08)
		CFB Difference vs. Placebo (SEM)	NR	NR	NR	NR	-0.199 (0.11)	-0.281 (0.12)	REF
		CFB, % (SD)	*-51 (3.5)*	*-6 (5.8)*	-53.5 (-64.6, -38.8)*	10.2 (-16.6, 45.7) *	-22.6 (NR)	-32 (NR)	0.5 (NR)
		Difference vs. Placebo, % (95% CI); p-Value	48 (36, 58); p<0.0001		58 (38, 72)		NR	NR	NR
		Ratio of Geometric LS Mean (95% CI); p-Value	NR	NR	NR	NR	0.77 (0.62, 0.96); p=0.01	0.68 (0.57, 0.96); p=0.0005	REF
	Month 18	CFB, % (95% CI)	NA	NA	-48.4	9	NA	NA	NA

Intervention			Nefecon						
Trial			NefIgArd - Part A FAS		NefIgArd - China Cohort		NEFIGAN		
Arm			Nefecon 16 mg	Placebo	Nefecon 16 mg	Placebo	Nefecon 8 mg	Nefecon 16mg	Placebo
N			97	102	32	30	51	48	50
					(-61.7, -30.4)	(-20.1, 48.8)			
		Difference vs. Placebo, %, (95% CI)	NA	NA	52.6 (27, 69.3)		NA	NA	NA
	Month 24	CFB, % (95% CI)	NA	NA	-32.9 (-51.8, -6.6)	18.6 (-16.9, 69.3)	NA	NA	NA
		Difference vs. Placebo, %, (95% CI)	NA	NA	43 (8, 65)		NA	NA	NA
Time-Averaged uPCR	Between 12 and 24 Months	CFB, % (95% CI)	NA	NA	-42 (-57, -22)	20 (-11, 61)	NA	NA	NA
		Difference vs. Placebo, % (95% CI)	NA	NA	52 (28, 68)		NA	NA	NA
Urine Protein Excretion (UPE)									
Change from Baseline In 24-Hour UPE, mg/day	Month 9	Ratio of Geometric LS Mean (95% CI); p-Value	NA	NA	NA	NA	0.8 (0.6, 1.0); p=0.043	0.7 (0.5, 0.9); p=0.004	REF
		% CFB, Difference vs. Placebo (95% CI); p-Value	NA	NA	NA	NA	NR	-31 (NR); p<0.0004	REF
	Month 12	% CFB, Difference vs. Placebo (95% CI); p-Value	NA	NA	NA	NA	NR	-38 (NR); p<0.0001	REF
		Ratio of Geometric LS Mean (95% CI); p-Value	NA	NA	NA	NA	0.8 (0.6, 0.9); p=0.009	0.6 (0.5, 0.8); p<0.00001	REF
Estimated Glomerular Filtration Rate (eGFR)									
Mean Change From Baseline, ml/min	Baseline	Mean (SD)	NR	NR	NR	NR	74.1 (25.8)	83.8 (25.9)	76.5 (23.2)
		Median (Range)	54.9 (46.4, 68.9)	55.5 (45.5, 67.7)	NR	NR	NR	NR	NR
	Month 6	CFB, Mean (SE)	*1.2 (0.1, 2.1)*	*-2.8 (-3.7, -2.2)*	1.8 (-1.4, 5.2) *	-5.2 (-8, -2.2) *	*-0.27 (1.7)*	*-1.2 (3.1)*	*-5.0 (1.5)*

Intervention			Nefecon						
Trial			NefIgArd - Part A FAS		NefIgArd - China Cohort		NEFIGAN		
Arm			Nefecon 16 mg	Placebo	Nefecon 16 mg	Placebo	Nefecon 8 mg	Nefecon 16mg	Placebo
N			97	102	32	30	51	48	50
per 1.73 m^2		Difference vs. Placebo, (95% CI)	NR	NR	7.0 (2.6, 12.5)		NR	NR	NR
	Month 9	CFB, Mean (SE)	-0.17 (*0.5*)	-4.04 (*0.8*)	0.5 (-3.8, 5.1) *	-6.9 (-10.7, -2.8) *	*0.02 (1.6)*	*1.8 (2.4)*	*-4.9 (1.8)*
		Difference vs. Placebo (95% CI)	3.87 (NR); p=0.001		7.4 (1.5, 14.8)		NR	NR	NR
		CFB, %	NR	NR	0.8	-11.8	-0.9	0.6	-9.8
		Geometric LS Mean (95% CI); p-Value	1 (0.96, 1.03); NR	0.93 (0.9, 0.96)	NR	NR	1.1 (1.02, 1.18); p=0.006	1.12 (1.0, 1.2); p=0.002	REF
		Ratio of Int. vs. Placebo (95% CI); p-Value	1.07 (1.03, 1.13); 0.0014		NR	NR	NR	NR	NR
	Month 12	Mean CFB (SE)	*-1.5 (1.1)*	*-4.9 (0.8)*	-4.5 (-8.8, 0.2) *	-10.8 (-14.8, -6.5) *	*-3.5 (1.6)*	*0.04 (1.5)*	*-6.1 (1.9)*
		Difference vs. Placebo (95% CI)	3.6 (NR)		6.4 (0.1, 14.2)		NA	NA	NA
		CFB, %	NR		NR	NR	NA	0.7	-10.9
		Difference vs. Placebo, % (95% CI)	7 (1, 13); p=0.01		NR	NR	NA	NR	NR
		Geometric LS Mean (95% CI); p-Value	0.97 (0.93, 1.01); NR	0.91 (0.88, 0.95)	NR	NR	1.03 (0.9, 1.1); p=0.25	1.11 (1.0, 1.2); p=0.013	REF
		Ratio of Int. vs. Placebo (95% CI); p-Value	1.07 (1.01, 1.13); 0.0106		NR	NR	NA	NA	NA
	Month 18	CFB, Mean (95% CI)	NA	NA	-7.0 (-13.6, 0.6)	-17.3 (-23.5, -10.1)	NA	NA	NA
		Difference vs. placebo (95% CI)	NA	NA	10.3 (0.2, 24.4)		NA	NA	NA
	Month 24	CFB, Mean (95% CI)	NA	NA	-7.1 (-14.6, 1.6)	-21.0 (-27.7, -12.8)	NA	NA	NA

Intervention			Nefecon						
Trial			NefIgArd - Part A FAS		NefIgArd - China Cohort		NEFIGAN		
Arm			Nefecon 16 mg	Placebo	Nefecon 16 mg	Placebo	Nefecon 8 mg	Nefecon 16mg	Placebo
N			97	102	32	30	51	48	50
		Mean CFB, %	NA	NA	-12	-35.6	NA	NA	NA
		Difference vs. Placebo (95% CI)	NA	NA	13.9 (2.5, 30.9)		NA	NA	NA
Annualized eGFR Slope from Baseline, ml/min/1.73 m^2/year		Mean (95% CI)	NA	NA	-4 (-7, -1)	-8.8 (-11.9, -5.7)	NA	NA	NA
		Difference vs. Placebo (95% CI); p-value	3.37 (NR); p=0.01		4.8 (0.5, 9.1)		NA	NA	NA
Time-Weighted Average of eGFR	Over 24 Months	CFB, Mean (95% CI)	NA	NA	-3.7 (-8.9, 2.0)	-13.3 (-18.1, -8)	NA	NA	NA
		Difference vs. Placebo (95% CI); p-Value	NA	NA	9.6 (2.0, 19.8)		NA	NA	NA
	Between Month 12 and 24	CFB, Mean (95%C)	NA	NA	-6.1 (-12.2, 0.7)	-16.4 (-21.9, -10.2)	NA	NA	NA
		Difference vs. Placebo (95% CI); p-Value	NA	NA	10.3 (1.4, 22.6)		NA	NA	NA
		Ratio of Geometric LS Mean (95% CI)	NA	NA	0.9 (0.79, 1.01)	0.72 (0.63, 0.83)	NA	NA	NA
		Difference vs. Placebo (95% CI); p-Value	NA	NA	1.24 (1.03, 1.5)		NA	NA	NA

CFB: Change from Baseline, CI: Confidence Interval, mL/min/1.73m^2: milliliter per minute per 1.73 meters squared, n: number, N: Total number, eGFR: Estimated Glomerular Filtration Rate, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, SD: Standard Deviation, SE: Standard Error, uPCR: Urine Protein-To-Creatinine Ratio

*95% CI

Table D3.12 Note: Italicized data has been digitized or calculated

Table D3.13. Systemic Glucocorticoids Key Efficacy [47,48,50]

Comparator			Methylprednisolone				STOP-IgAN	
Trial			TESTING					
Arm			Combined Full-Dose and Reduced-Dose Methylpred-nisolone	Placebo	Reduced Dose Methylpred-nisolone	Placebo	Supportive Care	Supportive Care + Immunosupp-resion
N			257	246	121	120	80	82
Remission								
In Full Clinical Remission	Full-Analysis Set	n (%)	NR	NR	NR	NR	4 (5)	14 (17)
		OR (95% CI); p-Value	NR	NR	NR	NR	4.82 (1.42, 16.3); 0.01	
	Available-Case Analysis	n (%)	NR	NR	NR	NR	4 (6)	14 (20)
		OR (95% CI); p-Value	NR	NR	NR	NR	5.38 (1.55, 18.66); 0.008	
Kidney Events								
Onset of End-Stage Renal Disease		n (%)	NR	NR	NR	NR	6 (8)	6 (8)
		OR (95% CI); p-Value	NR	NR	NR	NR	0.97 (0.29, 3.22); 0.96	
Kidney Failure Requiring Dialysis/Transplant		n (%)	50*	67*	3 (2.5)	10 (8.3)	NR	NR
		Annual Event Rate, % (95% CI)	4.9 (3.7, 6.6)	7.8 (5.9, 10.2)	0.9 (0.3, 2.9)	2.7 (1.3, 5.3)	NR	NR
		Rate Difference, % (95% CI)	-2.9 (-5.4, -0.3)		NR	NR	NR	NR
		HR (95% CI); p-Value	0.59 (0.4, 0.87); 0.008		0.26 (0.07, 1.03); 0.056		NR	NR
Composite Endpoints								
50% eGFR Reduction, Kidney Failure, or All-Cause Death		n (%)	71*	94*	7 (5.8)	17 (14.2)	NR	NR
		HR (95% CI); p-Value	0.62 (0.46, 0.85); 0.003		0.3 (0.11, 0.77); 0.013		NR	NR
		Annual Event Rate, % (95% CI)	7 (5.5, 9.1)	10.8 (8.6, 13.7)	2.2 (1, 4.6)	5.2 (3.1, 8.6)	NR	NR
		Rate Difference, % (95% CI)	-3.8 (-6.9, -0.7)		NR	NR	NR	NR
40% eGFR Reduction, Kidney Failure, or All-Cause Death		n (%)	78*	106*	8 (6.6)	22 (18.3)	NR	NR
		HR (95% CI); p-Value	0.56 (0.42, 0.76); <0.001		0.27 (0.11, 0.61); 0.003		NR	NR

Comparator			Methylprednisolone				STOP-IgAN	
Trial			TESTING					
Arm			Combined Full-Dose and Reduced-Dose Methylpred-nisolone	Placebo	Reduced Dose Methylpred-nisolone	Placebo	Supportive Care	Supportive Care + Immunosupp-resion
N			257	246	121	120	80	82
		Annual Event Rate (95% CI), %	7.7 (6.1, 9.8)	12.2 (9.8, 15.2)	2.5 (1.3, 5.1)	7.1 (4.6, 10.9)	NR	NR
		Rate Difference (95% CI), %	-4.5 (-7.7, -1.2)		NR	NR	NR	NR
40% eGFR Reduction, Kidney Failure, or Death Due to Kidney Disease		n (%)	74*	106*	7 (5.8)	22 (18.3)	NR	NR
		HR (95% CI); p-Value	0.53 (0.39, 0.72); <0.001		0.24 (0.10, 0.58); p=0.002		NR	NR
		Annual Event Rate (95% CI), %	7.3 (5.7, 9.4)	12.1 (9.7, 15.1)	2.2 (1.1, 4.6)	7.1 (4.6, 10.9)	NR	NR
		Rate Difference, % (95% CI)	-4.8 (-8, -1.6)		NR	NR	NR	NR
30% eGFR Reduction, Kidney Failure, or All-Cause Death		n (%)	86*	113*	11 (9.1)	25 (20.8)	NR	NR
		HR (95% CI); p-Value	0.56 (0.42, 0.75); <0.001		0.33 (0.15, 0.7); 0.004		NR	NR
		Annual Event Rate (95% CI), %	8.4 (6.7, 10.6)	12.8 (10.3, 15.8)	3.5 (2, 6.4)	8.4 (5.6, 12.7)	NR	NR
		Rate Difference (95% CI), %	-4.4 (-7.7, -1)		NR	NR	NR	NR
Proteinuria								
Time-Averaged Proteinuria, g/d		Mean (95% CI)	1.8 (1.57, 2.03)	2.38 (2.07, 2.68)	1.58 (1.36, 1.8)	2.41 (2.04, 2.78)	NR	NR
		Mean Difference (95% CI); p-Value	-58 (-0.96, -0.19); p=0.003		-0.83 (-1.25, -0.4); <0.001		NR	NR
Mean Change from Baseline	6 Months	Mean CFB	NR	NR	-1.15	-0.03	NR	NR
		Mean Difference (95% CI); p-Value	NR	NR	-1.14 (-1.8, 0.48); p=0.002		NR	NR
	12 Months	Mean	NR	NR	-1.01	0.1	NR	NR

Comparator			Methylprednisolone				STOP-IgAN	
Trial			TESTING					
Arm			Combined Full-Dose and Reduced-Dose Methylpred-nisolone	Placebo	Reduced Dose Methylpred-nisolone	Placebo	Supportive Care	Supportive Care + Immunosupp-resion
N			257	246	121	120	80	82
		Mean Difference (95% CI); p-Value	NR	NR	-1.15 (-1.68, -0.62); <0.001		NR	NR
Absolute Change From Baseline	6 Months	Mean (SD)	NR	NR	1.2 (1.31)	2.6 (3.99)	NR	NR
	12 Months	Mean (SD)	NR	NR	1.3 (1.47)	2.4 (2.49)	NR	NR
	24 Months	Mean (SD)	NR	NR	1.4 (1.47)	2 (1.73)	NR	NR
	36 Months	Mean (SD)	NR	NR	1.4 (1.36)	1.9 (1.4)	NR	NR
	48 Months	Mean (SD)	NR	NR	1.5 (1.48)	1.6 (1.29)	NR	NR
eGFR								
Absolute eGFR mL/min/1.73 m^2	6 Months	Mean (SD)	NR	NR	69.1 (24.6)	63.8 (27.1)	NR	NR
	12 Months	Mean (SD)	NR	NR	68.9 (26)	63.5 (28.8)	NR	NR
	24 Months	Mean (SD)	NR	NR	66.8 (27.6)	59.6 (28.2)	NR	NR
	36 Months	Mean (SD)	NR	NR	64.6 (27.4)	58.7 (32.1)	NR	NR
	48 Months	Mean (SD)	NR	NR	61.1 (24.9)	49.3 (31.4)	NR	NR
Absolute Change From Baseline, mL/min/1.73 m^2	Month 6	Mean	NR	NR	4.7	-3.2	NR	NR
		Mean Difference (95% CI); p-Value	NR	NR	7.6 (3.8, 11.4); <0.001		NR	NR
	Month 12	Mean	NR	NR	5	-3	NR	NR
		Mean Difference (95% CI); p-Value	NR	NR	7.9 (4.3, 11.5) < 0.001		NR	NR
eGFR Decrease ≥15	Full-Analysis Set	n (%)	NR	NR	NR	NR	22 (28)	21 (26)
		HR (95% CI); p-Value	NR	NR	NR	NR	0.89 (0.44, 1.81); 0.75	

Comparator			Methylprednisolone				STOP-IgAN	
Trial			TESTING					
Arm			Combined Full-Dose and Reduced-Dose Methylpred-nisolone	Placebo	Reduced Dose Methylpred-nisolone	Placebo	Supportive Care	Supportive Care + Immunosupp-resion
N			257	246	121	120	80	82
ml/min/1.73 m^2	Available-Case Analysis	n (%)	NR	NR	NR	NR	18 (24)	17 (22)
		HR (95% CI); p-Value	NR	NR	NR	NR	0.89 (0.41, 1.9); 0.76	
eGFR Decrease ≥30 ml/min/1.73 m^2		n (%)	NR	NR	NR	NR	7 (9)	10 (13)
		95% CI	NR	NR	NR	NR	1.45 (0.51, 4.1); 0.49	
eGFR Reduction, %	30%	N	67	98	9 (7.4)	22 (18.3)	NR	NR
		Annual Event Rate (95% CI), %	6.7 (5.2, 8.7)	11.4 (9.1, 14.3)	2.9 (1.5, 5.5)	8.1 (5.3, 12.3)	NR	NR
		Rate Difference (95% CI), %	-4.7 (-7.8, -1.6)		NR	NR	NR	NR
		HR (95% CI); p-Value	0.47 (0.34, 0.65); <0.001		0.29 (0.13, 0.66); 0.003		NR	NR
	40%	n (%)	57*	91*	6 (5)	19 (15.8)	NR	NR
		Annual Event Rate (95% CI), %	5.8 (4.4, 7.7)	10.9 (8.6, 13.7)	1.9 (0.9, 4.2)	6.7 (4.3, 10.5)	NR	NR
		Rate Difference (95% CI), %	-5 (-8, -2)		NR	NR	NR	NR
		HR (95% CI); p-Value	0.44 (0.31, 0.62); <0.001		0.22 (0.08, 0.56); 0.002		NR	NR
	50%	N	49*	76*	5 (4.1)	12 (10)	NR	NR
		Annual Event Rate, % (95% CI)	5 (3.7, 6.7)	9.1 (7, 11.7)	1.6 (0.7, 3.8)	4.2 (2.4, 7.3)	NR	NR
		Rate Difference, % (95% CI)	-4.1 (-6.8, -1.3)		NR	NR	NR	NR
		HR (95% CI); p-Value	0.52 (0.36, 0.74); 0.001		0.3 (0.1, 0.88); 0.029		NR	NR
Rate of eGFR Decline (Slope)	Using All Visits	Mean (95% CI)	-2.5 (-3.56, -1.44)	-4.97 (-6.07, -3.87)	-0.7	-3	NR	NR
		Mean Difference (95% CI)	2.46 (0.94, 3.99)		2.3 (-0.0, 4.6); p=0.05		NR	NR

Comparator			Methylprednisolone				STOP-IgAN	
Trial			TESTING					
Arm			Combined Full-Dose and Reduced-Dose Methylpred-nisolone	Placebo	Reduced Dose Methylpred-nisolone	Placebo	Supportive Care	Supportive Care + Immunosupp-resion
N			257	246	121	120	80	82
mL/min/1.73 m^2 /year	Excluding Values from Those Receiving High-Exposure Treatment	Mean (95% CI)	-2.18 (-3.16, -1.2)	-4.94 (-6.01, -3.87)	NR	NR	NR	NR
		Mean Difference (95% CI)	2.76 (1.32, 4.21)		NR	NR	NR	NR
	Excluding Values from Those Receiving Treatment	Mean (95% CI)	-2.11 (-3.03, -1.2)	-4.76 (-5.81, -3.72)	NR	NR	NR	NR
		Mean Difference (95% CI)	2.65 (1.27, 4.03)		NR	NR	NR	NR
	Excluding Values from Month 1 and 3	Mean (SD)	NR	NR	-0.6	-2.2	NR	NR
		Mean Difference (95% CI); p-Value	NR	NR	2.9 (0.6, 5.2); 0.01		NR	NR
	Excluding Values from Month 1,3, and 6	Mean (SD)	NR	NR	-0.2	-1.8	NR	NR
		Mean Difference (95% CI); p-Value	NR	NR	2.9 (0.6, 5.1); 0.01		NR	NR
Mortality								
Death Due to Kidney Failure		N	1	1	NR	NR	NR	NR
		Annual Event Rate (95% CI), %	0	0	NR	NR	NR	NR
		Rate Difference (95% CI), %	0		NR	NR	NR	NR
		HR (95% CI); p-Value	NA		NR	NR	NR	NR
		N	6	3	1 (0.8)	0 (0)	NR	NR

Comparator		Methylprednisolone				STOP-IgAN	
Trial		TESTING					
Arm		Combined Full-Dose and Reduced-Dose Methylpred-nisolone	Placebo	Reduced Dose Methylpred-nisolone	Placebo	Supportive Care	Supportive Care + Immunosupp-resion
N		257	246	121	120	80	82
Death Due to Any Cause	Annual Event Rate (95% CI), %	0.5 (0.2, 1.3)	0.3 (0.1, 1)	0.3 (0.0, 2.2)	0 (0, 0)	NR	NR
	Rate Difference (95% CI), %	0.2 (-0.4, 0.8)		NR		NR	NR
	HR (95% CI); p-Value	2.62 (0.53, 13.05)		NA	NA	NR	NR
Survival							
Probability of Event-Free Survival - Available Case	n (%)	NR	NR	NR	NR	36 (50)	35 (45.5)
Hematuria							
Disappearance of Microhematuria	n (%)	NR	NR	NR	NR	9 (16)	24 (42)
	95% CI	NR	NR	NR	NR	3.73 (0.52, 9.14); 0.004	
Other Outcomes							
Mean Annual Change in the Slope of the Reciprocal of Serum Creatinine Concentration (mg/dl)	Mean (SD)	NR	NR	NR	NR	-0.02 (0.06)	-0.01 (0.06)
	Month 12	NR	NR	NR	NR	0.8 (0.67)	0.57 (0.53)
	Month 36	NR	NR	NR	NR	0.85 (0.66)	0.76 (0.9)

CFB: Change from Baseline, CI: Confidence Interval, eGFR: Estimated Glomerular Filtration Rate, mL/min/1.73m^2: milliliter per minute per 1.73 meters squared, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, SD: Standard Deviation, SE: Standard Error, uPCR: Urine Protein-To-Creatinine Ratio

*N

Table D3.14. ORIGIN, ORIGIN OLE, NefIgArd, NefIgArd OLE Hematuria Outcomes[9,31,111,112]

Intervention			Atacicept				Nefecon			
Trial			ORIGIN		ORIGIN OLE		NefIgArd		NefIgArd OLE	
Arm			Ata 150	Placebo	Ata 150 mg	Placebo-Switched	Nefecon 16 mg	Placebo	2nd Course of Nefecon	1st Course of Nefecon
N			15	19	80	31	182	182	45	74
Hematuria (RBC/HPF)	≥1 Grade Improvement, %; p-Value	Month 9	87; p=0.002	32; REF	NR	NR	NR	NR	NR	NR
	Resolution to Negative/Trace, %; p-Value	Month 9	80; p<0.001	5; REF	NR	NR	NR	NR	NR	NR
	% CFB in Hematuria over Time	Month 9	NR	NR	-67*	-5*	NR	NR	NR	NR
		Month 18	NR	NR	-81	-59	NR	NR	NR	NR
	% Reduction in Those with Hematuria (95% CI)†	Week 96	NR	NR	-75 (-87, -59)		NR	NR	NR	NR
Microhematuria	During Observational Period	n (%)	NR	NR	NR	NR	94 (59.5)	59 (39)	NR	NR
		OR (95% CI)	NR	NR	NR	NR	2.5 (1.6, 4.1); p=0.0001		NR	NR
	Month 9	n (%)	NR	NR	NR	NR	NR	NR	10 (22.7)	17 (25.0)

Ata: Atacicept, CFB: Change from Baseline, CI: Confidence Interval, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, OR: Odds Ratio, PBO: Placebo, %: Percent

*Start of placebo group receiving Atacicept 150mg dose

† Among participants with hematuria at baseline

Table D3.14 Note: Italicized data has been digitized or calculated

Table D3.15. VISIONARY & ORIGIN 3 UARC Outcomes[24,29]

Intervention			Sibeprenlimab		Atacicept	
Trial			VISIONARY		ORIGIN 3	
Arm			Sib	Placebo	Ata	Placebo
N			152	168	106	97
uARC	Month 9	% CFB	NA	NA	-47.3	-8.8
		% Difference vs. Placebo, (95% CI)	NA	NA	42.2 (27.3, 54.1)	
		Ratio of Geometric Mean	0.42 (0.36, 0.49)	0.88 (0.76, 1.02)	NA	NA
		% Reduction (95% CI)	58.3 (51.5, 64.1)	11.9 (-1.9, 23.9)	NA	NA
		Treatment Effect vs. Placebo, Ratio of GM (95% CI)	0.47 (0.4, 0.56)		NA	NA
		% Reduction (95% CI)	52.7 (44.1, 59.9)		NA	NA
	Month 12	Ratio of Geometric Mean	0.36 (0.3, 0.42)	64.5 (58.4, 69.8)	NA	NA
		% Reduction (95% CI)	0.82 (0.71, 0.96)	17.8 (4.3, 29.3)	NA	NA
		Treatment Effect vs. Placebo, Ratio of GM (95% CI)	0.43 (0.36, 0.52)		NA	NA
		% Reduction (95% CI)	56.9 (48.4, 63.9)		NA	NA

CFB: Change from baseline, CI: Confidence Interval, GM: Geometric Mean, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, Sib: Sibeprenlimab, %: Percent

Table D3.16. NefIgArd & NefIgArd OLE UARC Outcomes[10,105]

TR-Budesonide					
Trial		NefIgArd		NefIgArd OLE	
Arm		Nefecon 16 mg	Placebo	2nd Course of Nefecon	1st Course of Nefecon
N		182	182	45	74
uARC					
Month 9	Ratio of Geometric LS Mean (95% CI)	NR	NR	0.6 (0.49, 0.75)	0.65 (0.55, 0.77)
Time-Averaged UARC, Between 12 and 24 Months	% Reduction from Baseline	48.2 (-54, -42)	3.7 (-15, 8)	NR	NR
	% Reduction vs. Placebo (95% CI); p-Value	46.3 (36.5, 54.5); p<0.0001		NR	NR

CI: Confidence Interval, GM: Geometric Mean, LS: Least Squares, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, %: Percent

Table D3.17. NefIgArd Part A, NefIgArd China Cohort, NEFIGAN UARC Outcomes[33,34,45,104,113]

Intervention		Nefecon						
Trial		Nefigard Part A		NefIgArd- China Cohort		NEFIGAN		
Arm		Nefecon 16 mg	Placebo	Nefecon 16 mg	Placebo	Nefecon 8 mg	Nefecon 16 mg	Placebo
N		97	102	32	30	51	48	50
uARC								
Month 9	% Change from Baseline (95% CI)	NR	NR	-50 (-63, -34)	5 (-22, 42)	NR	NR	NR
	Difference vs. Placebo (95% CI); p-Value	0.69 (0.55, 0.86); 0.0005		53 (28, 69)		NR	NR	NR
	Ratio of Geometric LS Mean (95% CI)	0.64 (0.55, 0.75)	0.93 (0.8, 1.09)	NR	NR	0.8 (0.6, 1.1); p=0.08	0.7 (0.5, 0.9); p=0.005	REF
	Difference vs Placebo, % (95% CI); p-Value	31 (14, 45); p=0.0005		NR	NR	NR	-33 (NR); p<0.005	REF
Month 12	Geometric LS Mean vs. Placebo (95% CI); p-Value	NR	NR	NR	NR	0.7 (0.6, 0.9); p=0.0068	0.6 (0.5, 0.8); p=0.0004	REF
	Difference vs. Placebo, % (95% CI); p-Value	54 (40, 64); p<0.0001		NR	NR	NR	-38 (NR); p<0.0001	REF

CI: Confidence Interval, LS: Least Squares, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, REF: Reference, %: Percent

Table D3.18. NefIgArd, NefIgArd OLE, NefIgArd China Cohort, NEFIGAN Medication Changes[33,34,45,105,113]

Trial	NefIgArd		NefIgArd OLE		NefIgArd - China Cohort		NEFIGAN		
Arm	Nefecon 16 mg	Placebo	2nd Course of Nefecon	1st Course of Nefecon	Nefecon 16 mg	Placebo	Nefecon 8 mg	Nefecon 16 mg	Placebo
N	182	182	45	74	32	30	NR	NR	NR

Medication Changes											
Proportion of Patients who Received Rescue Medication	**By Month 9**	**n (%)**	7 (3.8)	5 (2.7)	NR	NR	1 (3.1)	2 (6.7)	NR	NR	NR
	By Month 12	**n (%)**	NR	NR	1 (2.2)	0 (0)	NR	NR	NR	NR	NR
	By Month 24	**n (%)**	15 (8.2)	20 (11)	NR	NR	3 (9.4)	10(33.3)	NR	NR	NR
		HR (95% CI); p-Value	0.68 (0.34, 1.33); p=0.26		NR	NR	0.22 (0.05, 0.72); NR		NR	NR	NR
Changes in CVD Medication	**Treat-ment Period**	**Any Change in CVD Medication, n (%)**	NR	NR	NR	NR	NR	NR	10 (19.6)	12 (24.5)	14 (28)
		Agents Acting on RAS, n (%)	NR	NR	NR	NR	NR	NR	5 (9.8)	5 (10.2)	7 (14.0)
		Diuretics, n (%)	NR	NR	NR	NR	NR	NR	2 (3.9)	5 (10.2)	3 (6.0)
Increase in ACEi or ARB Medication		**Increase in ACEi or ARB, n (%)**	NR	NR	NR	NR	NR	NR	2 (3.9)	0	3 (6.0)
		Decrease in ACEi or ARB, n (%)	NR	NR	NR	NR	NR	NR	1 (2.0)	3 (6.1)	2 (4.0)

ACEi: Angiotensin-Converting Enzyme Inhibitor. ARB: Angiotensin Receptor Blocker, CI: Confidence Interval, CVD: Cardiovascular Disease, HR: Hazard Ratio, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, RAS: Renin–Angiotensin System, %: Percent

Table D3.19. VISIONARY Subgroup Outcomes[24]

Trial			VISIONARY	
Arm			Sib 400 mg	Placebo
N			152	168
Ethnic Group	Hispanic or Latinx	% Change vs. Placebo (95% CI)	-49.3 (-65.9, -24.4)	
	Not Hispanic or Latinx	% Change vs. Placebo (95% CI)	-50.9 (-57.9, -42.7)	
Sex at Birth	Male	% Change vs. Placebo (95% CI)	-51.9 (-60.4, -41.6)	
	Female	% Change vs. Placebo (95% CI)	-50.3 (-59.8, -38.5)	
Age	≤40 yr	% Change vs. Placebo (95% CI)	-51.8 (-60.3, -41.5)	
	>40 yr	% Change vs. Placebo (95% CI)	-51.8 (-60.7, -40.9)	
Race	Asian	% Change vs. Placebo (95% CI)	-53.8 (-61.8, -44.2)	
	White	% Change vs. Placebo (95% CI)	-45.8 (-56.6, -32.4)	
Geographic Region	North America	% Change vs. Placebo (95% CI)	-25.6 (-48.6, 7.5)	
	South America	% Change vs. Placebo (95% CI)	-37.1 (-60.8, 1.2)	
	Europe	% Change vs. Placebo (95% CI)	-54.1 (-66.2, -37.7)	
	East Asia	% Change vs. Placebo (95% CI)	-56.5 (-66.7, -43.3)	
	South and Southeast Asia	% Change vs. Placebo (95% CI)	-56.5 (-67.6, -41.4)	
24-Hr uPCR Based on IRT Record	≤2.0 g/g	% Change vs. Placebo (95% CI)	-45.9 (-53.9, -36.6)	
	>2.0 g/g	% Change vs. Placebo (95% CI)	-64.7 (-74.4, -51.3)	
Estimated GFR Based on IRT Record	30-44 ml/min/1.73m^2	% Change vs. Placebo (95% CI)	-44.7 (-59.4, -24.5)	
	≥45 ml/min/1.73m^2	% Change vs. Placebo (95% CI)	-52.6 (-59.8, -44.2)	
Screening SGLT2i Based on IRT Record	No	% Change vs. Placebo (95% CI)	-50 (-59, -39.1)	
	Yes	% Change vs. Placebo (95% CI)	-52.9 (-61.8, -42)	

CI: Confidence Interval, GFR: Glomerular Filtration Rate, IRT: Interactive Response Technology, mL/min/1.73m^2: milliliter per minute per 1.73 meters squared, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, SGLT2i: Sodium-Glucose Cotransporter 2 Inhibitor, Sib: Sibeprenlimab, uPCR: Urine Protein-To-Creatinine Ratio, %: Percent

Table D3.20. ORIGIN 3 Subgroup Outcomes[29]

Intervention			Atacicept	
Trial			ORIGIN 3	
Arm			Atacicept	Placebo
N			106	97
Overall		Mean % Change	-45.7	-6.8
		Mean % Difference vs. Placebo (95% CI)	41.8 (28.9, 52.3)	
Age, Years	<40	Mean % Change	-44.5	0.5
		Mean % Difference vs. Placebo (95% CI)	44.7 (22.7, 60.4)	
	≥40	Mean % Change	-46.4	-14.1
		Mean % Difference vs. Placebo (95% CI)	37.6 (21.2, 50.6)	
Sex	Male	Mean % Change	-41.1	-9.3
		Mean % Difference vs. Placebo (95% CI)	35.1 (13.5, 51.2)	
	Female	Mean % Change	-50.8	-2.4
		Mean % Difference vs. Placebo (95% CI)	49.6 (33.7, 61.7)	
Region	Asia	Mean % Change	-49.5	-13.7
		Mean % Difference vs. Placebo (95% CI)	41.5 (18.1, 58.2)	
	Other	Mean % Change	-42.5	1.4
		Mean % Difference vs. Placebo (95% CI)	43.2 (29, 54.6)	
Race	White	Mean % Change	-42.4	0.1
		Mean % Difference vs. Placebo (95% CI)	42.5 (25.9, 55.4)	
	Non-White	Mean % Change	-48.4	-11.1
		Mean % Difference vs. Placebo (95% CI)	42 (22.1, 56.9)	
Baseline uPCR, g/g	<1.5	Mean % Change	-44	3.3
		Mean % Difference vs. Placebo (95% CI)	45.8 (27.7, 59.4)	
	≥1.5	Mean % Change	-48.5	-13.4
		Mean % Difference vs. Placebo (95% CI)	40.5 (21.2, 44.1)	
Baseline eGFR, mL/min/1.73m^2	<60	Mean % Change	-35.3	-1.3
		Mean % Difference vs. Placebo (95% CI)	34.5 (13.2, 50.5)	
	≥60	Mean % Change	-53	-14
		Mean % Difference vs. Placebo (95% CI)	45.3 (27, 59.1)	
SGLT2i Use at Baseline	Yes	Mean % Change	-48.2	-6.9

Intervention			Atacicept	
Trial			ORIGIN 3	
Arm			Atacicept	Placebo
N			106	97
		Mean % Difference vs. Placebo (95% CI)	44.4 (26.4, 57.9)	
	No	Mean % Change	-42.9	-5.9
		Mean % Difference vs. Placebo (95% CI)	39.3 (19.1, 54.4)	

CI: Confidence Interval, eGFR: Estimated Glomerular Filtration Rate, g: gram, mL/min/1.73m^2: Milliliter per minute per 1.73 meters squared, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, SGLT2i: Sodium-Glucose Cotransporter 2 Inhibitor, uPCR: Urine Protein-To-Creatinine Ratio, %: Percent

Table D3.21. NefIgArd & NefIgArd Part A Subgroup Outcomes[10,45,104]

Trial				NefIgArd - Part A FAS (Barratt 2023)		NefIgArd (Lafayette 2023)	
Arm				Nefecon 16 mg	Placebo	Nefecon 16 mg	Placebo
N				97	102	182	182
Mean Absolute Change in eGFR by Baseline uPCR (SE)	Month 9	Absolute Change from Baseline	<1.5 g/g	*0.37 (1.1)*	*-1.4 (1.1)*	*+2.0 (0.9)*	*-2.9 (1.0)*
			≥1.5 g/g	*-0.75 (1.5)*	*-8.3 (1.5)*	*-1.1 (0.9)*	*-7.8 (1.0)*
	Month 12	Absolute Change from Baseline	<1.5 g/g	*-1.5 (1.2)*	*-2.1 (1.1)*	*+0.04 (0.75)*	*-3.8 (1.0)*
			≥1.5 g/g	*-1.03 (1.8)*	*-9.9 (1.5)*	*-3.5 (1.6)*	*-9.8 (1.2)*
	Month 18	Absolute Change from Baseline	<1.5 g/g	NA	NA	*-2.2 (0.8)*	*-6.8 (1.4)*
			≥1.5 g/g	NA	NA	*-9.1 (2.0)*	*-16.3 (2.1)*
	Month 24	Absolute Change from Baseline	<1.5 g/g	NA	NA	*-2.6 (1.0)*	*-8.4 (1.5)*
			≥1.5 g/g	NA	NA	*-12.1 (2.0)*	*-18.9 (1.7)*

eGFR: estimated glomerular filtration rate, N: Total Number, NA: Not Applicable, NR: Not Reported, SE: Standard Error, uPCR: urine protein to creatinine ratio

Table D3.21. Note: Italicized data has been digitized or calculated

Table D3.22. NefIgArd Part A & NefIgArd Subgroup Outcomes[10,45]

Intervention		Nefecon											
Trial		NefIgArd - Part A								NefIgArd - Part B Full Results			
Arm(s)		n	Nefecon 16 mg	Placebo	Ratio (95% CI)	n	Nefecon 16 mg	Placebo	Ratio (95% CI)	n	Nefecon 16 mg	Placebo	Difference (95% CI)
Outcome		uPCR at 9 Months				eGFR at 9 Months				Time-Weighted Average of eGFR Over 2 Years			
Overall		199	0.69	0.95	0.74 (0.61, 0.87)	199	1	0.93	1.07 (1.03, 1.13)	364	-2.47	-7.52	5.05 (3.24, 7.38)
Age	<45	108	0.7	0.96	0.72 (0.57, 0.92)	108	0.98	0.92	1.07 (1.00, 1.14)	202	-3.68	-8.87	5.19 (2.69, 8.3)
	≥45 - <65	83	0.73	0.94	0.78 (0.59, 1.02)	83	1.05	0.94	1.11 (1.03, 1.19)	151	-0.58	-5.98	5.4 (2.32, 9.13)
Sex	Male	135	0.73	1.01	0.72 (0.58, 0.9)	135	1.03	0.92	1.12 (1.06, 1.19)	240	-1.75	-7.30	5.58 (3.3, 8.45)
	Female	64	0.61	0.85	0.72 (0.53, 0.98)	64	0.92	0.94	0.98 (0.9, 1.07)	124	-3.70	-7.90	4.2 (0.85, 8.17)
Region	North America	42	0.76	0.92	0.82 (0.55, 1.21)	42	1.05	1.01	1.04 (0.93, 1.16)	73	-0.78	-6.32	5.54 (1.15, 10.79)
	Europe	122	0.65	0.97	0.67 (0.54, 0.84)	122	0.97	0.9	1.07 (1.01, 1.14)	197	-2.5	-8.11	5.61 (3.03, 8.84)
	Asia Pacific	NR	NR	NR	NR	NR	NR	NR	NR	76	-4.56	-6.6	2.05 (-2.31, 6.98)
Baseline uPCR	<1.5 g/g	126	0.72	0.93	0.78 (0.62, 0.97)	126	1	0.97	1.03 (0.97, 1.09)	235	-0.59	-5.22	4.63 (2.26, 7.5)
	≥1.5 g/g	73	0.64	0.98	0.65 (0.49, 0.88)	73	0.99	0.84	1.17 (1.08, 1.27)	129	-6.03	-12.63	6.59 (3.59, 10.46)
	<2 g/24h	82	0.62	0.9	0.69 (0.53, 0.91)	82	1.01	0.98	1.03 (0.96, 1.11)	157	0.55	-4.68	5.23

Intervention		Nefecon											
Trial		NefIgArd - Part A								NefIgArd - Part B Full Results			
Arm(s)		n	Nefecon 16 mg	Placebo	Ratio (95% CI)	n	Nefecon 16 mg	Placebo	Ratio (95% CI)	n	Nefecon 16 mg	Placebo	Difference (95% CI)
Outcome		uPCR at 9 Months				eGFR at 9 Months				Time-Weighted Average of eGFR Over 2 Years			
Baseline Mprotein-uria													(2.23, 8.85)
	≥2 g/24h	117	0.74	0.98	0.76 (0.6, 0.95)	117	0.99	0.89	1.11 (1.05, 1.19)	207	-4.89	-9.92	5.03 (2.5, 8.16)
Baseline eGFR	<60 ml/min per 1.73m^2	124	0.72	1	0.72 (0.58, 0.9)	124	0.98	0.92	1.06 (1.00, 1.13)	218	-3.55	-9.12	5.56 (3.21, 8.54)
	≥60 ml/min per 1.73m^2	75	0.64	0.89	0.72 (0.54, 0.96)	75	1.02	0.93	1.10 (1.01, 1.19)	146	-0.88	-5.06	4.18 (1.08, 7.82)
Dose of RASi	<50% of MAD	42	0.57	0.91	0.62 (0.42, 0.93)	42	0.95	0.94	1.01 (0.91, 1.13)	73	-0.64	-8.89	8.25 (3.68, 14.01)
	≥50 - 80% of MAD	55	0.7	0.99	0.71 (0.5, 1.0)	55	1.03	0.9	1.15 (1.05, 1.26)	89	-2.68	-7.82	5.14 (1.11, 9.98)
	≥80% of MAD	99	0.74	0.94	0.78 (0.61, 1.01)	99	1.01	0.95	1.06 (0.99, 1.13)	197	-3.4	-6.73	3.33 (0.71, 6.38)
Race	White	NR	NR	NR	NR	NR	NR	NR	NR	275	-2.34	-7.13	4.79 (2.64, 7.44)
	Other	NR	NR	NR	NR	NR	NR	NR	NR	89	-2.89	-8.33	5.44 (1.53, 10.16)
Baseline Hematuri-a	Presenc-e	NR	NR	NR	NR	NR	NR	NR	NR	250	-2.75	-8.56	5.81 (3.56, 8.7)
	Absence	NR	NR	NR	NR	NR	NR	NR	NR	114	-7	-5.26	3.21

Intervention		Nefecon											
Trial		NefIgArd - Part A								NefIgArd - Part B Full Results			
Arm(s)		n	Nefecon 16 mg	Placebo	Ratio (95% CI)	n	Nefecon 16 mg	Placebo	Ratio (95% CI)	n	Nefecon 16 mg	Placebo	Difference (95% CI)
Outcome		uPCR at 9 Months				eGFR at 9 Months				Time-Weighted Average of eGFR Over 2 Years			
													(-0.19, 7.11)

CI: Confidence Interval, eGFR: Estimated Glomerular Filtration Rate, mL/min/1.73m2: Milliliter per minute per 1.73 meters squared, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, RASi: Renin-Angiotensin System inhibitor, uPCR: Urine Protein-To-Creatinine Ratio, %: Percent

Table D3.23. NefIgArd Subgroup Outcomes [114,115]

TR-Budesonide								
NefIgArd (Barratt 2024)								
Ratio of AUC Over 2 Years of Time-Weighted Averages Compared with Baseline of eGFR								
	uPCR <0.8 g/g (N=72)		uPCR ≥0.8 g/g (N=72)		Asian (n=83)		White (n=275)	
	Nefecon (n=36)	Placebo (n=36)	Nefecon (n=146)	Placebo (n=146)	Nefecon (n=43)	Placebo (n=30)	Nefecon (n=138)	Placebo (n=137)
Baseline eGFR, Geometric Mean, mL/min/1.73m² (IQR)	54.1 (45.7, 62.6)	57.2 (44.1, 71.1)	56.5 (45.5, 72.0)	55.2 (46.0, 66.5)	56.8	54.2	55.8	55.8
Baseline eGFR, Geometric Mean, mL/min/1.73m² (SD)	NR	NR	NR	NR	59.4 (17.6)	56.0 (14.6)	57.8 (15.4)	57.8 (15.4)
Baseline uPCR Geometric Mean, g/g (IQR)	0.67 (0.62, 0.73)	0.63 (0.56, 0.72)	1.53 (1.11, 1.97)	1.5 (1.06, 1.85)	1.46 (0.77)	1.39 (0.77)	1.5 (0.88)	1.52 (1.26)
Baseline Proteinuria Geometric Mean, g/24 hr (IQR)	1.45 (1.21, 1.65)	1.46 (1.26, 1.69)	2.66 (1.91, 3.32)	2.6 (1.87, 3.62)	NR	NR	NR	NR
Weighted Average/Baseline Value								
Geometric LS Mean (95% CI)	1.02 (0.98, 1.06)	0.94 (0.91, 0.98)	0.94 (0.91, 0.97)	0.84 (0.82, 0.87)	0.95 (0.89, 1.01)	0.85 (0.8, 0.9)	0.96 (0.93, 0.99)	0.87 (0.84, 0.9)
Ratio of Geometric LS Mean vs. Placebo (95% CI)	1.08 (1.02, 1.15); one sided p=0.002		1.11 (1.06, 1.16); one sided p<0.0001		1.12 (1.03, 1.21); p=0.008		1.10 (1.05, 1.15); p<0.0001	
Estimated Absolute Change in eGFR from Baseline Over 2 Years mL/min/1.73m² (95% CI)	1.2 (-1, 3.6)	-5.7 (-5.2, -1.1)	-3.6 (-5.2, -1.9)	-8.7 (-10.3, -7.1)	-2.9	-8.37	-2.37	-7.17

TR-Budesonide								
NefIgArd (Barratt 2024)								
Ratio of AUC Over 2 Years of Time-Weighted Averages Compared with Baseline of eGFR								
	uPCR <0.8 g/g (N=72)		uPCR ≥0.8 g/g (N=72)		Asian (n=83)		White (n=275)	
	Nefecon (n=36)	Placebo (n=36)	Nefecon (n=146)	Placebo (n=146)	Nefecon (n=43)	Placebo (n=30)	Nefecon (n=138)	Placebo (n=137)
Estimated Absolute Change in eGFR vs. Placebo, mL/min/1.73m^2	4.4		5.1		5.47		4.8	
Month 9/Baseline Value								
Geometric LS Mean (95% CI)	NR	NR	NR	NR	0.76 (0.63, 0.92)	1.00 (0.83, 1.2)	0.64 (0.57, 0.71)	0.94 (0.83, 1.05)
Ratio of Geometric LS Mean vs. Placebo (95% CI); p-Value	NR	NR	NR	NR	0.77 (0.59, 1.00); p=0.047		0.68 (0.58, 0.8); p<0.0001	
Month 24/Baseline Value								
Geometric LS Mean (95% CI)	NR	NR	NR	NR	0.76 (0.58, 0.98)	1.03 (0.79, 1.35)	0.66 (0.57, 0.77)	0.98 (0.84, 1.13)
Ratio of Geometric LS Mean vs. Placebo (95% CI)	NR	NR	NR	NR	0.73 (0.5, 1.06); p=0.1		0.68 (0.55, 0.84); p=0.0003	
Time to Confirmed 30% Reduction in eGFR or Kidney Failure Event, HR (95% CI); p-Value	NR	NR	NR	NR	0.32 (0.09, 0.91); p=0.02		0.48 (0.28, 0.83); p=0.004	

CI: Confidence Interval, eGFR: Estimated Glomerular Filtration Rate, IQR: Interquartile Range, LS: Least Squares, mL/min/1.73m^2: Milliliter per minute per 1.73 meters squared, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, uPCR: Urine Protein-To-Creatinine Ratio, %: Percent

Table D3.24. NefIgArd Part B & NefIgArd OLE SF-36 Outcomes[58,105]

Intervention			TR-Budesonide							
Trial			NefIgArd Part B						NefIgArd OLE	
Outcome Timepoint			Baseline Score		Score at Month 9		Score at Month 24		CFB (SD) at Month 12	
Arms			Nefecon 16mg	Placebo	Nefecon 16mg	Placebo	Nefecon 16 mg	Placebo	2nd Course of Nefecon	1st Course of Nefecon
N			177	176	170	170	159	164	44	70
SF-36	Bodily Pain	Median (IQR)	55.6 (50.7, 62.0)	62 (51.1, 62.0)	55.6 (50.7, 62.0)	62 (50.7, 62.0)	55.6 (46.7, 62.0)	55.6 (46.7, 62.0)	-4.5 (10.1)	-3.8 (9.9)
	General Health	Median (IQR)	46.1 (40.4, 53.2)	48.4 (41.3, 55.6)	46.1 (41.3, 53.2)	48.4 (40.4, 55.6)	48.4 (38.9, 54.6)	48.4 (38.9, 53.2)	-4.3 (7.4)	-3.3 (5.8)
	Mental Component Summary	Median (IQR)	53.4 (47.6, 57.3)	53.1 (48.1, 57.8)	51.1 (45.2, 56.6)	50.8 (44.9. 56.2)	52.7 (47, 57.6)	52.5 (44.4, 56.9)	-2.3 (7.1)	-1.1 (6.6)
	Mental Health	Median (IQR)	53.5 (45.6, 56.1)	50.9 (45.6, 56.7)	50.9 (43, 56.1)	50.9 (45.6, 56.1)	53.5 (45.6, 58.7)	53.5 (45.7, 58.7)	-1.7 (7.2)	-1.6 (6.4)
	Physical Component Summary	Median (IQR)	53.8 (48.3, 57.2)	55.1 (49.9, 58.3)	54.3 (48.9, 57.5)	55.6 (50.6, 58.3)	53.7 (47.4, 57)	53.5 (47.5, 57.6)	-3.9 (6.6)	-3.4 (6.1)
	Physical Functioning	Median (IQR)	55.6 (51.8, 57.5)	55.6 (53.7, 57.5)	55.6 (51.8, 57.5)	55.6 (53.7, 57.5)	55.6 (51.8, 57.5)	55.6 (50.8, 57.5)	-2.6 (7.5)	-1.9 (6.7)
	Role Emotional	Median (IQR)	56.2 (49.2, 56.2)	56.2 (49.2, 56.2)	52.7 (45.7, 56.2)	56.2 (45.7, 56.2)	56.2 (45.7, 56.2)	56.2 (45.7, 56.2)	-2.9 (7.2)	-0.7 (7.5)
	Role Physical	Median (IQR)	57.2 (48.2, 57.2)	57.2 (50.4, 57.2)	54.9 (45.9, 57.2)	57.2 (50.4, 57.2)	54.9 (48.2, 57.2)	56 (45.9, 57.2)	-3.4 (7.2)	-2.7 (7.7)
	Social Function	Median (IQR)	57.3 (52.3, 57.3)	57.3 (47.3, 57.3)	57.3 (47.3, 57.3)	57.3 (47.3, 57.3)	57.3 (47.3, 57.3)	57.3 (47.3, 57.3)	-3.4 (7.2)	-2.3 (6.4)
	Vitality	Median (IQR)	52.6 (49.6, 58.5)	55.6 (49.6, 61.5)	52.6 (46.7, 58.5)	55.6 (46.7, 58.5)	55.6 (46.7, 61.5)	52.6 (46.7, 58.5)	-4.1 (8.5)	-2.4 (7.7)

CFB: Change from baseline, IQR: Interquartile Range, N: Total number, SD: Standard Deviation, SF-36: 36-Item Short Form Health Survey

Table D3.25. TESTING Subgroup [101,116]

Intervention			Oral Methylprednisolone			
Trial			TESTING			
Overall Cohort						
			n/N (%)	n/N (%)	Hazard Ratio (95% CI)	P-Value
Primary Composite Outcome*	Overall		74 / 257 (29)	106 / 246 (43)	0.53 (0.39, 0.72)	
	Sex	Female	26 / 102 (25)	30 / 96 (31)	0.64 (0.38, 1.09)	0.47
		Male	48 / 155 (31)	76 / 150 (51)	0.51 (0.35, 0.74)	REF
		Male v. Female	NR	NR	1.44 (1.05, 1.94)	Unadjusted p=0.03
	Proteinuria, g/day	1 - <1.5	12 / 74 (16)	24 / 63 (38)	0.37 (0.18, 0.75)	0.53†
		1.5 - <3	30 / 118 (25)	44 / 122 (36)	0.52 (0.33, 0.84)	REF
		≥3	32 / 65 (49)	38 / 61 (62)	0.6 (0.37, 0.98)	REF
	eGFR, mL/min/1.73m^2	60 - 120	19 / 109 (17)	31 / 119 (26)	0.57 (0.32, 1.01)	0.68†
		45 - <60	19 / 73 (26)	29 / 54 (54)	0.4 (0.23, 0.73)	REF
		30 - <45	29 / 65 (44)	31 / 58 (53)	0.6 (0.36, 1.01)	REF
		20 - <30	7 / 10 (70)	15 / 15 (100)	0.77 (0.31, 1.94)	REF
Kidney Failure	Sex	Female	17 / 102 (17)	17 / 96 (18)	0.72 (0.35, 1.48)	0.51
		Male	33 / 155 (21)	50 / 150 (33)	0.54 (0.33, 0.87)	REF
Total Annual eGFR Slope, mL/min/1.73m^2 per Year (95% CI)			Slope (95% CI)	Slope (95% CI)	Difference (95% CI)	P-value
	Proteinuria, g/day	1 - <1.5	3.19 (0.4, 5.98)	-1.26 (-4.17, 1.64)	4.45 (0.42, 8.48)	0.53
		1.5 - <3	0.68 (-1.49, 2.84)	-3.29 (-5.43, -1.15)	3.97 (0.92, 7.01)	NR
		≥3	-5.05 (-7.99, -2.10)	-6.45 (-9.45, -3.45)	1.4 (-2.8, 5.61)	NR
	eGFR, mL/min/1.73m^2	60 - 120	0.87 (-1.28, 3.01)	-2.63 (-4.62, -0.64)	3.5 (0.57, 6.42)	NR
		45 - <60	-1.01 (-3.68, 1.65)	-3.64 (-6.76, -0.51)	2.62 (-1.48, 6.73)	NR
		30 - <45	0.03 (-2.72, 2.79)	-3.8 (-6.6, -0.99)	3.83 (-0.10, 7.76)	NR
		20 - <30	-3.88 (-10.30, 2.54)	-3.87 (-10.52, 2.77)	-0.01 (-9.24, 9.23)	0.88

Relative Change in Proteinuria, % (95% CI)			**Relative Change, % (95% CI)**	**Relative Change, % (95% CI)**	**Difference (95% CI)**	**P-Value**
	Proteinuria, g/day	**1 - <1.5**	-70.2 (-76.9, -6.4)	-25.1 (-42.7, -2.0)	-60.2 (-70.6, -46.1)	0.14
		1.5 - <3	-61.2 (-67.0, -54.3)	-15.4 (-28.6, 0.3)	-54.1 (-63.6, -42.3)	NR
		≥3	-56.5 (-67.4, -41.9)	-13.5 (-35.6, 16.3)	-49.7 (-63.4, -30.8)	NR
	eGFR, mL/min/1.73m^2	**60 - 120**	-64.3 (-71.1, -55.9)	-23.6 (-38.2, -5.7)	-53.2 (-63.2, -40.6)	NR
		45 - <60	-63.2 (-70.3, -54.4)	-15.7 (-33.8, 7.3)	-56.3 (-68.1, -40.1)	NR
		30 - <45	-63.4 (-71.6, -52.9)	-6.4 (-28.2, 22.2)	-60.9 (-71.5, -46.3)	NR
		20 - <30	-40.8 (-67.3, 7.4)	-31.4 (-58.2, 12.7)	-13.7 (-59.4, 83.5)	0.67
Full-Dose Cohort						
			n/N (%)	**n/N (%)**	**Hazard Ratio (95% CI)**	**P-Value**
Primary Composite Outcome	**Sex**	**Female**	24 / 50 (48)	24 / 46 (52)	0.74 (0.42, 1.31)	0.4
		Male	43 / 86 (50)	60 / 80 (75)	0.55 (0.37, 0.82)	REF
Kidney Failure	**Sex**	**Female**	16 / 50 (32)	13 / 46 (28)	0.92 (0.42, 2.02)	0.29
		Male	31 / 86 (36)	44 / 80 (55)	0.55 (0.36, 0.91)	REF
Reduced-dose Cohort						
			n/N (%)	**n/N (%)**	**Hazard Ratio (95% CI)**	**P-Value**
Primary Composite Outcome	**Sex**	**Female**	2 / 52 (4)	6 / 50 (12)	0.2 (0.03, 1.14)	0.84
		Male	5 / 69 (7)	16 / 70 (23)	0.24 (0.08, 0.71)	REF
Kidney Failure	**Sex**	**Female**	1 / 52 (2)	4 / 50 (8)	0.02 (0.00, 0.36)	0.06
		Male	2 / 69 (3)	6 / 70 (9)	0.5 (0.09, 2.9)	REF

CI: Confidence Interval, eGFR: estimated glomerular filtration rate, mL/min/1.73m^2: Milliliter per minute per 1.73 meters squared, n: number, N: Total Number, NR: Not Reported, %: Percent

*40% decline in eGFR, kidney failure, or death due to kidney disease

†Outcome fitted as categorical variable. Interaction p-value between subgroups and treatment were calculated with a likelihood ratio test

Table D3.26. TESTING Total Annual eGFR Slope Subgroup[101]

Oral Methylprednisolone				
TESTING				
Total Annual eGFR Slope, mL/min/1.73m^2 per Year (95% CI)				
	Male	**Female**	**Difference**	**P-Value**
Overall Cohort	-3.08 (-4.5, -1.67)	0.05 (-1.65, 1.75)	3.13 (0.92, 5.34)	0.006
Full-Dose	-4.51 (-6.34, -2.68)	-2.28 (-4.63, 0.06)	2.23 (-0.75, 5.2)	0.14
Reduced-Dose	-1.67 (-3.79, 0.45)	1.79 (-0.6, 4.18)	3.46 (0.26, 6.66)	0.03

CI: Confidence Interval, eGFR: estimated glomerular filtration rate, mL/min/1.73m^2: Milliliter per minute per 1.73 meters squared, %: Percent

Table D3.27. VISIONARY & ENVISION Biomarker[8,24]

Intervention			**Sibeprenlimab**					
Trial			**VISIONARY**		**ENVISION**			
Arm			**Sib**	**Placebo**	**Sib 2 mg/kg**	**Sib 4 mg/kg**	**Sib 8 mg/kg**	**Placebo**
N			**152**	**168**	**38**	**41**	**38**	**38**
Gd-IgA1	**Week 48**	**CFB, (95% CI)**	67.1 (62.8, 71.3)	*1.03 (-4.14, 6.64)*	NA	NA	NA	NA
	Month 16	**Mean % of Baseline Level (SD)**	NA	NA	*93.9 (67.6, 120.6)*	*96.2 (69.2, 123.3)*	*82.7 (56.0, 110.1)*	*126.8 (92.8, 160.8)*
IgA, g/L	**Week 48**	**CFB, (95% CI)**	68.8 (67.2, 70.5)	NA	NA	NA	NA	NA
	Day 420	**Geometric Mean (95% CI)**	NA	NA	*2.42 (2.13, 2.72)*	*1.73 (1.43, 2.02)*	*1.13 (0.93, 1.32)*	*3.13 (2.83, 3.53)*
IgG, g/L	**Week 48**	**CFB, (95% CI)**	35 (32.8, 37.3)	NA	NA	NA	NA	NA
	Day 420	**Geometric Mean (95% CI)**	NA	NA	*10.5 (9.49, 11.59)*	*9 (8.2, 9.82)*	*6.86 (6.21, 7.71)*	*11.54 (10.72, 12.71)*
IgM, g/L	**Week 48**	**CFB, (95% CI)**	74.5 (73.1, 75.9)	NA	NA	NA	NA	NA
	Day 420	**Geometric Mean (95% CI)**	NA	NA	*0.7 (NR, 0.9)*	*0.5 (NR, 0.6)*	*0.29 (0.2, NR)*	*1 (0.8, 1.2)*
APRIL, pg/mL	**Week 48**	**CFB, (95% CI)**	95.8 (93.9, 97.7)	*25.56 (12.23, 38.34)*	NA	NA	NA	NA

Intervention			Sibeprenlimab					
Trial			VISIONARY		ENVISION			
Arm			Sib	Placebo	Sib 2 mg/kg	Sib 4 mg/kg	Sib 8 mg/kg	Placebo
N			152	168	38	41	38	38
	Month 16	Mean (SD)	NA	NA	*3807.5 (2221.3, 5435.1)*	*4118.7 (2471.2, 5752.2)*	*3655.43 (2082.4, 5183.5)*	*4232.9 (2342.5, 6164.4)*

CFB: Change from baseline, CI: Confidence Interval, mg/kg: milligrams per kilogram, mL/min/1.73m^2: Milliliter per minute per 1.73 meters squared, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, SD: Standard Deviation, Sib: Sibeprenlimab, %: Percent

Table D3.27. Note: Italicized data has been digitized or calculated

Table D3.28. ORIGIN 3 Biomarker[29]

Intervention			Atacicept	
Trial			ORIGIN 3	
Arm			Atacicept	Placebo
N			106	97
Gd-IgA1	Month 9	% CFB	-68.3	-6.8
		% Difference vs. Placebo (95% CI)	67.4 (63.8, 70.6)	
IgG	Month 9	% CFB	-35.5	-2.9
IgA	Month 9	% CFB	-63.5	
IgM	Month 9	% CFB	-74.6	-8.8

CFB: Change from baseline, CI: Confidence Interval, N: Total Number, %: Percent

Table D3.29. ORIGIN, ORIGIN OLE, JANUS Biomarker[9,30,31,56,110]

Intervention		Atacicept								
Trial		ORIGIN					ORIGIN OLE	JANUS		
Arm		Ata 25	Ata 75	Ata 150	Combined Ata*	Placebo	Ata 150	Ata 25	Ata 75	Placebo
N		16	33	33	66	34	112†	6	5	5
Gd-IgA1										
Month 9	Mean % CFB, (SE)	-35	-59 *(NR, -58.96)*	-64 *(-65.83, NR)*	-62.51 *(-64.15, -60.87)*	-7 *(-12.11, -0.76)*	NR	NR	NR	NR
	Difference vs. Placebo, % (95% CI)	35 (19.99, 47.18)	NR	NR	NR	NR	NR	NR	NR	NR
	Mean % CFB	-39	NR	NR	NR	NR	NR	NR	NR	NR
Week 72	Absolute Levels (ng/mL), Median (Q1, Q3)	NR	NR	NR	NR	NR	NR	5120 (3570, 7750)	1700 (843, 3750)	10200 (6670, 11300)
	% CFB	NR	NR	NR	NR	NR	NR	-14 (-33, -5)	-61 (-70, -57)	19 (-19,54)
Week 96	Mean % CFB, (SE)	NR	NR	NR	NR	NR	*-65.9 (2)*	NR	NR	NR
Week 96 + 26	Mean % CFB, (SE)	NR	NR	NR	NR	NR	117 *(107, 126)*	NR	NR	NR
IgA, g/L										
Month 9	Mean % CFB, (SE)	-32 *(4.2)*	-54 *(2.1)*	-63 *(1.5)*	NR	-4 *(4.1)*	NR	NR	NR	NR
Week 72	Absolute Levels (ng/mL), Median (Q1, Q3)	NR	NR	NR	NR	NR	NR	3.2 (2.9, 4.1)	1.5 (0.8, 1.6)	3.4 (2.4,5.1)
	% CFB	NR	NR	NR	NR	NR	NR	-21.3 (-24.9, -19.6)	-50.3 (-62.4, -33.63)	10.2 (-1.2, 38.1)
Week 96	Mean % CFB, (SE)	NR	NR	NR	NR	NR	*-69.96*	NR	NR	NR
IgG, g/L										
Month 9	Mean % CFB, (SE)	-14 *(3.4)*	-32 *(2.1)*	-37 *(1.8)*	NR	0 *(2.9)*	NR	NR	NR	NR
Week 72	Absolute Levels (ng/mL), Median (Q1, Q3)	NR	NR	NR	NR	NR	NR	8.3 (7.7, 11.4)	6.2 (5.8, 8.6)	9 (9, 12.9)

Intervention		Atacicept								
Trial		ORIGIN					ORIGIN OLE	JANUS		
Arm		Ata 25	Ata 75	Ata 150	Combined Ata*	Placebo	Ata 150	Ata 25	Ata 75	Placebo
N		16	33	33	66	34	112†	6	5	5
	% CFB	NR	NR	NR	NR	NR	NR	-9.5 (-14.8, 0.3)	-38.1 (-41.6, -22.5)	2.3 (-11.8, 11.3)
Week 96	Mean % CFB, (SE)	NR	NR	NR	NR	NR	*-43.32*	NR	NR	NR
IgM, g/L										
Month 9	Mean % CFB, (SE)	-59 *(3.5)*	-70 *(1.5*)	-73 *(1.3)*	NR	-3 *(5.6)*	NR	NR	NR	NR
Week 72	Absolute Levels (ng/mL), Median (Q1, Q3)	NR	NR	NR	NR	NR	NR	0.2 (0.2, 0.3)	0.2 (0.2, 0.4)	1 (0.8, 1.7)
	% CFB	NR	NR	NR	NR	NR	NR	-50 (-67.7, -39.4)	-77.5 (-84.3, -71.3)	-3.4 (-4, -0.6)
Week 96	Mean % CFB, (SE)	NR	NR	NR	NR	NR	*-73.68*	NR	NR	NR
IgA-IgG										
Week 72	Mean CFB, %	NR	NR	NR	NR	NR	NR	-29	-26	-13

Ata: Atacicept, CFB: Change from baseline, CI: Confidence Interval, n: number, N: Total Number, NA: Not Applicable, ng/mL: nanograms per milliliter, NR: Not Reported, SE: Standard Error, %: Percent

*Combined atacicept dose of 75mg and 150mg

†All patients receiving atacicept dose at any timepoint

Table D3.29 Note: Italicized data has been digitized or calculated

Table D3.30. VISIONARY & ENVISION Safety [8,24-26,108]

Intervention		Sibeprenlimab					
Trial		VISIONARY		ENVISION			
Arm		Sib 400 mg	Placebo	Sib 2 mg/kg	Sib 4 mg/kg	Sib 8 mg/kg	Placebo
N		259	251	38	41	38	38
Treatment-Emergent Adverse Event (TEAE)	Any TEAE, n (%)	192 (74.1)	206 (82.1)	28 (73.7)	33 (80.5)	31 (81.6)	27 (71.1)
	Treatment-Related AE, n (%)	75 (29)	67 (26.7)	7 (18.4)	7 (17.1)	4 (10.5)	5 (13.2)
	TEAE Leading to Discontinuation, n (%)	1 (0.4)	4 (1.6)	1 (2.6)	0	0	0
	Mild TEAE, n (%)	NR		19 (50)	22 (53.7)	22 (57.9)	23 (60.5)
	Moderate TEAE. N (%)	NR		7 (18.4)	9 (22.0)	8 (21.1)	3 (7.9)
	Serious TEAE, n (%)	9 (3.5)	11 (4.4)	2 (5.3)	2 (4.9)	1 (2.6)	2 (5.3)
	Serious Treatment-Related AE, n (%)	1 (0.4)		NR	NR	NR	NR
	Severe TEAE, n (%)	4 (1.5)	8 (3.2)	2 (5.3)	2 (4.9)	1 (2.6)	1 (2.6)
	TEAE leading to Death, n (%)	0		0	0	0	1 (2.6)
	Infection, n (%)	6 (1.2)		NR	NR	NR	NR
All-cause mortality, n (%)		0		0	0	0	1 (2.6)
Most Common TEAEs (≥5%) by Treatment Group, n (%)	Abdominal Pain	NR		NR	1 (2.4)	0	0
	Arthralgia	NR		NR	2 (4.9)	0	0
	Back Pain	17 (6.6)	14 (5.6)	NR	2 (4.9)	1 (2.6)	0
	Covid-19	25 (9.7)	17 (6.8)	11 (28.9)	11 (26.8)	13 (34.2)	16 (42.1)
	Cough	NR		NR	2 (4.9)	0	0
	Dermatitis	NR		NR	1 (2.4)	0	0
	Diarrhea	NR		0	4 (9.8)	2 (5.3)	1 (2.6)
	Dyspepsia	NR		NR	1 (2.4)	1 (2.6)	1 (2.6)
	Dyspnea	NR		NR	0	0	0
	Face Oedema (Swelling)	NR		NR	0	1 (2.6)	1 (2.6)
	Fatigue	NR		NR	2 (4.9)	0	0
	Gout	NR		NR	1 (2.4)	0	0
	Headache	NR		1 (2.6)	5 (12.2)	3 (7.9)	4 (10.5)

Intervention		Sibeprenlimab					
Trial		VISIONARY		ENVISION			
Arm		Sib 400 mg	Placebo	Sib 2 mg/kg	Sib 4 mg/kg	Sib 8 mg/kg	Placebo
N		259	251	38	41	38	38
	Hypertension	NR		4 (10.5)	3 (7.3)	0.0	1 (2.6)
	Influenza	21 (8.1)	16 (6.4)	NR	1 (2.4)	1 (2.6)	0
	Injection Site Erythema	34 (13.1)	30 (12)	NR	NR	NR	NR
	Injection Site Pain	26 (10)	23 (9.2)	NR	1 (2.4)	0	0
	Injection Site Induration	NR		NR	0	0	0
	Injection Site swelling	16 (6.2)	13 (5.2)	NR	NR	NR	NR
	Insomnia	NR		NR	2 (4.9)	0	1 (2.6)
	Muscle Spasm	NR		1 (2.6)	4 (9.8)	1 (2.6)	1 (2.6)
	Nasopharyngitis	32 (12.4)	25 (10)	4 (10.5)	5 (12.2)	6 (15.8)	3 (7.9)
	Nausea	NR		NR	2 (4.9)	0	1 (2.6)
	Peripheral Edema	2 (1.3)	12 (7.1)	NR	2 (4.9)	0	1 (2.6)
	Pyrexia	14 (5.4)	10 (4)	5 (13.2)	5 (12.2)	6 (15.8)	6 (15.8)
	Rash	NR		NR	2 (4.9)	1 (2.6)	0
	Tonsillitis	NR		NR	0	1 (2.6)	0
	Upper Respiratory Tract Infection	38 (14.7)	35 (13.9)	3 (7.9)	5 (12.2)	2 (5.3)	0.0
	Urinary Tract Infection	NR		NR	0	0	2 (5.3)
	Viral Infection	NR		NR	1 (2.4)	0	0
Adverse Events of Special Interest	AEs Related to Infections and Infestations System Organ Class	NR		15 (39.5)	23 (56.1)	20 (52.6)	21 (55.3)
	New Onset of Diabetes	NR		NR	1 (2.4)	0	0

AE: Adverse event, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, TEAE: Treatment Emergent Adverse Event, %: Percent

Table D3.31. ORIGIN 3 Safety[29]

Intervention		Atacicept	
Trial		ORIGIN 3	
Arm		Atacicept	Placebo
N		214	214
Patients with any Adverse Events		127 (59.3)	107 (50.0)
Adverse Events in >5% of Patients in Either Treatment	Injection Site Reaction	41 (19.2)	4 (1.9)
	Upper Respiratory Tract Infection	26 (12.1)	19 (8.9)
	Nasopharyngitis	17 (7.9)	13 (6.1)
	Injection Site Erythema	12 (5.6)	1 (0.5)
Any Adverse Event by Severity	Mild	90 (42.1)	74 (34.6)
	Moderate	34 (15.9)	24 (11.2)
	Severe	3 (1.4)	9 (4.2)
Any Study Drug Related Adverse Event by Severity		63 (29.4)	22 (10.3)
Mild		55 (25.7)	15 (7.0)
Moderate		8 (3.7)	5 (2.3)
Severe		0	2 (0.9)
Any Serious Adverse Events		1 (0.5)*	11 (5.1)
Any Adverse Events of Infections and Infestations by Severity		68 (31.8)	60 (28.0)
Mild		55 (25.7)	48 (22.4)
Moderate		13 (6.1)	10 (4.7)
Severe		0	2 (0.9)
Any Adverse Events Associated with Injection Site Reactions by Severity		62 (29.0)	11 (5.1)
Mild		56 (26.2)	10 (4.7)
Moderate		6 (2.8)	1 (0.5)
Severe		0	
Any Study Drug Related Adverse Events Associated with Injection Site Reactions		51 (23.8)	11 (5.1)
Any Adverse Events Leading to Study Drug Interruption		5 (2.3)	5 (2.3)
Any Adverse Events Leading to Study Drug Discontinuation		2 (0.9)	8 (3.7)
Any Adverse Events Leading to Death		0	

n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, %: Percent

* Unrelated to treatment, event of cholecystitis

Table D3.32. ORIGIN, ORIGIN OLE, JANUS Safety[9,30,31,105,117]

Intervention		Atacicept								
Trial		ORIGIN					ORIGIN OLE	JANUS		
Arm		Ata 25 mg	Ata 75 mg	Ata 150 mg	Combined Ata[†]	Placebo	Ata 150 mg[*]	Ata 25 mg	Ata 75 mg	Placebo
N		16	33	33	66	34	113	6	5	5
Treatment-Emergent Adverse Event (TEAE), n (%)	Any TEAE	11 (69)	24 (73)	25 (76)	49 (74)	27 (79)	85 (77)	6 (100)	3 (60)	5 (100)
	Treatment-Related TEAE	6 (38)	17 (52)	19 (58)	36 (55)	14 (41)	52 (47)	5 (83)	3 (60)	1 (20)
	During the Treatment Period	NR	NR	NR	NR	NR	NR	6 (100)	3 (60)	5 (100
	In the Post-Treatment Period	NR	NR	NR	NR	NR	NR	3 (50)	0	0
	Treatment-Related Serious TEAE	0	0	0	0	0	NR	NR	NR	NR
	Leading to Discontinuation	0	0	1 (3)	1 (2)	1 (3)	2 (2)	1 (17)	0	0
	Mild TEAE	NR	NR	NR	NR	NR	NR	6 (100)	3 (60)	5 (100)
	Moderate TEAE	NR	NR	NR	NR	NR	NR	5 (83)	1 (20)	3 (60)
	Serious TEAE	0	1 (3)	1 (3)	2 (3)	3 (9)	12 (11)	3 (50)	0	1 (20)
	Severe TEAE	NR	NR	NR	NR	NR	NR	1 (17)	0	0
	Serious TEAEs in the Treatment Period	NR	NR	NR	NR	NR	NR	2 (33)	0	1 (20)
	Serious TEAEs in the Post-Treatment Period	NR	NR	NR	NR	NR	NR	1 (17)	0	0
	TEAE Leading to Death	NR	NR	NR	NR	NR	NR	0	0	0
	Infection-Related TEAE	6 (38)	16 (49)	13 (39)	29 (44)	11 (32)	NR	5 (83)	1 (20)	2 (40)
	Infections and Infestations	NR	NR	NR	NR	NR	43 (39)	NR	NR	NR
All-Cause Mortality, n (%)		0	0	0	0	0	0	NR	NR	NR
	Covid-19	4 (25)	9 (27)	8 (24)	17 (26)	6 (18)	11 (10)	NR	NR	NR

Intervention			Atacicept								
Trial			ORIGIN					ORIGIN OLE	JANUS		
Arm			Ata 25 mg	Ata 75 mg	Ata 150 mg	Combined Ata[†]	Placebo	Ata 150 mg[*]	Ata 25 mg	Ata 75 mg	Placebo
N			16	33	33	66	34	113	6	5	5
Most Common TEAEs (≥5%) by Treatment Group, n (%)		Influenza	0	1 (3)	0.0	1 (2)	1 (3)	5 (5)	NR	NR	NR
		Injection Site Erythema	NR	NR	NR	NR	NR	NR	5		
		Injection Site Pain	NR	NR	NR	NR	NR	NR	3		
		Nasopharyngitis	0	1 (3)	3 (9)	4 (6)	1 (3)	12 (11)	NR	NR	NR
		Tonsillitis	1 (6)	1 (3)	0.0	1 (2)	0	1 (1)	NR	NR	NR
		Upper Respiratory Tract Infection	0	3 (9)	2 (6)	5 (8)	0	14 (13)	NR	NR	NR
		Urinary Tract Infection	2 (13)	1 (3)	1 (3)	2 (3)	0	3 (3)	3		
		Viral Infection	0	2 (6)	0	2 (2)	2 (6)	1 (1)	2		
Covid-19 Infections n (%) or Median (IQR)	Covid-19 Vaccine Prior to Infection		4 (100)	9 (100)	8 (100)	NR	6 (100)	NR	NR	NR	NR
	Severity	Mild	3 (75)	8 (88.9)	7 (87.5)	NR	6 (100)	NR	NR	NR	NR
		Moderate	1 (25)	1 (11.1)	1 (12.5)	NR	0	NR	NR	NR	NR
		Severe	0	0	0	NR	0	NR	NR	NR	NR
	Outcome	Recovered	4 (100)	9 (100)	7 (87.5)	NR	6 (100)	NR	NR	NR	NR
		Recovering	0	0	1 (12.5)	NR	0	NR	NR	NR	NR
	Action Taken	No Dose Change	2 (50)	4 (44.4)	5 (62.5)	NR	3 (50)	NR	NR	NR	NR
		Drug Interrupted	2 (50)	5 (55.6)	3 (37.5)	NR	3 (50)	NR	NR	NR	NR
	Duration of Covid-19 Infection, Days		11.5 (8.5, 14)	8 (7, 9)	8 (6, 8)	NR	6.5 (6, 7)	NR	NR	NR	NR

Ata: Atacicept, IQR: Interquartile Range, n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, TEAE: Treatment Emergent Adverse Event, %: Percent

*From week 36 to 96

† Combined atacicept dose of 75mg and 150mg

Table D3.33. NefIgArd & NefIgArd OLE Safety[10,105]

Intervention		Nefecon					
Trial		Ph 3 NefIgArd				NefIgArd OLE	
Arm		Nefecon 16 mg 9-Month Treatment	Placebo	Nefecon 16 mg/day 15-Month Observational Follow-Up	Placebo	2nd Course of Nefecon	1st Course of Nefecon
N		182	182	175	174	45	74
Treatment-Emergent Adverse Event (TEAE), n (%)	Any TEAE	159 (87)	125 (69)	127 (73)	124 (71)	NR	NR
	Treatment-Related Serious TEA	4 (2)	4 (2)	0	1 (1)	NR	NR
	Leading to Discontinuation	17 (9)	3 (2)	NA	NA	NR	NR
	Mild TEAE	93 (51)	75 (41)	62 (35)	73 (42)	NR	NR
	Moderate TEAE	57 (31)	46 (25)	49 (28)	43 (25)	NR	NR
	Serious TEAE	18 (10)	9 (5)	14 (8)	14 (8)	5 (11.1)	5 (6.8)
	Severe TEAE	9 (5)	4 (2)	16 (9)	8 (5)	NR	NR
	TEAE Leading to Death	1 (1)	0	1 (1)	0	NR	NR
	Infection-Related TEAE	63 (35)	57 (31)	NR	NR	NR	NR
	Serious Infection-Related TEAEs	5 (3)	2 (1)	NR	NR	NR	NR
All-Cause Mortality, n (%)		NR	NR	NR	NR	0	0
	Acne	20 (11)	2 (1)	NR	NR	NR	NR
	Arthralgia	12 (7)	4 (2)	NR	NR	4 (8.9)	3 (4.1)
	Back Pain	NR	NR	NR	NR	3 (6.7)	3 (4.1)
	Covid-19	NR	NR	26 (15)	30 (17)	12 (26.7)	13 (17.6)
	Cushingoid	NR	NR	NR	NR	2 (4.4)	6 (8.11)

Intervention		Nefecon					
Trial		Ph 3 NefIgArd				NefIgArd OLE	
Arm		Nefecon 16 mg 9-Month Treatment	Placebo	Nefecon 16 mg/day 15-Month Observational Follow-Up	Placebo	2nd Course of Nefecon	1st Course of Nefecon
N		182	182	175	174	45	74
Most Common TEAEs (≥5%) by Treatment Group, n (%)	Dyspepsia	13 (7)	4 (2)	NR	NR	NR	NR
	Face Edema (Swelling)	14 (8)	1 (0.5)	NR	NR	NR	NR
	Fatigue	10 (5)	7 (4)	NR	NR	4 (8.9)	2 (2.7)
	Gout	NR	NR	11 (6)	8 (5)	NR	NR
	Headache	19 (10	14 (8)	NR	NR	4 (8.9)	3 (4.1)
	Hypertension	22 (12)	6 (3)	10 (6)	12 (7)	8 (17.8)	12 (16.2)
	Insomnia	10 (5)	7 (4)	NR	NR	3 (6.7)	6 (8.1)
	Muscle Spasm	22 (12)	7 (4)	NR	NR	6 (13.3)	5 (6.8)
	Nasopharyngitis	17 (9)	19 (10)	NR	NR	1 (2.2)	4 (5.4)
	Nausea	NR	NR	NR	NR	3 (6.7)	2 (2.7)
	Peripheral Edema	31 (17)	7 (4)	14 (8)	10 (6)	1 (2.2)	10 (13.5)
	Pyrexia	NR	NR	NR	NR	0	4 (5.4)
	Rash	10 (5)	7 (4)	NR	NR	NR	NR
	Upper Respiratory Tract Infection	10 (5)	10 (5)	NR	NR	3 (6.7)	2 (2.7)
	Weight Increased	10 (5)	5 (3)	NR	NR	3 (6.7)	8 (10.8)

n: number, N: total number, NA: not applicable, NR: not reported, TEAE: treatment emergent adverse event, %: Percent

Table D3.34. NefIgArd Part A, NefIgArd China Cohort, and NEFIGAN Safety[33,34,45]

Intervention		Nefecon						
Trial		NefIgArd - Part A FAS		NefIgArd - China Cohort		NEFIGAN		
Arm		Nefecon 16 mg	Placebo	Nefecon 16 mg	Placebo	Nefecon 8 mg	Nefecon 16 mg	Placebo
N		97	100	32	30	51	48	50
Treatment-Emergent Adverse Event (TEAE), n (%)	Any TEAE	84 (86.6)	73 (73.0)	31 (96.9)	24 (80.0)	48 (94)	48 (88)	42 (84)
	In the Post-Treatment Period	NR	NR	23 (71.9)	25 (83.3)	NR	NR	NR
	Treatment-Related Serious TEAE	2 (2.1)	2 (2.0)	1 (3.1)	0 (0)	NR	NR	NR
	TEAE Leading to Discontinuation	9 (9.3)	1 (1.0)	1 (3.1)	0 (0)	NR	NR	NR
	Mild TEAE	49 (50.5)	46 (46.0)	21 (65.6)	16 (53.3)	NR	NR	NR
	Moderate TEAE	31 (32.0)	26 (26.0)	10 (31.3)	8 (26.7)	NR	NR	NR
	Serious TEAE	11 (11.3)	5 (5.0)	1 (3.1)	0 (0)	NR	NR	NR
	Severe TEAE	4 (4.1)	1 (1.0)	0 (0)	0 (0)	NR	NR	NR
	TEAE Leading to Death	0	0	0 (0)	0 (0)	NR	NR	NR
	Infection-Related TEAE	38 (39.2)	41 (41)	NR	NR	NR	NR	NR
Most Common TEAEs (≥5%) by Treatment Group, n (%)	Abdominal Pain	5 (5.2)	6 (6)	NR	NR	4 (8)	3 (6)	1 (2)
	Acne	11 (11.3)	2 92)	NR	NR	8 (16)	9 (18)	3 (6)
	Alopecia	NR	NR	NR	NR	4 (8)	4 (80	2 (4)
	Back Pain	0 (0)	6 (6.0)	NR	NR	6 (12)	3 (6)	1 (2)
	Blood Creatinine Phosphokinase Increased	NR	NR	NR	NR	3 (6)	3 (6)	3 (6)
	Covid-19	NR	NR	12 (37.5)	11 (36.7)	NR	NR	NR
	Cough	NR	NR	2 (6.3)	1 (3.3)	NR	NR	NR
	Cushingoid	NR	NR	NR	NR	5 (10)	8 (16)	3 (6)
	Dermatitis	7 (7.2)	1 (1)	2 (6.3)	0 (0)	NR	NR	NR
	Diarrhea	6 (6.2)	7 (7.0)	2 (6.3)	1 (3.3)	1 (2)	5 (10)	7 (14)
	Dyspepsia	5 (5.2)	2 (2.0)	NR	NR	2 (4)	7 (14)	4 (8)

Intervention		Nefecon						
Trial		NefIgArd - Part A FAS		NefIgArd - China Cohort		NEFIGAN		
Arm		Nefecon 16 mg	Placebo	Nefecon 16 mg	Placebo	Nefecon 8 mg	Nefecon 16 mg	Placebo
N		97	100	32	30	51	48	50
	Dyspnea	6 (6.2)	0 (0)	NR	NR	NR	NR	NR
	Face Edema (Swelling)	6 (6.2)	1 (1)	NR	NR	NR	NR	NR
	Fatigue	5 (5.2)	2 (2.0)	NR	NR	NR	NR	NR
	Gout	NR	NR	NR	NR	NR	NR	NR
	Headache	11 (11.3)	11 (11.0)	NR	NR	3 (6)	6 (12)	3 (6)
	Hirsutism	NR	NR	NR	NR	3 (6)	5 (10	1 (2)
	Hepatic Steatosis	NR	NR	2 (6.3)	0 (0)	NR	NR	NR
	Hyperuricemia	NR	NR	2 (6.3)	3 (10)	NR	NR	NR
	Hypertension	15 (15.5)	2 (2.0)	0 (0)	5 (16.7)	3 (6)	5 (10)	1 (2)
	Insomnia	NR	NR	NR	NR	6 (12)	8 (16)	2 (4)
	Joint Swelling	NR	NR	NR	NR	8 (16)	9 (18)	2 (4)
	Mood Swings	NR	NR	NR	NR	3 (6)	5 (10)	2 (4)
	Muscle Spasm	13 (13.4)	4 (4.0)	NR	NR	5 (10)	2 (4)	2 (4)
	Nasopharyngitis	13 (13.4)	12 (12.0)	NR	NR	8 (16)	10 (20)	10 (20)
	Nausea	6 (6.2)	9 (9.0)	NR	NR	4 (8)	3 (6)	1 (2)
	Peripheral Edema	14 (14.4)	4 (4.0)	0 (0)	1 (3.3)	2 (4)	6 (12)	2 (4)
	Pyrexia	0 (0)	6 (6.0)	3 (9.4)	5 (16.7)	NR	NR	NR
	Pulmonary Mass	NR	NR	2 (6.3)	0 (0)	NR	NR	NR
	Rash	4 (4.1)	5 (5)	NR	NR	NR	NR	NR
	Upper Respiratory Tract Infection	5 (5.2)	9 (9.0)	2 (6.3)	3 (10)	2 (4)	3 (6)	3 (6)
	Weight Increased	7 (7.2)	3 (3.0)	NR	NR	NR	NR	NR
Adverse Events of Special Interest	New Onset of Diabetes	2 (2.1)	0	NR	NR	NR	NR	NR
	GI-Related AEs During Treatment	NR	NR	NR	NR	6 (11.8)	18 (36.7)	14 (28)
	GI-Related AEs During Follow-Up	NR	NR	NR	NR	5 (9.8)	6 (12.2)	4 (8.0)

Intervention		Nefecon						
Trial		NefIgArd - Part A FAS		NefIgArd - China Cohort		NEFIGAN		
Arm		Nefecon 16 mg	Placebo	Nefecon 16 mg	Placebo	Nefecon 8 mg	Nefecon 16 mg	Placebo
N		97	100	32	30	51	48	50
Corticosteroid-Related AEs	Run-In	NR	NR	NR	NR	6 (11.8)	10 (20.4)	10 (20)
	Treatment	NR	NR	NR	NR	20 (39.2)	20 (40.8)	11 (22)
	Follow-Up	NR	NR	NR	NR	12 (23.5)	14 (28.6)	10 (20)

n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, TEAE: Treatment Emergent Adverse Event, %: Percent

Table D3.35. Systemic Glucocorticoids Safety[47-50]

Trial		TESTING				STOP-IgAN	
		Full-Dose		Reduced Dose			
Arm		Methylprednisolone	Placebo	Methylprednisolone	Placebo	Supportive Care	Supportive Care + Immuno-suppression
N		136	126	121	120	80	82
Patients with ≥1 Serious Adverse Event, n (%)	Total, p-Value	22 (16)	4(3)	6 (5); 0.5	3 (3); REF	21 (26.2)	29 (35.3)
	Hospitalization/Prolongation of Hospitalization, p-Value	19 (14)	4 (3)	6 (5); 0.5	3 (3); REF	NR	
	Resulted in Death, p-Value	4 (2)	0 (0)	1 (0.8); 1	0 (0); 1	1 (1.2)*	1 (1.2)
	Life-Threatening	4 (2)	0 (0)	1 (0.8)	0 (0)	NR	
	Important Medical Event	2 (0.8)	0 (0)	1 (0.8)	0 (0)	NR	
	Persistent/Significant Disability/Incapacity	1 (0.7)	0 (0)	0 (0)	0 (0)	NR	
Severe Infection Requiring Hospitalization (AE of Special Interest), n (%)		11 (8.1)	1 (0.8)	5 (4.1); 0.45	2 (1.7); REF	NR	
Total Number of Serious Adverse Events, n		30	5	7	3	29 (36.2)	33 (40.2)
Total Number of Events of Infection, n		NR	NR	NR	NR	111	174
Total Number	Total	NR	NR	NR	NR	3	8
	Diverticulitis or Appendicitis	NR	NR	NR	NR	1	3

Trial		TESTING				STOP-IgAN	
		Full-Dose		Reduced Dose			
Arm		Methylprednisolone	Placebo	Methylprednisolone	Placebo	Supportive Care	Supportive Care + Immuno-suppression
N		136	126	121	120	80	82
of Serious Adverse Events of Infection, n	Pneumonia or Respiratory Tract Infection	3 (2)	0	0 (0)	0 (0)	1	3
	Viral Exanthema	NR	NR	NR	NR	1	
	Knee Empyema	NR	NR	NR	NR	0	1
Additiona-l Adverse Events of Interest, n (%)	Malignant Neoplasm	NR	NR	NR	NR	0	2 (2.4)
	Impaired Glucose Tolerance or Diabetes Mellitus	NR	NR	NR	NR	1 (1.2)	9 (10.9)
	Gastrointestinal Bleeding	4 (2.9)	1 (0.8)	0 (0)	0 (0)	0	
	Fracture	3 (2.2)	0 (0)	NR	NR	0	1 (1.2)
	Weight Gain (≥5 kg within the First Year)	NR	NR	NR	NR	5 (6.3)	14 (17.1)
	Severe Infection Requiring Hospitalization	12 (9)	1 (0.8)	5 (4)	2 (2)	NR	
	Pneumocystis Jirovecii Pneumonia	4 (3)	0 (0)	0 (0)	0 (0)	NR	
	Sepsis	0 (0)	0 (0)	2 (2)	1 (0.8)	NR	
	Urinary Tract Infection	1 (0.7)	0 (0)	1 (0.8)	0 (0)	NR	
	Multiple Skin Infection	0 (0)	0 (0)	1 (0.8)	0 (0)	NR	
	Nocardia Infection	1 (0.7)	0 (0)	0 (0)	0 (0)	NR	
	Cryptococcal Meningitis	1 (0.7)	0 (0)	0 (0)	0 (0)	NR	
	Tuberculosis with Bacterial Infection	0 (0)	0 (0)	1 (0.8)	0 (0)	NR	
	Perianal Abscess	1 (0.7)	0 (0)	0 (0)	0 (0)	NR	
	Acute Febrile Illness	0 (0)	0 (0)	0 (0)	1 (0.8)	NR	
	Other Infection	1 (0.7)	1 (0.8)	0 (0)	0 (0)	NR	
	Gastrointestinal Bleeding Requiring Hospitalization	3 (2)	1 (0.8)	0 (0)	0 (0)	NR	

Trial		TESTING				STOP-IgAN	
		Full-Dose		Reduced Dose			
Arm		Methylprednisolone	Placebo	Methylprednisolone	Placebo	Supportive Care	Supportive Care + Immuno-suppression
N		136	126	121	120	80	82
	Clinically Evident Fracture or Osteonecrosis	3 (2)	0 (0)	0 (0)	0 (0)	NR	
	New Onset Diabetes Mellitus, p-Value	0 (0)	0 (0)	2 (2); 0.5	0 (0); REF	NR	

n: number, N: Total Number, NA: Not Applicable, NR: Not Reported, TEAE: Treatment Emergent Adverse Event, %: Percent

* Death due to a motor vehicle accident

Table D3.36. NefIgArd Biomarker[107]

Intervention			Nefecon		
Trial			NefIgArd (Lafayette 2023)		
Arm			Nefecon 16 mg	Placebo	Significance
N			182	182	
Gd-IgA1	Month 9	Mean % CFB, (SE)	*-18.42 (2.5)*	*11.2 (3.3)*	<0.0001
	Month 18	Mean % CFB, (SE)	*7 (3.3)*	*11.6 (3.5)*	NR
IgG	Month 9	Mean % CFB, (SE)	*-10 (3.2)*	*1.5 (3.6)*	0.0193
	Month 18	Mean % CFB, (SE)	*4.9 (3.5)*	*3.6 (3.4)*	NR
IgA	Month 9	Mean % CFB, (SE)	*-7 (2.4)*	*-0.4 (2.5)*	NR
	Month 18	Mean % CFB, (SE)	*-0.6 (2.7)*	*2.7 (2.8)*	NR

CFB: Change from Baseline, N: Total Number, NR: Not Reported, SE: Standard Error, %: Percent

Table D3.36 Note: Italicized data has been digitized or calculated

D4. Ongoing Studies

Table D4.1. Ongoing Studies

Title/Trial Sponsor	Study Design	Patient Population	Primary Outcomes	Estimated Completion Date
Phase II/III Open-Label Trial of Sibeprenlimab in the Treatment of Immunoglobulin A Nephropathy **NCT05248659**	Phase II/III, Multicenter, Open-Label Trial Enrollment Estimate: N=600 Single-Arm: Sibeprenlimab 400 mg Q4W SC	**Inclusion:** •Completed Trial 417-201-00007 or VIS649-201 • eGFR ≥ 45 mL/min/1.73 m^2, calculated using the CKD-EPI formula. **Exclusion:** •Not completed participation in trials 417-201-00007 or VIS649-201. •Subjects who, following enrollment in trials 417-201-00007 or VIS649-201 developed a condition or characteristic that would have excluded them from participation in these trials.	• Adverse Events [Baseline to Week 112]	December 2028
Trial of the Impact of Sibeprenlimab on Immunoglobulin A Nephropathy Kidney Tissue **NCT06740526**	Phase IIb, Multicenter, Open-Label, Single-Arm trial Estimated enrollment: N=25 Single-Arm: Sibeprenlimab	**Inclusion:** • Male and female patients ≥16 years of age with biopsy-confirmed IgAN • eGFR ≥ 45 mL/min/1.73 m^2, calculated using the CKD-EPI formula. **Exclusion:** •Coexisting chronic kidney disease, other than IgAN. •Serum IgG value <600 mg/dL at screening.	• Change from Baseline in Glomerular IgA Deposition by Immunofluorescence in Kidney Tissue [Baseline to Week 52]	April 2029

Title/Trial Sponsor	Study Design	Patient Population	Primary Outcomes	Estimated Completion Date
		•Uncontrolled hypertension (defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg). •Received immunosuppressive therapies or systemic corticosteroids within 24 weeks		
ORIGIN EXTEND **NCT06674577**	Multicenter, Rollover Study Estimated enrollment: N=476 Single-arm: Atacicept 150mg SC injection	Inclusion: • For Atacicept Drug Holiday Group only: Systolic blood pressure ≤150 mmHg and diastolic blood pressure ≤90mmHg at screening and Day Exclusion: • Evidence of rapidly progressive glomerulonephritis (loss of ≥50% of eGFR within 3 months of screening) • Evidence of nephrotic syndrome (serum albumin <30g/L in association with uPCR >3.5 mg/mg) within 6 months of screening • Use of systemic corticosteroids or immunosuppressive medications within 2 months prior to screening • Use of B-cell directed therapies within 12 months of screening	• Incidence of adverse events observed during the dosing period [Baseline up to Week 156]	May 2028
Efficacy and Safety of Extended TARPEYO® Treatment Beyond 9 Months in Adult Patients With Primary IgA Nephropathy (NefXtend)	Phase IV, Open-Label Study Estimated Enrollment: N=60	Inclusion: • Male and female patients ≥18 years of age with biopsy-confirmed IgAN •Completion of 9 months of treatment with TARPEYO® 16 mg QD at the Baseline visit	Ratio of Urine Protein to Creatinine Ratio (uPCR) at 6 months compared to baseline	November 2027

Title/Trial Sponsor	Study Design	Patient Population	Primary Outcomes	Estimated Completion Date
NCT06712407	Tarpeyo 16 mg QD then 8 mg QD	•On stable treatment with renin-angiotensin system (RAS) inhibitor therapy or SGLT2 for at least 8 weeks prior to the Baseline visit. Exclusion: •Participants who have been treated with systemic immunosuppressive medications including glucocorticosteroids •Presence of other glomerulopathies or nephrotic condition •Undergone kidney transplant		

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

eGFR: estimated glomerular filtration rate, mg/dL: milligrams per deciliter, mL/min/1.73 m2: Milliliter per minute per minute per 1.73 meters squared, N: number, SGLT2i: Sodium-Glucose Cotransporter 2 Inhibitor, Q4W: Every 4 weeks, SC: subcutaneous, UPCR: Urine Protein-To-Creatinine Ratio, QD: once daily

D5. Previous Systematic Reviews and Technology Assessments

We identified one health technology assessments (HTA) of targeted-release budesonide for the treatment of IgAN initiated by the National Institute for Health and Care Excellence (NICE). One meta-analysis regarding targeted-release budesonide and one systematic review of corticosteroids was identified at the time of our review.

NICE Technology Assessment for Targeted-Release Budesonide [TA937][118]

NICE conducted a health technology assessment assessing targeted-release budesonide for the treatment of primary IgAN in adults with a risk of rapid disease progression, indicated by a uPCR ratio of 170 mg/mmol and over. NICE recommended the treatment as an add-on to optimized standard care with the highest dose of ACE inhibitors or ARBs.

Li, J, Hongquin, T, Yang, B, et al. Efficacy and Safety of TRF-Budesonide in IgA Nephropathy Treatment: A Meta-Analysis. *Journal Of Nephrology.* 2025.[119]

This meta-analysis reviews the benefits and safety of TRF-budesonide among moderately severe IgAN patients enrolled in trials comparing TRF-budesonide to a placebo or another active agent. The analysis identified four RCTS that involve 774 participants. For eGFR, the TRF-budesonide group in all studies had a higher eGFR compared with the placebo group. For uPCR, the reduction in uPCR remained at a greater extent in the TRF-budesonide group compared to the placebo group. The authors noted a sustained reduction in uPCR and eGFR after the follow-up period. In addition, the analysis demonstrates that TRF-budesonide patients experienced a higher incidence of adverse events compared with the placebo group. Overall, treatment with TRF-budesonide demonstrated improvements in eGFR and uPCR compared to placebo but was associated with greater adverse events.

Ali, S, Fusco, N. Makhija, D, et al. Burden of Corticosteroid Therapy in Patients with Immunoglobulin A Nephropathy (IgAN): A Systematic Literature Review. *BMC Nephrology*. 2025.[59]

This systematic literature review provides an overview of the burden associated with corticosteroid treatment among IgAN patients globally, using evidence from observational studies and RCTs. Over half of the studies indicated that corticosteroids were administered to IgAN patients for longer than 6 months (KDIGO guidelines recommend as add-on therapy for up to six months). Across the 63 identified studies, the evidence indicates more adverse events among the corticosteroids group than the comparator group and particularly with long-term use. Hypertension was reported at higher rates in groups receiving corticosteroid, both in short-term and long-term use. A variety of infections were reported across studies. The authors highlight that the RCTs demonstrate some concern of risk of bias regarding lack of blinding and reporting of allocation concealment methods.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if Quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	X	X	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[120]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[66]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps three and four.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The population of focus included recent clinical trial participants. Because treated patient baseline age, percent female, and eGFR were similar in each of the most recent published clinical trials that reported changes in eGFR,[8-10] we assumed the same baseline population characteristics for each treatment. Baseline model distribution across CKD stages was reported in a previous cost-effectiveness model assessing Nefecon as a treatment for IgA nephropathy.[12]

Table E1.2. Base-Case Model Cohort Characteristics

	Model-Wide Baseline Characteristics	Source
Mean Age, Years	43	Lafayette et al.[10]
Female, %	36	Lafayette et al.[10]
Initial State Distribution Across CKD Stage, %	CKD 1: 3% CKD 2: 34% CKD 3a: 39% CKD 3b: 24% CKD 4: 0% CKD 5/ESKD: 0% Dialysis: 0% Post-transplant: 0%	Ramjee et al.[12]

CKD: Chronic kidney disease, ESKD: End-stage kidney disease

Treatment Strategies

Treatment with Nefecon involves nine months of treatment. The base-case analysis assumed one treatment course.

For atacicept and sibeprenlimab, patients in the model were assumed to remain on treatment until reaching ESKD.

E2. Model Inputs and Assumptions

Key model assumptions are described in Table 4.1, and key model inputs are summarized in Table 4.2. Additional model assumptions include the following:

- We excluded home hemodialysis from dialysis costs. Evidence indicated most IgA nephropathy patients opt for in-center hemodialysis or peritoneal dialysis, with a negligible proportion of patients opting for home hemodialysis.[121]
- Given a lack of data on time to progression of kidney failure after eGFR falls below 15 within this patient population, patients in the model spent one cycle (one month) in CKD stage 5/ESKD before requiring pre-emptive transplant or dialysis.
- Although some patients with a failed transplant will pursue re-transplant, we made a simplifying assumption to exclude re-transplants from the model after determining the overall impact was negligible.

Clinical Inputs

Table E2.1. Model Inputs

Parameter	Input	Source
Transition from CKD 5/ESKD Tunnel State to Post-Transplant (Representing Pre-Emptive Transplant) per Cycle	0.151	Bensink et al.[121]
Transition from CKD 5/ESKD Tunnel State to Dialysis per Cycle	0.849	Bensink et al.[121]
Transition from Dialysis to Post-Transplant per Cycle	0.0068	Bensink et al.;[121] Authors' calculation
Transplant Failure per Cycle	0.002	Aydin-Ghormoz et al. ;[122] Kadiyala et al. ;[123] Authors' calculation
Standardized Mortality Ratio by eGFR Category (Pre-ESKD) (95% CI)	CKD stage 1 and 2: 0.7 (0.4-1.2) CKD stage 3a and 3b: 1.8 (1.2-2.7) CKD stage 4 and 5: 1.9 (1.1-3.3)	Knoop et al.[124]
Hazard Ratio for All-Cause Mortality Among Those Treated with Glucocorticoids (95% CI)	2.62 (0.52-13.05)	Lv et al.[47]
All-Cause Mortality Among Hemodialysis Patients, Deaths per 1,000 Person-Years	Ages 18-44: 92.1 Ages 45-64: 142.2 Ages 65-74: 221.1 Ages 75+: 318.3	USRDS[74]
All-Cause Mortality Among Peritoneal Dialysis Patients, Deaths per 1,000 Person-Years	Ages 18-44: 56.9 Ages 45-64: 109.0 Ages 65-74: 186.4 Ages 75+: 275.7	USRDS[74]
All-Cause Mortality Among Transplant Patients, Deaths per 1,000 Person-Years	Ages 18-44: 13.3 Ages 45-64: 36.1 Ages 65-74: 79.8 Ages 75+: 154.7	USRDS[74]
All-Cause Mortality	Varies by age and gender	US Life Tables

CKD: Chronic kidney disease, eGFR: estimated glomerular filtration rate, ESKD: End-stage kidney disease

Clinical Probabilities/Response to Treatment

Without access to patient-level data for all interventions, we could not derive transition probabilities separately by treatment arm. However, a prior cost-effectiveness analysis of Nefecon to treat IgA nephropathy used individual patient-level data provided by the manufacturer to derive transition probabilities for movement between CKD stages in both the treatment and placebo arms.[11] Based on changes in eGFR from baseline to follow-up compared to placebo and reported in published clinical trials,[8-10,47] we calibrated transition probabilities separately for each treatment using forward and backward multipliers applied to the best supportive care transitions underlying the prior cost-effectiveness analysis of Nefecon. We "re-traced" the best supportive care mean eGFR trajectories across time and generated a cycle-specific mean eGFR weighted by proportions of patients within each cycle. We then re-calibrated to fit any treatment-specific trajectory in eGFR values across health states. Table E2.2 shows the parameters used in calibration. We calibrated based on incremental treatment effects demonstrated from clinical trials and shown in Table 3.3. For example, annualized slope estimates in the first row of Table E2.2 may differ from clinical trial effects but the difference between each treatment and no specific immunomodulatory therapy meets observed estimates from clinical trials. Sensitivity analyses further explored lower and upper bounds from these clinical trials and are reflected in the one-way sensitivity analyses.

Table E2.2. Approximate Modeled eGFR Slope by Intervention and versus No Specific Immunomodulatory Therapy

Model output	No Specific Immunomodulatory Therapy	Sibeprenlimab	Atacicept	Nefecon	Systemic Glucocorticoids
Annualized Slope Using 3 Years Of Model (mL/min/1.73m^2/year)	-7.14	-1.17	-1.23	-4.06	-4.82
Difference vs. No Specific Immunomodulatory Therapy	n/a	5.96	5.89	3.07	2.31

mL/min/1.73m^2: Milliliter per minute per 1.73 meters squared, vs: versus

In the base case, we modeled treatment duration and durability separately for each intervention with patients continuing treatment until ESKD or as recommended by prior evidence, clinical expert opinion, or Food and Drug Administration (FDA) label recommendations. For Nefecon, the base-case analysis applied on-treatment transitions for two years, reflecting Phase III evidence of treatment efficacy from baseline to two years of follow-up.[10,11] The base-case analysis for Nefecon assumed one treatment course. For atacicept and sibeprenlimab, the base-case analysis incorporated ongoing on-treatment transitions as long as patients continued treatment without reaching ESKD. The on-treatment transitions for atacicept and sibeprenlimab were calibrated using

changes in eGFR from baseline to follow-up associated with the best available evidence on most efficacious dosing or the dosage currently being studied in Phase III trials.[8,9] For systemic glucocorticoids, the base-case analysis assumed one treatment course lasting eight months and on-treatment transitions were applied for two years, to match the treatment durability of Nefecon.

From the CKD stage 5/ESKD tunnel state, 15.1% of patients immediately transitioned each cycle to the post-transplant state, representing pre-emptive transplantation. The remaining patients immediately transitioned to dialysis. We used the overall transplant incidence at 10 years (62.8%; competing risk estimate), accounting for the initial patients who received pre-emptive transplant, to calibrate the transition probability from dialysis to post-transplant. These estimates were identified in a retrospective cohort study of patients with IgA nephropathy-attributed kidney failure in the US Renal Data System.[121]

The cycle probability of transplant failure was calibrated using a weighted average 5-year death-censored graft failure rate calculated from data reporting living- and deceased-donor failure rates in the US IgA nephropathy population (9% and 15.1%, respectively) and the proportion of US IgA nephropathy patients who receive living donor transplants (49.9%).[122,123] Failed transplants (and the subsequent cost of returning to dialysis) were incorporated within the post-transplant state, rather than as a separate health state. We made a simplifying assumption to exclude the possibility of re-transplant as the impact on the model was negligible.

Mortality

To reflect different risks of mortality across CKD health states, we applied standardized mortality ratios by eGFR category derived in an analysis of Norwegian Kidney Biopsy Registry data (pre-ESKD IgA nephropathy patients).[124] These data were chosen to reduce the risk of double-counting mortality due to dialysis or transplant. The standardized mortality ratios were applied to US life table data that varies by age and sex.

An increased risk of mortality relative to the general population was applied to patients in the systemic glucocorticoid comparator arm.[47] This increased risk was applied for two years to match the assumed duration of treatment benefit.

Mortality rates by age group for the dialysis and post-transplant health states were calculated using adjusted all-cause mortality rates among transplant patients reported in the US Renal Data System 2024 Annual Data Report.[74]

Utilities

Previous models differed in their choice of utilities for the different stages of CKD, including dialysis-dependence.[11,12] Our choice of utilities is described in the main report text.

For each intervention, the incidence of treatment-related serious adverse events was low (<2%).[8-10] As such, we did not include intervention-related disutilities related to serious adverse events in the model. A disutility representing adverse events for systemic glucocorticoids is described in the main text.

Economic Inputs

All costs in the model were inflated to 2025 US dollars using the medical care component of the Consumer Price Index.

Drug Acquisition Costs

For sibeprenlimab, the WAC per package is $30,000 (RedBook). Each package contains four weeks of medication, resulting in 13 courses of treatment annually. IPD Analytics estimated a 25% discount for sibeprenlimab. For atacicept, we assumed an annual placeholder price estimated by IPD Analytics. This price will be updated if list prices become available. For Nefecon, the WAC per package is $17,850 (RedBook). Each package contains one month of medication. A full course of treatment was estimated as requiring 9.25 packages to reflect the dosing procedure in the Phase III trial. Additionally, IPD Analytics forecast a 19% discount in 2025 for Nefecon. SSR Health gross-to-net estimates were not available for sibeprenlimab or Nefecon.

Table E2.3. Drug Cost Inputs

Drug	WAC per Package	Discount from WAC	Net Price per Package	Annual WAC	Net Price per Year/Placeholder Price per Year
Atacicept	n/a	n/a	n/a	n/a	$292,500†
Sibeprenlimab	$30,000 (every 4 weeks)	25%*	$22,500	$390,000	$292,500‡
Nefecon	$17,850 (monthly)	19%*	$14,459	$165,113	$133,741‡

WAC: wholesale acquisition cost

*IPD Analytics forecasted discount

†Placeholder price per year

‡Estimated net price per year; For Nefecon, the price represents one 9-month course of treatment over the course of one year.

Administration and Monitoring Costs

Because Nefecon is an oral medication and atacicept and sibeprenlimab may be administered subcutaneously at home, we did not include costs of administration and monitoring.

Health Care Utilization Costs

A retrospective cohort study using Optum's Market Clarity database and natural-language processing to identify US patients with IgA nephropathy estimated the health care resource utilization costs across CKD stages.[70] These estimates are inclusive of inpatient visits, emergency department visits, outpatient visits, and pharmacy claims and represent spending by commercial payers, Medicaid, and Medicare. Because these estimates include pharmacy claims, we assumed they include spending on the drugs expected to be used by patients in the comparator arms of this model (i.e. no specific immunomodulatory therapy or systemic glucocorticoids). We disaggregated these estimates to separately represent health care resource utilization costs attributable to patients who do and do not use systemic glucocorticoids by applying a ratio of costs attributable to these two groups identified in a recent analysis of US IgA nephropathy patients and assuming that one-half of patients would initiate treatment with systemic glucocorticoids.[71] Beyond CKD stage 3, we assumed no further excess cost related to the use of systemic glucocorticoids, as treatment with systemic glucocorticoids is not recommended beyond this stage.[23] Additionally, we assumed these costs excluded the costs of dialysis or kidney transplant as only a small percentage of the sample (1.2%) had experienced either of these events at study baseline.

We calculated a weighted average cost of dialysis based on the proportion of IgA nephropathy patients on dialysis who opt for in-center hemodialysis (approximately 75%) versus peritoneal dialysis.[121] Because a negligible proportion of patients opt for home hemodialysis,[121] we excluded these costs from the weighted average. Medicare costs of dialysis were identified using the US Renal Data System 2024 Annual Data Report.[74] The national average commercial hemodialysis cost per session was reported in a study drawing on Health Care Cost Institute data, inclusive of employer-sponsored health insurance plans that covered approximately 55 million people per year from 2012-2019.[72] We assumed patients needed three sessions of dialysis each week.[73] We then estimated the commercial cost of peritoneal dialysis using this estimate of hemodialysis costs and the ratio of Medicare spending on hemodialysis versus peritoneal dialysis. Dialysis health state costs replaced the CKD stage health care utilization costs.

In the US, Medicare coverage for dialysis starts on the first day of the fourth month of dialysis treatment. However, a 30-month coordination period is required before Medicare may become the primary payer.[63] To reflect this reimbursement policy in the model, we applied a one-time cost to the cycle in which each patient transitioned to dialysis that was equal to the monthly cost of dialysis multiplied by either 33 months or the number of months remaining until age 65 if fewer than 33 months remained; in all subsequent cycles, we applied the per cycle Medicare cost of dialysis. An important limitation of this approach is that commercial dialysis costs were applied regardless of mortality from the dialysis health state. Additionally, these costs were more heavily discounted over time due to being concentrated earlier as a one-time cost. However, we adopted this approach so that scenario analyses could explore different coordination period lengths. An analysis of US Renal

Data System data found that 33% of dialysis patients prematurely switched to Medicare as a primary payer (e.g., due to unemployment) on average at the eleventh month of this coordination period, while 40% switched to Medicare late or never.[64]

A one-time cost of transplantation was estimated from billed charges reported in the 2025 Milliman Research Report.[75] This report estimates the average total billed charges of a kidney transplant episode in the US across payers (commercial, Medicare, and Medicaid) and including costs of 30 days pre-transplant, organ procurement, hospital admission, physician services, 180 days of post-transplant discharge, and 180 days of post-transplant outpatient immunosuppressants and other prescription drugs. Additionally, we assumed that the costs associated with outpatient immunosuppressants and other prescription drugs would continue for patients in the post-transplant state, representing ongoing care associated with the transplant. The cost of failed transplants were incorporated within the post-transplant state and reflect the Medicare cost of dialysis multiplied by the probability of a failed transplant. We did not include any additional costs for transplant failure as we assumed patients in the model would immediately transition back to dialysis, the cost of which is similar to the medical costs associated with transplant failure.[78]

The model also included the cost of mortality, identified in a large study drawing on a US hospital-based all-payer database of the costs associated with end-of-life care for patients with CKD.[76]

Finally, the model included future gender- and age-specific unrelated health care costs, additive to health state costs over the lifetime of the model.[77]

Adverse Event Costs

For each intervention, the incidence of treatment-related serious adverse events was low (<2%).[8-10] As such, we did not include intervention-related costs related to serious adverse events in the model.

The health care utilization costs described above are higher for patients receiving systemic glucocorticoids (vs. those receiving no specific immunomodulatory therapy), reflecting the costs of treating steroid-related adverse events.

Productivity Costs

We incorporated the cost of lost productivity resulting from absenteeism and early workforce exit in the modified societal perspective analysis. A recent cross-sectional survey found that US adults with IgA nephropathy (not dialysis-dependent) and their caregivers reported missing 8.8% and 9.4% of working time, respectively.[125] This survey also reported the percent of IgA nephropathy patients and their caregivers who were employed. A separate survey found that CKD patients on dialysis and caregivers for dialysis-dependent patients reported missing 21.6% and 14.8% of working time, respectively.[126] Moreover, an analysis of data from the US Renal Data System found that 38% of

people who were employed six months prior to ESKD had stopped working once they began dialysis.[127] Using these estimates as well as national employment statistics and average pre-tax wage plus fringe benefits data (reported in the ICER Reference Case document), we estimated the per-patient per-cycle costs of absenteeism and early workforce exit. We assumed employed individuals held full-time positions and 80% employment among healthy adults. In the model, we applied these cycle costs to post-transplant and dialysis only to demonstrate the impact of treatment (i.e., slowing progression to ESKD) on absenteeism and early workforce exit.

Table E2.4. Patient and Caregiver Lost Productivity

Parameter	Value	Source
Lost Productivity Due to Absenteeism, Mean per Patient per Cycle (Includes Caregiver Absenteeism) (2025 USD)	Post-transplant: $1,283 Dialysis: $1,991	Szklarzewicz et al. ;[125] Chadban et al. ;[126] Erickson et al. ;[127] Authors' calculation
Lost Productivity Due to Early Workforce Exit, Mean per Patient per Cycle (Patient Only) (2025 USD)	Post-transplant: $452 Dialysis: $2,812	Szklarzewicz et al. ;[125] Chadban et al. ;[126] Erickson et al. ;[127] Authors' calculation

E3. Results

Base-case results are described in the main report.

E4. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per evLY. Similar key drivers were related to both cost per evLY and cost per QALY changes, therefore we focus here on cost per evLY.

Figure E4.1. Tornado Diagram for Cost per evLY for Sibeprenlimab versus Systemic Glucocorticoids

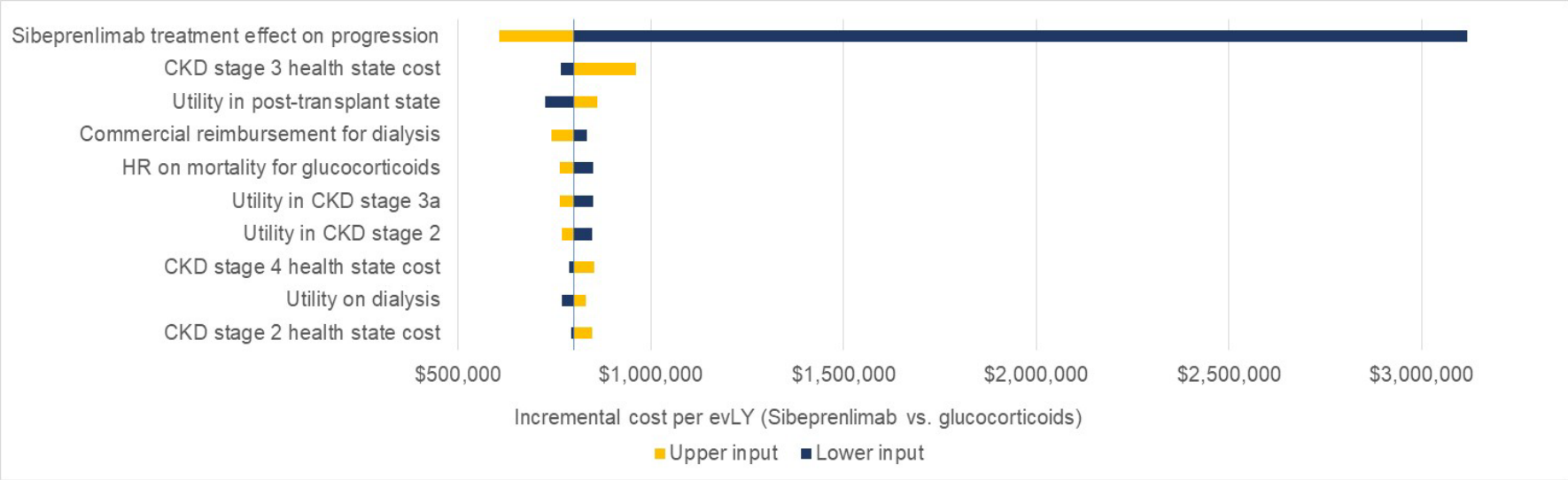
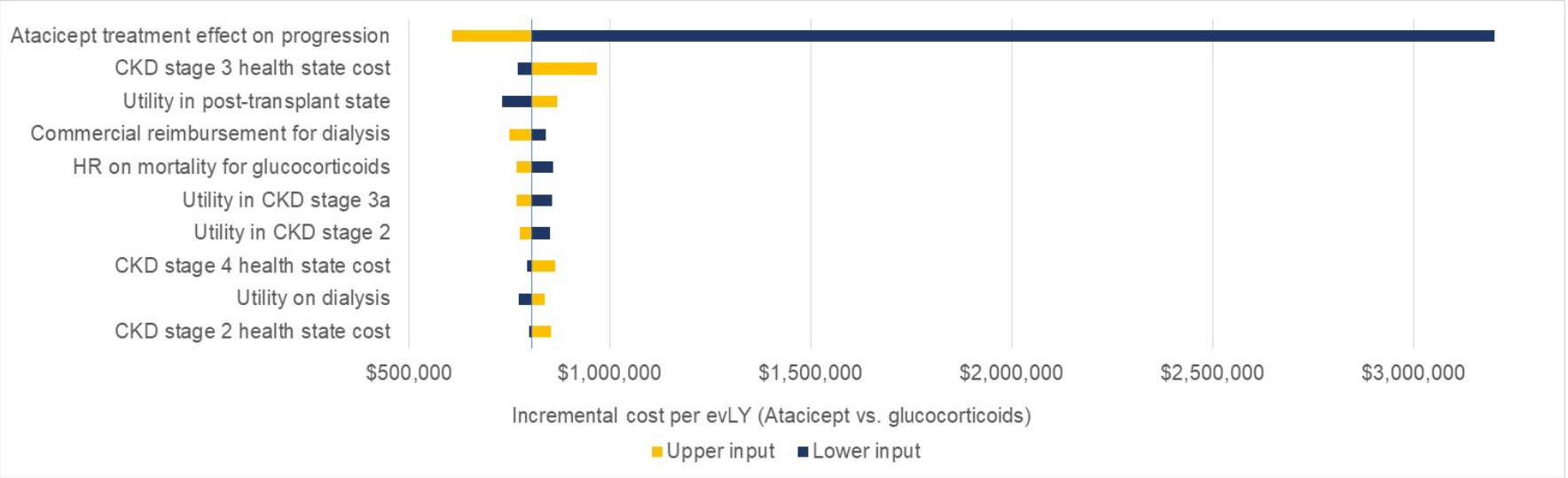


Figure E4.2. Tornado Diagram for Cost per evLY for Atacicept versus Systemic Glucocorticoids*



*Results are based on placeholder price for atacicept.

Figure E4.3. Tornado Diagram for Cost per evLY for Nefecon versus Systemic Glucocorticoids

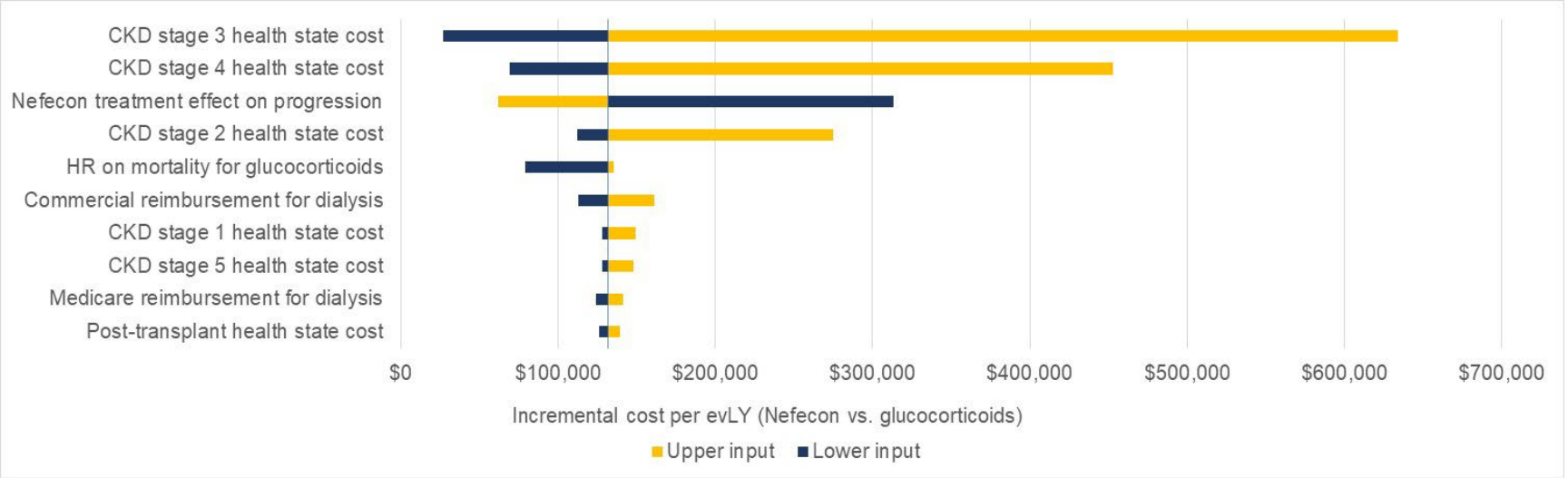


Table E4.1. Tornado Diagram Inputs and Results for Sibeprenlimab versus Systemic Glucocorticoids

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Sibeprenlimab Treatment Effect on Progression†	$607,000	$3,117,000	1.5	10.4
CKD Stage 3 Health State Cost	$765,000	$960,000	$0	$11,184
Utility In Post-Transplant State	$726,000	$861,000	0	0.94
Commercial Reimbursement For Dialysis	$834,000	$743,000	$5,938	$38,586
Hazard Ratio For All-Cause Mortality Among Those Treated With Glucocorticoids	$851,000	$764,000	0.52	3.50
Utility In CKD Stage 3a	$849,000	$763,000	0.60	0.90
Utility In CKD Stage 2	$846,000	$769,000	0.63	0.95
CKD Stage 4 Health State Cost	$788,000	$853,000	$0	$36,449
Utility On Dialysis	$768,000	$831,000	0.45	0.67
CKD Stage 2 Health State Cost	$792,000	$848,000	$0	$7,053

CE: cost-effectiveness, CKD: Chronic Kidney Disease

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

†Represents eGFR slope versus placebo, modeled using calibration multipliers that increase or decrease progression; The base-case assumes a mean eGFR versus placebo of 5.96 ml/min per 1.73 m^2

Table E4.2. Tornado Diagram Inputs and Results for Atacicept versus Systemic Glucocorticoids‡

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Atacicept Treatment Effect On Progression†	$609,000	$9,778,000	0.5	12.5
CKD Stage 3 Health State Cost	$772,000	$968,000	$0	$11,184
Utility In Post-Transplant State	$732,000	$869,000	0.63	0.94
Commercial Reimbursement For Dialysis	$842,000	$751,000	$5,938	$38,586
Hazard Ratio For All-Cause Mortality Among Those Treated With Glucocorticoids	$860,000	$770,000	0.52	3.50
Utility In CKD Stage 3a	$857,000	$770,000	0.60	0.90
Utility In CKD Stage 2	$853,000	$776,000	0.63	0.95
CKD Stage 4 Health State Cost	$795,000	$864,000	$0	$36,449
Utility On Dialysis	$775,000	$839,000	0.45	0.67
CKD Stage 2 Health State Cost	$799,000	$855,000	$0	$7,053

CE: cost-effectiveness, CKD: chronic kidney disease, mL/min/1.73m^2: Milliliter per minute per minute per 1.73 meters squared
*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.
†Represents eGFR slope versus placebo, modeled using calibration multipliers that increase or decrease progression; The base-case assumes a mean eGFR versus placebo of 5.9 ml/min per 1.73 m^2
‡Results are based on placeholder price for atacicept.

Table E4.3. Tornado Diagram Inputs and Results for Nefecon versus Systemic Glucocorticoids

	Lower Incremental Costs	Upper Incremental Costs	Lower Input*	Upper Input*
CKD Stage 3 Health State Cost	$27,000	$634,000	$0	$11,184
CKD Stage 4 Health State Cost	$69,000	$453,000	$0	$36,449
Nefecon Treatment Effect On Progression†	$62,000	$313,000	1.70	4.60
CKD Stage 2 Health State Cost	$112,000	$275,000	$0	$7,053
Hazard Ratio For All-Cause Mortality Among Those Treated With Glucocorticoids	$79,000	$135,000	0.52	3.50
Commercial Reimbursement For Dialysis	$113,000	$161,000	$5,938	$38,586
CKD Stage 1 Health State Cost	$128,000	$149,000	$0	$7,857
CKD Stage 5 Health State Cost	$128,000	$148,000	$0	$64,788

CE: cost-effectiveness
*Note lower input may reflect either upper or lower output value depending on the direction that the input has on the ICER output.
†Represents eGFR slope versus placebo, modeled using calibration multipliers that increase or decrease progression; The base-case assumes a mean eGFR versus placebo of 3.07 ml/min per 1.73 m^2

Table E4.4. Results of Probabilistic Sensitivity Analysis for Sibeprenlimab versus Systemic Glucocorticoids

	Sibeprenlimab Mean	Systemic Glucocorticoids Mean	Incremental
Costs	$5,914,000	$1,388,000	$4,526,000
QALYs	14.30	9.22	5.08
evLYs	14.86	9.22	5.64
Incremental CE Ratio	$891,000 per QALY and $802,000 per evLY		

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year

Table E4.5. Results of Probabilistic Sensitivity Analysis for Atacicept versus Systemic Glucocorticoids*

	Atacicept Mean	Systemic Glucocorticoids Mean	Incremental
Costs	$5,819,000	$1,404,000	$4,415,000
QALYs	14.15	9.22	4.93
evLYs	14.71	9.22	5.48
Incremental CE Ratio	$896,000 per QALY and $805,000 per evLY		

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year

*Results are based on placeholder price for atacicept.

Table E4.6. Results of Probabilistic Sensitivity Analysis for Nefecon versus Systemic Glucocorticoids

	Nefecon Mean	Systemic Glucocorticoids Mean	Incremental
Costs	$1,458,000	$1,400,000	$57,700
QALYs	9.58	9.22	0.36
evLYs	9.64	9.22	0.42
Incremental CE Ratio	$160,700 per QALY and $137,000 per evLY		

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year

E5. Scenario Analyses

All scenario analyses are shown in the main report.

E6. Heterogeneity and Subgroups

We did not explore heterogeneity or conduct subgroup analyses.

E7. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, one independent modeler tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other models and observed findings. Specifically, we compared model outcomes from the Ramjee et al. publication[12] (e.g., discounted life years and discounted total lifetime costs in the best supportive care arm) as well as observed evidence on mortality among persons with IgA nephropathy. Using the same transition matrix we generated a total discounted life years gained of 15.1 as compared to 15.3 in the best supportive care arm. Lifetime discounted costs were also similar at $1,100,000 as compared with $1,200,000 in Ramjee et al. The one major difference found between models was the baseline mortality which produced differences in incremental survival that was not similar to Ramjee et al. Despite the differences in incremental survival between arms, median death was approximately 64 years of age, similar to a publication by Hastings et al. and one used in Ramjee et al.[128] Calibration details can be found in E2 and Table E2.2.

Prior Economic Models

There are two prior, published cost-effectiveness analyses of Nefecon versus best supportive care in people with IgA nephropathy in the US.[11,12] These analyses were funded by Calliditas, the manufacturer of Nefecon. Yaghoubi et al. concluded in the base case that Nefecon is dominant compared to best supportive care in people with IgA nephropathy. Ramjee et al. reported base case ICERs of $16,919 per QALY, $17,119 per evLY, and $21,386 per life year (inflated to 2025 USD).

These prior models used the same Markov model structure consisting of nine health states, cycle lengths of one month, a lifetime horizon, and 3% discounting of future costs and benefits. However, there are several key differences between the two prior models. As noted in the Uncertainty and Controversies section, these prior models differed in their choice of utilities. Yaghoubi et al. adopted substantially lower utilities than Ramjee et al. across the CKD, dialysis, and post-transplant health states. Yaghoubi et al. also included updated transitions between CKD health states based on two-year follow-up data from the NefIgArd trial. These two models also differed significantly in their base case assumptions regarding treatment patterns. While Ramjee et al. applied one round of treatment in the base case (with up to four rounds of additional treatment explored in scenario analyses), the Yaghoubi et al. base case allowed re-treatment assuming the same treatment effect every two years over the lifetime horizon (with a single treatment round and different assumptions regarding treatment durability explored in scenario analyses). Additionally, Yaghoubi et al. applied dynamic pricing in the base case with an assumption that the price of Nefecon would drop by 50% in 2032 and by 80% in 2034.

In addition to assessing the value of three treatments for IgA nephropathy, our analysis differed from these prior models in several important ways. First, we incorporated utility estimates that represent a middle-ground between the estimates used by Ramjee et al. and Yaghoubi et al. Second, we did not apply dynamic pricing assumptions, consistent with the current ICER Value Assessment Framework. Third, our estimate of the cost of dialysis is lower than in both prior

models. One reason for our lower estimate is that we assumed a smaller proportion of IgA nephropathy patients will opt for in-center hemodialysis (the more expensive option) versus peritoneal dialysis. The prior models assumed that 90% of patients would opt for hemodialysis, but this figure is based on all dialysis patients. Since IgA nephropathy patients tend to be younger and healthier than the average person with kidney failure,[129] they are more likely to be candidates for peritoneal dialysis. Our model instead assumed that 75% of IgA nephropathy patients will opt for hemodialysis, a figure derived from a recent study focused on this specific patient population.[121] Additionally, our estimates of the cost of commercial hemodialysis and peritoneal dialysis are lower than what was used in the prior models. The prior models cite Optum claims data as the source of their commercial dialysis cost estimates. We were unable to access this data to verify these figures. Instead, our estimate of these costs was derived from a study drawing on Health Care cost Institute claims data inclusive of employer-sponsored health insurance plans covering more than 55 million people annually from 2012-2019.[72] Fourth, we incorporated future unrelated health care costs whereas the prior models did not. Fifth, our analysis of Nefecon assumed only one treatment course in the base case. This differs from the assumption in Yaghoubi et al. that patients would repeat treatment every two years. Data regarding the safety and efficacy of additional courses of Nefecon are not yet available to support this assumption. Finally, the prior models used data from a study of IgA nephropathy patients in southeastern Kentucky to parameterize mortality across CKD stages.[128] However, this study does not distinguish between pre-ESKD deaths and deaths during dialysis or post-transplant. We adopted an alternative approach that combined national statistics from the USRDS to parameterize mortality from dialysis and post-transplant and pre-ESKD mortality data from a Norwegian cohort to parameterize mortality across CKD stages.[124]

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons.

To estimate the size of the potential candidate populations for treatment, we used the prevalence of IgA nephropathy in the US (approximately 40 per 100,000) multiplied by the total US population averaged over the next five years (approximately 341,000,000).[16,79] We then excluded the portion of the IgA nephropathy population that is already being treated with Nefecon, which is estimated to be approximately 20%,[80] and the portion of the IgA nephropathy population that is not in CKD stage 1 to 4, which is approximately 19.4%.[81] This results in an estimated 87,932 eligible patients in the US. For the purposes of this analysis, we assume that 20% of these patients would initiate treatment in each of the five years, or 17,586 patients per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[130,131] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Once estimates of budget impact are calculated, we compare our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2025-2026, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $821 million per year for new drugs.

G. Supplemental Policy Recommendations

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy in the report: Cornerstones of "Fair" Drug Coverage: Appropriate Cost-Sharing and Utilization Management Policies for Pharmaceuticals. The relatively large number of **patients with IgAN, combined with high annual prices for newer treatments, will lead payers to develop prior authorization criteria and to consider other limits on utilization.**

None of these limits, however, should undermine the tenets of fair access to which all patients have a fundamental right.[132] To explore the appropriate application of evidence to coverage policy, and to reflect the views of patient experts, manufacturers, payers, and clinicians on specific ways that payers might appropriately use coverage policy to manage resources prudently, we present the following perspectives on specific elements of cost sharing and coverage criteria for Nefecon, sibeprenlimab, and atacicept.

Coverage Criteria

- **Age:** These treatments are likely to be covered for adult patients, in line with clinical trial eligibility criteria. If policies exclude children, there should be flexibility when evaluation by a glomerulonephritis expert recommends the use of these agents in a patient under 18.

- **Clinical Eligibility**: Although KDIGO guidelines are relatively new (2025), they do not yet describe the role of the newest therapies (sibeprenlimab and atacicept). Until new clinical guidelines are available, trial inclusion and exclusion criteria are reasonable to define eligibility criteria for therapy. Biopsy should be required to confirm diagnosis of IgAN, consistent with clinical guidelines.

- **Combination Therapy**: There are presently inadequate data on combination therapy of B-cell inhibitors with sparsentan, an endothelin receptor antagonist, which is an expensive medication. Until further clinical information is available, consistent with current clinical guidelines, eligibility for B-cell inhibitors should not depend on whether a patient is also receiving sparsentan.

- **Duration of Coverage and Renewal Criteria**: There are not currently adequate data to inform the duration of effective and safe treatment for sibeprenlimab and atacicept or the efficacy and safety of repeat courses of Nefecon. Given concerning signals in changes of key biomarkers after cessation of therapy, until further data are available, there should not be limitations on duration of approved therapy with sibeprenlimab or atacicept as long as

these drugs are effective and reducing eGFR loss in individual patients. If prolonged courses of sibeprenlimab or atacicept are authorized by payers, prices should be introduced as/reduced to a value-based price. Similarly, if repeated/prolonged courses of Nefecon are authorized by payers, potentially as new efficacy and safety data emerge, its price should be reduced to meet a value-based price for ongoing therapy.

H. Public Comments

This section includes summaries of the public comments prepared for the IgA Nephropathy Public Meeting on February 26, 2026, including one manufacturer's feedback on economic modeling. These summaries were prepared by those who delivered public comments at the meeting. One speaker did not submit summaries of their public comments.

A video recording of all comments can be found here beginning at minute 00:16:10. Conflict of interest disclosures for all public commenters can be found in Supplement I.

Susan Brisendine, NephCure
Vice President of Partnerships and Innovation

NephCure is a nonprofit patient advocacy organization founded in 2000 and dedicated to improving health access and outcomes for people living with rare, protein-spilling kidney diseases.

NephCure applauds ICER for shining an important light on IgA nephropathy and for soliciting community input to inform this assessment and whole process. We agree with many of ICER's conclusions and we understand that cost-effectiveness is an important consideration in selecting a therapy.

However, we are concerned that the ICER review may create additional barriers to access – an outcome that will result in further treatment delays and kidney disease progression. And based on what was discussed during the public meeting, those delays may be based on a wrong model.

We view this interim assessment as fundamentally flawed, incomplete, and in direct conflict with medical evidence and established guidance from medical experts and regulatory authorities.

It is fundamentally flawed given the Institute's use of systemic steroids as a comparator to novel, advanced therapies. We now have extensively studied FDA approved therapies that demonstrate efficacy and safety. High-dose systemic steroids are not FDA-approved for IgAN and are not standard of care. Their use in this setting has been extensively adjudicated and ruled against by the world's leading academic and regulatory authorities. The KDIGO clinical practice guideline recommends using disease-modifying agents as first-line therapy.

The FDA and NICE have rejected the inclusion of steroids as a comparator and the use of steroids in IgAN.

We also believe this interim report is incomplete given the absence of eGFR outcomes data for the advanced disease-modifying therapies.

Certainly, we acknowledge the need for real-world evidence, but that evidence will remain elusive if there are barriers to clinicians prescribing these therapies.

Further, we cannot underestimate the negative impact of long-term, systemic steroid use on patient and caregiver quality of life. Remember not all steroids are the same. In IgAN patients, systemic steroids are typically administered at high doses, often causing life-altering and devastating side effects including swelling; weight gain; muscle, bone, and joint damage; and irritability, moodiness, and aggressiveness and infertility.

We urge ICER to please consider these issues and work toward a more complete, updated guidance that reflects the totality of clinical evidence and expert opinion.

NephCure and the IgAN Alliance will help lead the IgAN community and its stakeholders to the best decisions for patients, guided by the evidence and expert consultation. The voice that matters the most is the voice of the patient, which we are honored to represent.

Below are quotes from the Voice of the Patient Report on the Externally Led Patient-Focused Drug Development Meeting on IgA Nephropathy

“I have body aches, especially from the residual side effects of prednisone treatment six years ago, such as torn muscles, muscle and joint aches. The tearing of the muscle led to missing work, physical therapy, as well as pain I felt from simple things, such as walking."

“Prednisone has altered my life so much that I didn't want to burden anyone. I stayed alone and single for eight years. I isolated myself because of the effects of prednisone and sometimes I wonder, ‘What if I didn't take it?’”

“I've had an 80-pound weight gain due to…prednisone, and now I can't get rid of it. I have an irregular heartbeat. One day it's tachycardia, next day it's bradycardia. Next day I'm having a-fib…”

“…for me the biggest thing [in a future therapy] would have been disease management without the use of steroids... the use of prednisone with the amount of side effects that come with it is unfortunate.”

And patients continue sharing. Just this week we heard from patients who told us:

"(Prednisone) was terrible because of all the side effects. I gained over 50 pounds … and I could not control my diabetes. I thought my 50-year marriage was going to end because my husband, in my eyes, could not do anything correct and I yelled at him constantly. I do not think it was worth it."

"My personal experience with high dose steroids was an absolutely miserable time…" I had many side effects such as severe weight gain of over 30 lbs, muscle weakness, joint discomfort and insomnia... This was the only option at the time… I am very happy there are many other options now for patients with IGAN as high dose steroids are not the answer."

That's the voice of the patient.

That's who we're advocating for.

We're here to help save kidneys -- without delay.

Thank you for your consideration.

Kirk Campbell, MD, University of Pennsylvania Perelman School of Medicine
Professor of Medicine and Chief of the Renal-Electrolyte and Hypertension Division

IgAN is a disease that can look deceptively "quiet" at first—sometimes a young adult who feels well, who is working, raising a family, going to school. But beneath the surface, it can be relentlessly disruptive. Patients often describe the diagnosis as a long-term cloud: *"Is my kidney function going to drop?" "Will I need dialysis?" "What does this mean for pregnancy, for my job, for insurance?"* The uncertainty is its own burden, and it's compounded by a reality we all know: once significant kidney function is lost, we can only slow decline, but we cannot restore what's gone. We do not have regenerative therapy available.

In my practice, we begin where guidelines and common sense align: optimize supportive care—blood pressure control, RAAS blockade when appropriate, lifestyle measures, addressing cardiovascular risk, and other kidney-protective therapies. Many patients do benefit from that foundation. But a meaningful number continue to have persistent proteinuria, ongoing inflammation, and gradual decline despite doing "everything right." Those are the patients where the conversation becomes difficult, because for years the next step too often meant some version of systemic steroids.

Steroids can help some patients, and they have been an important tool historically. But there are real reasons why clinicians and patients are often resistant to using them in IgAN.

From the clinician and patient perspective, the resistance comes down to risk, unpredictability, and tradeoffs. Systemic steroids aren't a small intervention. Even "short courses" can trigger serious complications: infections, severe mood changes, insomnia, weight gain, worsening blood sugar or new diabetes, hypertension, bone loss, and other downstream effects. Many IgAN patients are relatively young, so these adverse effects land in the middle of working years and family life. And because IgAN is heterogeneous, we're frequently balancing imperfect predictors: *who will meaningfully benefit, and who will pay the price without durable kidney protection?* That uncertainty understandably makes both clinicians and patients cautious.

This is why the promise of advanced therapies in IgAN matters so much. Newer approaches—therapies that are more targeted to disease mechanisms, potentially more kidney-specific, and designed to reduce proteinuria and slow progression with a more tolerable side-effect profile—represent something my patients have not consistently had: options.

Options that can be individualized. Options that respect quality of life. Options for those who cannot take systemic steroids safely, or who have already "failed" them. Or a patient I saw recently, where I needed to prioritize managing a drop in eGFR in a short period of time.

When I talk with patients about these newer therapies, the emotion I hear is not hype; it's relief. Relief that we might be able to treat IgAN without asking them to accept side effects that jeopardize their mental health, their metabolic health, or their ability to function. Hope that we can intervene earlier, preserve kidney function longer, and delay—or ideally prevent—dialysis and transplant.

But I also want to share a major concern: access.

In the real world, many of my patients already face barriers just to receive standard kidney care—limited specialist availability, transportation challenges, time off work, and high out-of-pocket costs. Now layer on what typically happens with newer therapies: prior authorizations, repeated documentation requirements, narrow eligibility thresholds, step therapy, and appeals processes. Each administrative step is not just paperwork—it is time, and in IgAN, time can equal irreversible nephron loss.

My worry is that we are at risk of creating yet another barrier: policies that effectively require patients to "earn" access to advanced therapies by first trying systemic steroids, even when steroids are clinically inappropriate, poorly tolerated, or misaligned with patient needs. Step therapy may look reasonable on paper, but it can become a form of rationing that disproportionately harms

patients with fewer resources, less ability to navigate appeals, and less flexibility to attend repeated visits and labs.

The ask is straightforward: as you evaluate advanced therapies for IgAN, please ensure that any value framework or policy recommendations do not unintentionally translate into mandatory step therapy, one-size-fits-all restrictions, or burdensome access hurdles that delay care. There is a crucial need to preserve room for clinician judgment and shared decision-making and recognize that protecting kidney function is more than a clinical outcome – it is essential to maintaining patient independence.

Robert Brenner, MD, Vera Therapeutics
Chief Medical Officer

Good afternoon, and thank you to ICER, to the clinicians here today, and especially to the patients and caregivers who have joined this discussion.

I want to begin by acknowledging what brings us here today. IgA nephropathy is not an abstract diagnosis. It is a lifelong burden carried by young adults, parents, professionals, people who often look healthy on the outside while living with the steady uncertainty of kidney function that may decline year after year. For them, GFR is not just a number. It represents time. Time before dialysis. Time before transplant. Time to live fully.

At Vera, we began our work in IgA nephropathy in 2020 with a simple but ambitious belief: that by harnessing the power of biologic understanding, we can lift the burdens of disease and illuminate the path to healing.

Atacicept, a rationally designed dual BAFF and APRIL inhibitor, is intended to address the upstream immune dysregulation of IgA nephropathy. Rather than attempting to blunt the consequences of kidney damage after it occurs, we set out to try and intervene at its source.

Over the past several years, that belief has been tested through rigorous clinical development. The results we have generated are consistent, biologically coherent data demonstrating meaningful reductions in proteinuria and data suggesting stabilization of kidney function over time. These findings have been peer-reviewed and published in the leading journals in nephrology and medicine.

The strength of this evidence reflects more than statistical outcomes. It reflects a sustained and reproducible effect aligned with the mechanism of action and a clinical program executed deliberately and transparently.

And yet, today's evaluation occurs before the full maturation of long-term Phase III GFR data, data that will further clarify the impact of atacicept on the course of disease. GFR is the currency of kidney preservation. A comprehensive judgment of value must consider long-term outcomes. Assessing value with a partial Phase III dataset will undoubtedly underestimate what sustained stabilization of kidney function could truly mean.

Because value in IgA nephropathy cannot be reduced to a model alone.

A cursory assessment may quantify proteinuria changes and projected cost offsets. But it cannot fully measure the relief of a patient who sees their kidney function hold steady. It cannot quantify the reduced anxiety for a caregiver who no longer worries whether he or she will be a match for a kidney transplant. It cannot capture the preservation of careers, family roles, or independence. Those benefits are real, even if they resist precise calculation.

The FDA granted Breakthrough Therapy Designation to atacicept in 2024 as well as a Priority Review for the Biologics License Application that was submitted in November 2025. These recognitions reflect not hope alone, but confidence grounded in data.

To patients and families: we see your courage. Our commitment has always been to deliver science and medicine that earns your trust.

To physicians: we respect the responsibility you carry in guiding treatment decisions. Our goal is to provide evidence that is rigorous, transparent, and clinically meaningful.

And to the Vera team: your dedication has transformed an idea into a body of evidence strong enough to reshape conversations about what is possible in IgA nephropathy.

Atacicept represents a belief that by precisely targeting disease biology, we can potentially stabilize kidney function and change the long-term outlook for people living with this condition.

Thank you for the opportunity to share our perspective, and I encourage your open-mindedness to what meaningful innovation can bring to people living with IgA nephropathy.

Jay Jackson, PharmD, MPH, Vera Therapeutics
Vice President, Health Economics & Outcomes Research

Modeling a chronic, heterogeneous disease like IgAN is inherently challenging. Long-term randomized data are limited, progression is variable, and cross-trial comparisons require structural assumptions. The ICER model attempts to translate patients lived experience into transition probabilities and health states. As the panel considers the results and today's voting questions, I

want to highlight a few major concerns. My comments focus on how certain assumptions meaningfully influence projected long-term outcomes.

First, baseline disease progression.
The model's long-term projections are anchored to transition probabilities derived from a study cohort enriched for progression. As a result, the modeled base-case population progresses to ESKD relatively quickly compared with broader natural history cohorts.

This matters because when treatment effects are layered onto a population assumed to decline rapidly, long-term projections become highly sensitive to that starting trajectory. If baseline kidney function decline is faster than what many patients experience in routine practice, the model will reach ESKD sooner, and incremental life-years gained will appear smaller.

Second, face validity of the 17.06-ESKD estimate for atacicept.
The model projects patients treated with atacicept reach ESKD in 17.06 years. This conservative estimate implies an effective annual eGFR decline of 2 to 3 times faster than the annualized decline observed in clinical trials and long-term extension data for atacicept.

If a therapy meaningfully stabilizes kidney function and that stabilization persists, one expects a substantially longer delay to ESKD, potentially extending beyond a patient's natural lifetime in some cases.
The discrepancy between observed slope and modeled time-to-ESKD warrants careful examination of how transition probabilities and calibration multipliers are applied.

Finally, value beyond stage transitions.
It's important to recognize that some meaningful humanistic disease impacts of IgAN, and potential treatment benefits, are not fully captured in the current model. Because of data limitations, the model focuses on long-term CKD stage transitions. But the value of therapy in IgAN extends beyond delaying dialysis or transplant.

IgAN affects many patients in early adulthood. Stabilizing kidney function can help preserve employment, independence, and reduce caregiver burden years before kidney failure occurs. The day-to-day symptom burden, psychosocial impact, and lived experience of irregular systemic steroid exposure are not directly reflected in stage-based utilities.

In closing, we appreciate the difficulty in modeling a hypothetical IgAN cohort, especially given the disease modification potential of atacicept demonstrated in our clinical trial program thus far. Our comments are intended to contextualize how baseline progression assumptions and calibration methods may underestimate the long-term clinical impact of sustained eGFR stabilization. Given the progressive nature of IgAN and the age of affected patients, careful attention to structural

modeling assumptions is essential to ensure that projected value aligns with clinical reality. Our comments are provided to help contextualize the limitations of the model results, and we ask the CTAF members to strongly consider during the voting session.

I. Conflict of Interest Disclosures

Tables I1 through I4 contain conflict of interest (COI) disclosures for all participants at the February 26, 2026, public meeting of IgA Nephropathy. You can find any conflicts reported by the authors of the report, or expert reviewers, on page v.

Table I1. CTAF Panel Member Participants and Conflict of Interest Disclosures

CTAF Member	Conflict of Interest
Ralph Brindis, MD, MPH Clinical Professor of Medicine, UCSF	No conflicts to disclose.
Bob Collyar Patient Advocate, Patient Advocates in Research, Co-Founder, Clinical Trials Information Project	No conflicts to disclose.
Felicia Cohn, PhD Bioethics Director, Kaiser Permanente Orange County	No conflicts to disclose.
Sanket Dhruva, MD, MHS, FACC Associate Professor of Medicine, UCSF School of Medicine	No conflicts to disclose.
Rena Fox, MD Professor of Medicine, UCSF	No conflicts to disclose.
Jeffrey Hoch, PhD Professor, University of California, Davis	No conflicts to disclose.
Jeffrey Klingman, MD Neurologist, Kaiser Permanente, Walnut Creek	No conflicts to disclose.
Sei Lee, MD, MAS Professor of Medicine, UCSF Geriatrics	No conflicts to disclose.
Joy Melnikow, MD, MPH Professor emeritus, University of California, Davis	No conflicts to disclose.
Elizabeth Murphy, MD, DPhil Professor of Clinical Medicine, UCSF, Chief of Endocrinology and Metabolism Division	No conflicts to disclose.
Kavita V. Nair, PhD Professor of Neurology and Pharmacy, CU Skaggs School of Pharmacy & Pharmaceutical Sciences, Anschutz Medical Campus	No conflicts to disclose.
Ann Raldow, MD, MPH Associate Professor, UCLA	No conflicts to disclose.
Rita Redberg, MD, MSc, FACC, FAHA Professor of Medicine, Araxe Vilensky Endowed Chair in Cardiology, Core Faculty, Philip R Lee Institute for Health Policy Studies, Director, Inquiry Program, UCSF Division of Cardiology	No conflicts to disclose.
Anthony Sowry Patient Advocate, National Patient Advocacy Foundation	No conflicts to disclose.

Table I2. Clinical and Patient Experts and Conflict of Interest Disclosures

Clinical and Patient Experts	Conflict of Interest
Jonathan Barratt, PhD, FRCP Professor of Renal Medicine, University of Leicester	Dr. Jonathan Barratt has received funds from health care companies including: Calliditas, Vera Therapeutics, Otsuka, AstraZeneca, Argenx, Biogen, Novartis,Vertex, Takeda, Biohaven.
Anthony "Tony" Pisa Individual Living with IgAN	Tony Pisa is a volunteer Patient Advocate with NephCure.
Samantha Schweisthal Individual Living with IgAN	Samantha Schweisthal is a volunteer Patient Ambassador for the state of Alabama with the IgAN Foundation.
Shikha Wadhwani, MD, MS, FASN Associate Professor of Medicine, Division of Nephrology & Hypertension, University of Texas Medical Branch	Dr. Shikha Wadhwani has received funds from health care companies including; Calliditas, Vera Therapeutics, Otsuka, Alexion, Biogen, Boehringer Ingelheim, Dimerix, Novartis, and Travere.

Table I3. Health Care Companies and Conflict of Interest Disclosures

Health Care Company Representatives	Conflict of Interest
Leslie Fish, PharmD Executive Vice President, Clinical Pharmacy, IPD Analytics	Dr. Leslie Fish is a full-time employee at IPD Analytics.
Lobat Hashemi, PhD Global Head, Health Economics and Outcomes Research, Veloxis Pharmaceuticals	Dr. Lobat Hashemi is a full-time employee at Veloxis Pharmaceuticals and Calliditas Therapeutics.
Jay Jackson, PharmD, MPH Vice President, Health Economics & Outcomes Research	Dr. Jay Jackson is a full-time employee at Vera Therapeutics.

Table I4. All Other Participants and Conflict of Interest Disclosures

All Other Participants	Conflict of Interest
Susan Brisendine Vice President of Partnerships and Innovation at NephCure	NephCure received 60% of its funding from healthcare companies including Calliditas, Otsuka, and Vera Therapeutics.
Kirk Campbell, MD Professor of Medicine and Chief of the Renal-Electrolyte and Hypertension Division at the University of Pennsylvania Perelman School of Medicine	Dr. Kirk Campbell has received funds from Calliditas, Vera Therapeutics, Otsuka, AstraZeneca, and Novartis. Dr. Kirk Campbell serves as volunteer Co-Medical Director and Advisor on Board of Directors with NephCure.
Steve Rizk, PharmD, JD Senior Vice President, Medical Affairs, Veloxis Pharmaceuticals	Dr. Steve Rizk is a full-time employee of Veloxis Pharmaceuticals and Calliditas Therapeutics.
Robert Brenner, MD Chief Medical Officer, Vera Therapeutics	Dr. Robert Brenner is a full-time employee at Vera Therapeutics.