January 14, 2026

Submitted electronically to: mbooth@icer.org
Sarah K. Emond, MPP
Institute for Clinical and Economic Review (ICER)
14 Beacon Street, 8th Floor
Boston, Massachusetts 02108

Re: ICER's Draft Evidence Report for Immunoglobulin A Nephropathy (IgAN)

Calliditas Therapeutics and Veloxis Pharmaceuticals, Asahi Kasei companies, appreciate the opportunity to respond to the draft evidence report for ICER's evaluation of Tarpeyo®, a prescription medicine used to reduce the loss of kidney function in adults with a kidney disease called primary IgAN who are at risk for their disease getting worse.

Tarpeyo, a once-daily oral targeted release capsule, is the first FDA-approved potentially disease-modifying therapy demonstrated to reduce the loss of kidney function in adults with primary IgAN who are at risk for disease progression with a 9-month course of treatment.[1,2] Full approval was granted by health authorities based on its proven benefit/risk profile and ability to stabilize the eGFR decline with a 9-month treatment course in a 2-year study.[2,3]

Cumulative patient exposure to the Nefecon (Tarpeyo), targeted release form of budesonide, product in the US, EU, Iceland, Norway, Liechtenstein, UK, China, Macau, Hong Kong, Taiwan, South Korea, and Singapore through July 31, 2025 is 13,174 patient-years. Based on this experience, there have been no changes to the established safety profile for Tarpeyo. No new safety risks have been identified to date.

We have provided additional clarifications and considerations for the ICER team below.

1. ***Clinical Practice Guidelines support that Tarpeyo be considered a first choice for IgAN treatment to address the immune-mediated cause of the disease***

The 2025 Kidney Disease: Improving Global Outcomes (KDIGO) clinical guidelines recommend, where otherwise not available, that Tarpeyo be considered a first choice for IgAN treatment to address the immune-mediated cause of the disease, while simultaneously managing the generic responses to nephron loss.[4] Specifically, the guidelines suggest treatment with a 9-month course of Tarpeyo for patients who are at risk of progressive loss of kidney function with IgAN. The KDIGO guidelines support Tarpeyo, at the time of the guideline issuance, as the only FDA-approved treatment that had shown to reduce the levels of pathogenic forms of IgA (Gd-AgA1),[4] a key driver of the IgAN-specific pathogenic pathway leading to nephron loss. Tarpeyo,a potentially disease-modifying treatment for IgAN, has beneficial effects on pathogenic forms of IgA1, proteinuria and rate of eGFR decline.[4] Consistent with the US prescribing information for Tarpeyo, the KDIGO guidelines note that the rates of adverse events were low and generally mild to moderate in severity and reversible following cessation of Tarpeyo, in line with clinical expectations for a locally acting budesonide product.

2. *Clinical Practice Guidelines only recommend systemic glucocorticoids when Tarpeyo is not available*

KDIGO guidelines have progressively narrowed the role of systemic glucocorticoids in IgAN.[4-6] Due to lack of benefit and well documented risk, the latest KDIGO guidelines only recommend systemic glucocorticoids for the treatment of IgAN in settings where Tarpeyo is not commercially available.[4] Systemic glucocorticoids are therefore not a clinically appropriate or policy-relevant comparator to Tarpeyo in the US setting where Tarpeyo is commercially available.

If ICER continues to include systemic glucocorticoids in its assessment, the following should be described and taken into account.

(1) Population differences

The population studied in TESTING is very different to a US patient population. The KDIGO 2025 Work Group specifically noted that the almost exclusively Asian patients in TESTING was a factor to consider when considering treatment for IgAN. The draft ICER report notes that *"although some clinical experts criticize the external validity of the TESTING trial given that so many enrolled individuals were in China, we were unpersuaded by that concern for multiple reasons. First, in TESTING, there was no suggestion of different treatment effects among participants in China and other participants."* We, in concurrence with the KDIGO 2025 Work Group, strongly disagree with this position. The vast majority of "other" participants in the TESTING study were also of Asian racial origin (93% of the study population was Asian, including 53% Chinese), which is not representative of the US patient population. There were only 7% Caucasian patients. Only 8 Caucasian patients were treated with reduced-dose glucocorticoids and there was no mention of how many, if any, of these 8 patients were Hispanic/Latino.

Conflicting efficacy estimates

The draft ICER evidence fails to appropriately weigh the significance of the STOP-IgAN trial, a randomized controlled trial conducted in a Caucasian population from Germany, which included more Caucasians that TESTING. Rather, the report focuses on data from the reduced-dose cohort of the TESTING study, a randomized controlled trial of oral methylprednisolone in patients with IgAN, to characterize the efficacy and safety of systemic glucocorticoids.[7,8] The rationale for exclusion of the STOP-IgAN trialin the ICER analysis, was that it compared the use of high-dose glucocorticoids with or without additional immunosuppressive therapy to supportive care alone in patients with IgAN in a smaller study.[9] STOP-IgAN showed no long-term renal protection with high-dose systemic glucocorticoid treatment versus placebo,[9,10] in either the overall study population or the subset of patients who received glucocorticoid monotherapy.[10]

As discussed by Seikrit et al 2022, the most prominent difference between the two trials is ethnicity, with STOP-IgAN conducted in Caucasian German patients and TESTING conducted in a predominantly Asian population.[11] It was noted that this difference may be of central relevance given that patients of Asian origin, for example, "Pacific Asians" living in Toronto are known to have a higher risk of kidney failure compared to other IgAN patients in Toronto.[12] This potential influence of ethnicity on efficacy outcomes is further supported by both a real-world study conducted in the US and a retrospective study conducted in Norway, both of which failed to

demonstrate improved kidney outcomes in US/Caucasian patient populations treated with systemic glucocorticoids.[13,14]

Therefore, considering the totality of evidence for systemic glucocorticoids, the failure of high-dose glucocorticoids in STOP-IgAN and other studies in Caucasian patients to demonstrate a statistically significant benefit on eGFR endpoints warrants careful consideration when evaluating the estimated treatment effect for a US patient population and the associated uncertainty around the efficacy estimates for the reduced-dose systemic glucocorticoid regimen.

(2) The need for repeat courses of systemic glucocorticoid therapy is unlikely to be feasible

The likely need for repeated courses of systemic glucocorticoids does not appear to have been taken into consideration within the ICER analysis, in addition to the use of long-term broad-spectrum antibiotics with a documented concern for sudden death in IgAN patients treated with RASi.[15] Upon stopping methylprednisolone in the TESTING study, it is noted that an increase in proteinuria and decline in eGFR were observed, , and even at the reduced dose used in TESTING this will put patients at risk of long-term complications from systemic steroid exposure, such as bone disease and metabolic syndrome, in addition to the acute metabolic, cosmetic, and neuropsychiatric side effects.[4] The authors of the low-dose TESTING study came to a similar conclusion, noting that there are no data to support the efficacy of repeated courses of corticosteroids; and that long-term metabolic, cardiovascular, and infective side effects are likely to offset any benefits.[7]

(3) The impact of the systemic glucocorticoid safety profile has not been adequately captured

Systemic glucocorticoids are widely known to be associated with a range of adverse events (AEs), which negatively impact patients' health and quality of life which the KDIGO 2025 Work Group concluded patients would prefer to avoid, if possible.[4,8,9] The lack of ICH GCP-compliant safety reporting, given there was no general AE data collection, gives rise to significant concerns when considering the ability to determine the effect on patient health and quality of life.

After halting the TESTING trial due to an excess of serious infections and mortality in the high-dose glucocorticoids group, the trial re-started with a new protocol using a 30% reduced dose of glucocorticoids in the active arm. All patients in the reduced-dose cohort received broad-spectrum antibiotic prophylaxis with sulfamethoxazole/trimethoprim for the first 12 weeks of treatment. Although the risk of severe infection and mortality may have been somewhat mitigated in the reduced-dose group of the TESTING study with this prophylactic antibiotic use, the total number of serious adverse events (SAEs) reported was still higher than the number reported with placebo and included 1 death,[7] and severe infections requiring hospitalization still occurred in 4% of patients on the reduced dose regimen.[7,8]

Only reportable SAEs and a few reportable AEs of special interest were collected in TESTING. Without systematic AE collection and reporting, recommendations based on incomplete safety data may expose patients to unforeseen harm. Therefore, in the absence of standard ICH GCP-compliant safety reporting in the TESTING study, there is no overall comprehensive risk assessment for the reduced-dose glucocorticoid regimen.

The proposed regimen introduces significant and well-documented risks when trimethoprim-sulfamethoxazole is combined with angiotensin converting enzyme inhibitors (ACEIs)/angiotensin II type I receptor blockers (ARBs), which is standard of care background therapy for IgAN patients. This combination is associated with an increased incidence of severe hyperkalemia requiring hospitalization and a significantly higher risk of sudden death.[15,16] To our knowledge, this combination has only been studied in IgAN patients in the TESTING study. Due to the flawed safety surveillance in that trial, there is no reliable information on the magnitude of these risks, but they would likely be amplified in IgAN patients with impaired renal function. Furthermore, antimicrobial resistance is a critical and growing global health concern. Antimicrobial stewardship, particularly the judicious use of broad-spectrum antibiotics in immunosuppressed patients, is strongly emphasized in multiple international guidelines. Advocating prophylactic antibiotic use to mitigate life-threatening infections arising from off-label systemic glucocorticoids is a cause for concern when safer approved treatment alternatives are available.

3. The ICER report misrepresents and over-simplifies eGFR treatment effects

In Table 3.3 of the draft report, ICER presents annualized eGFR slope for the three interventions and methylprednisolone. We appreciate ICER's efforts to synthesize heterogeneous data across multiple clinical programs. However, this comparison of eGFR outcomes is derived using different time horizons and analytic methods and risks misrepresenting relative treatment effects.

It is important to note that the values presented for Tarpeyo are based on an annualized difference in eGFR at 2 years following a 15-month off-treatment period.[17] To enable a fair comparison of the on-treatment effects between interventions we request that ICER also present the difference in eGFR at the end of the 9-month treatment period (mean change from baseline 0.7 mL/min/1.73 m^2 with Tarpeyo versus -4.6 mL/min/1.73 m^2 with placebo, a difference of 5.2 mL/min/1.73 m^2).

For systemic glucocorticoids, ICER focuses on the reduced-dose cohort from TESTING. It is important to note that the results presented in Table 3.3 of the ICER report demonstrate that the difference in the annualized eGFR slope between the reduced-dose cohort and placebo was not statistically significant. The lack of a statistically significant benefit on eGFR should be emphasized in ICER's report, inform the model inputs, and considered in ICER's conclusions.

For the reasons outlined above, we believe it is also important to put the TESTING results in the context of other negative trials. Estimates of eGFR slope have not been published for the STOP-IgAN trial, however, from Figure S1B of the Supplement, we estimate an eGFR slope of approximately -1.3 mL/min/1.73 m² per year with supportive therapy compared to -1.0 mL/min/1.73 m² per year with glucocorticoids +/- additional immunosuppression. Supportive of there being no evidence of efficacy for Caucasian patients treated with high-dose glucocorticoid monotherapy in STOP-IgAN, it was stated in Rauen et al 2020 that analyses in subgroups failed to detect significant differences in the primary endpoint between the treatment strategies (Figure 2b and c of Rauen at al 2020).[10]

4. *The results of ICER's economic model do not have face validity*

There is a fundamental disconnect between current Clinical Practice Guidelines and the ICER cost-effectiveness analysis that finds systemic glucocorticoids to be economically dominant. The

caveats around the ICER analysis assumptions are not clearly set out in the draft ICER report to enable interpretation of the model framework and applicability to real-world practice. Peer-reviewed, published economic models suggest that Tarpeyo is expected to be cost effective for the treatment of US adults with IgAN.[18] [19]

As outlined above, clinical evidence from both the TESTING reduced dose cohort and STOP-IgAN studies demonstrated no statistically significant difference in eGFR slope between systemic glucocorticoids and best supportive care. However, ICER concludes that "systemic glucocorticoids were found to be a dominant strategy compared with no specific immunomodulatory therapy", which does not have face validity when considering the model inputs. Specifically, the lack of statistically significant results for systemic glucocorticoids in Table 3.3 indicates that patients on systemic glucocorticoids in the model progress at a similar rate as those in the no specific immunomodulatory therapy arm of the model. In addition, ICER notes that those on systemic glucocorticoids also are assigned an increased risk of mortality, additional disutility for chronic steroid use, and increased health state costs compared with no treatment. When considering these negative impacts, it is not plausible that treatment with systemic glucocorticoids yields higher quality-adjusted life years and lower costs compared with no treatment. The lack of validity for this comparison raises concerns about the entire model.

In addition, we strongly disagree with ICER's approach of modelling a similar safety profile for Tarpeyo compared to reduced-dose glucocorticoids. In the NefIgArd study, Tarpeyo was well tolerated, with low rates of adverse events that were generally mild to moderate in severity and reversible, a safety profile that was as expected for a locally acting budesonide product. The need for mandatory broad-spectrum antimicrobial prophylaxis with reduced-dose systemic glucocorticoids is indicative of an overall more clinically challenging side effect profile. We do not believe that a simple steroid-mortality adjustment in the model is sufficient to account for the health implications that would be associated with the overall safety profile of the reduced-dose glucocorticoid regimen compared with Tarpeyo.

If ICER corrects the errors in the model, the updated results are likely to align more closely with other economic models. In a model evaluating the cost effectiveness of Tarpeyo as a 9-month course of treatment every 2 years, adding Tarpeyo to optimized RASi resulted in a cost reduction of over $105 thousand and an increase of over 1.1 quality-adjusted life-years.[19] The model also predicts that fewer patients will reach end stage kidney disease within 10 years with Tarpeyo + optimized RASi compared with optimized RASi alone (23.55% vs 70.75%). Patients on Tarpeyo + optimized RASi experience a median delay of 14.9 years (95% CI = 4.25-36.25) in reaching end stage kidney disease compared with those on optimized RASI alone. By reducing eGFR loss in patients with IgAN and preserving kidney function, Tarpeyo was estimated to improve health-related quality of life and reduce future overall net health care costs from the payer and societal perspectives in the US. Results were robust in scenario analyses exploring alternative assumptions in the model.

Sincerely,

Lobat Hashemi
Global Head, HEOR, Veloxis Pharmaceuticals

References:

1. TARPEYO. Prescribing Information. Calliditas Therapeutics AB; 2024.
2. Calliditas Therapeutics announces full FDA approval of TARPEYO, the only FDA-approved treatment for IgA nephropathy to significantly reduce the loss of kidney function. PR Newswire; 2023.
3. Everest medicines announces China NMPA's approval of Nefecon® for the treatment of primary IgA nephropathy in adult patients. PR Newswire; 2023.
4. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2025 clinical practice guideline for the management of immunoglobulin A nephropathy (IgAN) and immunoglobulin A vasculitis (IgAV). 2025.
5. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. Oct 2021;100(4s):S1-s276. doi:10.1016/j.kint.2021.05.021
6. Cattran DC, Feehally J, Cook HT, et al. Kidney disease: Improving global outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis. Article. *Kidney International Supplements*. 2012;2(2):139-274. doi:10.1038/kisup.2012.9
7. Kim D, Lv J, Hladunewich M, et al. The Efficacy and Safety of Reduced-Dose Oral Methylprednisolone in High-Risk Immunoglobulin A Nephropathy. *Kidney Int Rep*. Jul 2024;9(7):2168-2179. doi:10.1016/j.ekir.2024.03.032
8. Lv J, Wong MG, Hladunewich MA, et al. Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. *Jama*. May 17 2022;327(19):1888-1898. doi:10.1001/jama.2022.5368
9. Rauen T, Eitner F, Fitzner C, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. *N Engl J Med*. Dec 3 2015;373(23):2225-36. doi:10.1056/NEJMoa1415463
10. Rauen T, Wied S, Fitzner C, et al. After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy. *Kidney Int*. Oct 2020;98(4):1044-1052. doi:10.1016/j.kint.2020.04.046
11. Seikrit C, Stamellou E, Rauen T, Floege J. TESTING the effects of corticosteroids in patients with IgA nephropathy. *Nephrol Dial Transplant*. Sep 22 2022;37(10):1786-1788. doi:10.1093/ndt/gfac221
12. Barbour SJ, Cattran DC, Kim SJ, et al. Individuals of Pacific Asian origin with IgA nephropathy have an increased risk of progression to end-stage renal disease. *Kidney Int*. Nov 2013;84(5):1017-24. doi:10.1038/ki.2013.210
13. Pesce G, Patel M, Gusto G, Kadambi A, Chandak A, Madison T. Real-world challenges associated with the use of four common systemic glucocorticoids in a United States IgAN cohort. *Front Nephrol*. 2025;5:1574239. doi:10.3389/fneph.2025.1574239
14. Rivedal M, Haaskjold YL, Eikrem Ø, Bjørneklett R, Marti HP, Knoop T. Use of corticosteroids in Norwegian patients with immunoglobulin a nephropathy progressing to end-stage kidney disease: a retrospective cohort study. *BMC Nephrol*. Jan 29 2024;25(1):42. doi:10.1186/s12882-024-03481-6
15. Fralick M, Macdonald EM, Gomes T, et al. Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system: population based study. *Bmj*. Oct 30 2014;349:g6196. doi:10.1136/bmj.g6196

16. Antoniou T, Gomes T, Juurlink DN, Loutfy MR, Glazier RH, Mamdani MM. Trimethoprim-sulfamethoxazole-induced hyperkalemia in patients receiving inhibitors of the renin-angiotensin system: a population-based study. *Arch Intern Med*. Jun 28 2010;170(12):1045-9. doi:10.1001/archinternmed.2010.142
17. Lafayette R, Kristensen J, Stone A, et al. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial. *Lancet*. 2023;402(10405):859-870. doi:10.1016/S0140-6736(23)01554-4
18. Ramjee L, Vurgun N, Ngai C, Patel M, Tremblay G. Cost-Effectiveness Analysis of Nefecon versus Best Supportive Care for People with Immunoglobulin A Nephropathy (IgAN) in the United States. *Clinicoecon Outcomes Res*. 2023;15:213-226. doi:10.2147/ceor.S389456
19. Yaghoubi M, Jiang H, Casciano R, Ngai C, Patel M. Cost-effectiveness analysis of targeted-release formulation of budesonide (Tarpeyo) in conjunction with optimized renin-angiotensin system inhibitor (RASi) therapy relative to optimized RASi therapy alone for adults with primary immunoglobulin A nephropathy in the United States. *J Manag Care Spec Pharm*. May 2025;31(5):499-509. doi:10.18553/jmcp.2025.31.5.499

Otsuka
Otsuka-people creating new products for better health worldwide

January 14, 2026

Submitted electronically to publicccomments@icer.org

RE: ICER Draft Evidence Report: Immunoglobulin-Directed Therapies for IgA Nephropathy

Otsuka America Pharmaceutical, Inc. (Otsuka) would like to thank the Institute for Clinical and Economic Review's (ICER) for the evaluation of IgA nephropathy (IgAN) therapies. We appreciate the opportunity to submit comments on ICER's Draft Evidence Report for its review of immunoglobulin-directed therapies for IgAN.

IgAN is a progressive, immune-mediated, chronic kidney disease that can lead to progressive loss of kidney function and, eventually, end-stage kidney disease (ESKD), imposing a significant burden on patients and the healthcare system.[1,2,3] IgAN is the result of production of galactose-deficient IgA, resulting in the production of autoantibodies, immune complex (IC) formation, and mesangial deposition of ICs, leading to inflammation, fibrosis and kidney damage.[4] Despite supportive care, there is an unmet need for treatments that address the root causes of the condition.[5] Recent KDIGO guidelines for IgAN treatment highlighted the need to address IgAN specific drivers for nephron loss and managing generic response to IgAN-induced nephron loss simultaneously.[6] Sibeprenlimab-szsi seeks to fulfill the need to address IgAN specific drivers of nephron loss per the treatment strategy outlined in KDIGO guidelines.

Elements of ICER's approach are not comprehensive for evaluating the true benefit of therapies in IgAN. The ultimate value of these therapies stems from long-term reductions in ESKD, dialysis, and transplantation, which are not adequately accounted for in the current assessment. These long-term benefits also make it inappropriate to compare long-term options like sibeprenlimab-szsi to short-term treatments. Further, the current assessment does not account for the value of proteinuria reduction associated with these therapies. Improving proteinuria – a surrogate marker correlated with delayed progression to kidney failure – may spare patients from costly and life-threatening outcomes such as dialysis or kidney transplantation, and kidney failure itself has a similar or higher five-year mortality rate as certain forms of cancer.[7] A recently published study further reinforces the clinical importance of proteinuria control, demonstrating that complete remission of proteinuria is associated with greater eGFR preservation and fewer kidney failure events. These findings reinforce recommendations to maintain proteinuria levels ideally <0.3 g/day underscoring its relationship with kidney function preservation.[8] To avoid disincentivizing innovation and undermining the value that new therapies bring to the nephrology space, we offer the following questions and comments on key sections of the Draft Evidence Report below.

Report Timing and Data Availability:

ICER's review is inconsistent in the use of pivotal clinical trial data, and any findings should be caveated as limited and conditional. We concur with ICER's recognition that all outputs of its report are limited by the lack of long-term and head-to-head evidence. Though ICER acknowledges the potential clinical value of these interventions, there are a lack of mature 2-5 year

data which are critical for evaluating long-term effectiveness and making comprehensive conclusions regarding comparative efficacy and safety. As part of sibeprenlimab-szsi's ongoing review via the Accelerated Approval Pathway, the FDA has proscribed the public release of Phase 3 estimated glomerular filtration rate (eGFR) data until expected completion of the VISIONARY confirmatory clinical trial.[9] Because of this, Otsuka was unable to provide ICER with such evidence, but we anticipate it will meaningfully shape ICER's conclusions. Until then, we strongly recommend that ICER reframe its results as interim findings. We also recommend that ICER stress that its choice to pursue an assessment without mature data may lead to subpar valuations of relative efficacy and cost-effectiveness, making the report unsuitable for informing payer policies or decision-making.

Intervention and Comparator Choice:

We recommend ICER to reconsider its inclusion of systemic glucocorticoids as a comparator, which fails to reflect the treatment paradigm in real-world clinical practice. Unlike B-cell directed therapies intended for long-term therapy, systemic glucocorticoids' short-term effects make them suitable for only acute, temporary treatment. Even in the TESTING trial ICER used for its clinical review and model inputs, short-course corticosteroids only temporarily delayed kidney events for 2-3 years, after which outcomes paralleled placebo.[10] Prior cost-effectiveness analyses have recognized this, instead employing no specific immunomodulatory therapy as the most appropriate comparator for B-cell directed therapies.[11,12] Tellingly, ICER's scenario analysis comparing interventions to no specific immunomodulatory therapy substantially reduced the cost per QALY and cost per evLY versus the base case. Clearly, comparator choice is highly impactful for this assessment. The inclusion of systemic glucocorticoids disregards the actual course of care, compromising the clinical validity and generalizability of ICER's findings.

If ICER must include systemic glucocorticoids as a comparator, we recommend that it diversify its evidence base to avoid bias. ICER's clinical review and model inputs employ data from the TESTING trial's reduced dose methylprednisolone cohort, however, these data 1) are some of the most positive available, 2) directly conflict with other literature, and 3) come from a sample poorly representative of the U.S. population.[10] For example, the STOP-IgAN trial – performed by the same researchers as the TESTING trial – observed *no* additional benefit and significantly more infectious adverse events with high-dose corticosteroid therapy vs. supportive care alone after a median follow-up of 7.4 years.[10] Marked population differences may explain this discrepancy: 95% of the TESTING trial's population were Southeast Asian, whereas STOP-IgAN participants were predominately Caucasian. Because Asian populations have faster disease progression than Caucasian and Black populations, the racial distribution of selected studies may meaningfully shape cost-effectiveness outcomes and STOP-IgAN results are more appropriate for a U.S. cost-effectiveness analysis.[13] Further, as noted in ICER's Supplemental Information, the TESTING trial's eGFR data had a high risk of bias and therefore may not be reflective of real-world outcomes. As such, we encourage ICER to diversify its evidence base to better represent the U.S. patient population and avoid favorably skewing glucocorticoid modelling inputs.

We recommend that ICER include all approved IgAN therapies focused on managing IgAN-specific drivers for nephron loss. This includes Fabhalta (iptacopan) which was approved for IgAN patients in August of 2024.

Trial Population Differences:

Trial population differences are not sufficiently adjusted, impacting the relative efficacy of interventions. ICER makes note of significant heterogeneity in the trials' "study populations, study design, intervention type, outcome definition and measurement, and analytic methods, as well as quality." Given that the cost effectiveness model's average time to ESKD depends on whether trials included late or early-stage disease, population discrepancies across trials, in the absence of standardization, may skew the relative efficacy and cost-effectiveness of interventions. For example, eGFR change from baseline in the control group in the TESTING trial was -3 mL/min/1.73m^2 whereas the control group in the ENVISION trial had a change of -7.4 mL/min/1.73m^2.[14,15] Some attempt to ameliorate these between-trial differences is indispensable to any discussion of comparative efficacy. However, ICER deemed conducting an indirect treatment comparison (ITC) unfeasible because of these very differences. ICER should instead consider a matched adjusted indirect comparison (MAIC) to shore up the methodological rigor of its review and minimize the influence of population differences on comparative treatment benefits.

Outcomes:

ICER's cost effectiveness analysis does not fully account for the cost offsets of delaying dialysis or potentially preventing kidney transplantation in a patient's lifetime. Because mortality and quality of life impacts are relatively small in early stages of IgAN, the prevention of dialysis and kidney transplant make up the majority of cost offsets and QALY gains for most kidney disease interventions. Therefore, to avoid undervaluing these interventions, we recommend that ICER fully incorporate these health states and costs in the model and evaluate a range of outcomes assumptions in a sensitivity analysis. As ICER acknowledges, utilities for dialysis and post-kidney transplant vary. However, ICER's conservative extrapolation of long-term renal benefits threatens to undervalue these treatments. Further, in addition to dialysis and kidney transplantation, ICER does not adequately capture loss of productivity in its base case.

Pricing and Model Inputs:

We recommend that ICER does not blend WAC, placeholder, and net prices in its model inputs. For consistency, ICER should consider using publicly available WAC pricing for all therapies and avoid using a blend of published WAC, speculative net pricing (since discounts are not publicly available), and assumed WAC or net price for unapproved therapies. We recognize that this choice was driven by available data, however, presenting these results side by side can prompt misleading conclusions about both cost-effectiveness and affordability. In particular, applying different pricing for treatments in the same category of APRIL and APRIL/BAFF inhibitors, *i.e.*, using a speculative net price for atacicept and established WAC for sibeprenlimab-szsi, adds considerable uncertainty and makes cost-effectiveness estimates incomparable. The launch price of atacicept is not likely to reflect pricing strategies for second entrant within class therapies in the US and we recommend that to be revisited.

Budget Impact:

ICER overestimated the number of eligible patients. ICER estimated that there will be 167,191 eligible patients over five years, based on a prevalence estimate of 61.3 per 100,000 persons. However, this source is limited by the restricted availability of biopsy results and the possibility of overcounting due to the possible inclusion of multiple biopsy claims from the same individuals.[17] A study with a larger sample and a 12-year rather than one-year timeframe estimated a prevalence of 40 cases per 100,000 persons, or 104,400 people using the current U.S. adult

population.[18] Of these, 84,146 would be treatment eligible given that ~80.6% are in CKD stage 1 to 4.[19] We recommend that ICER reduce its estimated patient population accordingly.

Rare Disease:

IgAN is a rare, chronic renal disease, making ICER's $100,000 per QALY threshold relatively low by international standards. As stated in Otsuka's Draft Scoping Document comments, economic reviews in other countries (*e.g.,* the United Kingdom, Sweden, Canada, Germany, France, and the Netherlands) have removed or amended cost-effectiveness thresholds for orphan and ultra-orphan treatments, and some have also permitted higher levels of uncertainty to account for the challenges of generating robust evidence in small populations.[20,21,22] In the U.S., the FDA has similarly implemented protections and incentives to promote innovation in rare diseases, since the economic viability of products intended for very small patient populations would otherwise pose barriers to market entry.[23] ICER's typical cost-effectiveness standards are inappropriate for rare conditions like IgAN, and we recommend applying disease severity and disease rarity-based willingness to pay thresholds to avoid excessively penalizing these therapies.

* * * * *

Conclusion

Otsuka appreciates the opportunity to comment on ICER's Draft Evidence Report for the IgAN review. We respectfully recommend that ICER apply these recommendations in the revised evidence report to best reflect the unique value that these innovative interventions offer to patients and society as a whole.

If you have any questions about these comments, please contact: Sasikiran Nunna, PhD, Director Global Value Evidence Strategy at Sasikiran.Nunna@otsuka-us.com.

Sincerely,

Ainslie Forbes

VP, Global Integrated Evidence Generation & Innovation

Otsuka Pharmaceutical Development & Commercialization, Inc.

REFERENCES

1. Pitcher D, Braddon F, Hendry B, et al. Long-Term Outcomes in IgA Nephropathy. *Clin J Am Soc Nephrol*. 2023;18(6):727-738. doi:10.2215/CJN.0000000000000135. Link
2. Lai KN, Tang SC, Schena FP, et al. IgA nephropathy. *Nat Rev Dis Primers*. 2016;2:16001. Published 2016 Feb 11. doi:10.1038/nrdp.2016.1. Link
3. Cheung CK, Boyd JKF, Feehally J. Evaluation and management of IgA nephropathy. *Clinical Medicine*. 2012;12:s27-s30. Link

4. Suzuki H, Novak J. IgA Nephropathy: Significance of IgA1-Containing Immune Complexes in Clinical Settings. *J Clin Med*. 2024;13(15):4495. Published 2024 Aug 1. doi:10.3390/jcm13154495. Link
5. Cheung CK, Barratt J, Liew A, Zhang H, Tesar V, Lafayette R. The role of BAFF and APRIL in IgA nephropathy: pathogenic mechanisms and targeted therapies. *Front Nephrol*. 2024;3:1346769. Published 2024 Feb 1. doi:10.3389/fneph.2023.1346769. Link
6. Kidney Disease: Improving Global Outcomes (KDIGO) IgAN and IgAV Work Group, Rovin BH, Barratt J, et al. KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV). *Kidney Int*. 2025;108(4S):S1-S71. doi:10.1016/j.kint.2025.04.004. Link
7. Stedman MR, Kurella Tamura M, Chertow GM. Using Relative Survival to Estimate the Burden of Kidney Failure. *Am J Kidney Dis*. 2024;83(1):28-36.e1. doi:10.1053/j.ajkd.2023.05.015. Link
8. Heerspink HJ, Rovin BH, Komers R, Hendry B, Mercer A, Preciado P, Murphy E, Tesar V. Association between Complete Proteinuria Remission and Kidney Function in the Phase 3 PROTECT Trial of Sparsentan in IgA Nephropathy. Clin J Am Soc Nephrol. 2025 Dec 22. doi: 10.2215/CJN.0000000961. Link
9. Visionary Study: Phase 3 Trial of Sibeprenlimab in Immunoglobulin A Nephropathy (IgAN). ClinicalTrials.gov identifier: NCT05248646. Updated September 10, 2025. Link
10. Seikrit C, Stamellou E, Rauen T, Floege J. TESTING the effects of corticosteroids in patients with IgA nephropathy. *Nephrol Dial Transplant*. 2022;37(10):1786-1788. doi:10.1093/ndt/gfac221. Link
11. Ramjee L, Vurgun N, Ngai C, Patel M, Tremblay G. Cost-Effectiveness Analysis of Nefecon versus Best Supportive Care for People with Immunoglobulin A Nephropathy (IgAN) in the United States. *Clinicoecon Outcomes Res*. 2023;15:213-226. Published 2023 Mar 29. doi:10.2147/CEOR.S389456. Link
12. Yaghoubi M, Jiang H, Casciano R, Ngai C, Patel M. Cost-effectiveness analysis of targeted-release formulation of budesonide (Tarpeyo) in conjunction with optimized renin-angiotensin system inhibitor (RASi) therapy relative to optimized RASi therapy alone for adults with primary immunoglobulin A nephropathy in the United States. *J Manag Care Spec Pharm*. 2025;31(5):499-509. doi:10.18553/jmcp.2025.31.5.499. Link
13. Sim JJ, Cannizzaro NT, Chen Q, Nunna S, Mathur M, Pinto C. Progression of immunoglobulin A nephropathy (IgAN) in a Hispanic/Latinx population in the United States. *Front Nephrol*. 2026 Jan 8; 5:1744454. doi: 10.3389/fneph.2025.1744454. Link
14. Kim D, Lv J, Hladunewich M, et al. The Efficacy and Safety of Reduced-Dose Oral Methylprednisolone in High-Risk Immunoglobulin A Nephropathy. *Kidney Int Rep*. 2024;9(7):2168-2179. Published 2024 Apr 3. doi:10.1016/j.ekir.2024.03.032. Link
15. Mathur M, Barratt J, Chacko B, et al. A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy. *N Engl J Med*. 2024;390(1):20-31. doi:10.1056/NEJMoa2305635. Link
16. Mercer A, Carroll KJ, Conley L, et al. Estimating delay in time to kidney failure or death for treatment effects on proteinuria in IgA nephropathy. Presented at: 60th ERA Congress 2023; June 15-18, 2023; Milan, Italy. Link
17. DeCongelio M, Ali SN, Furegato M, Bhattacharjee S, Fernandes AW. The incidence and prevalence of immunoglobulin A nephropathy in the United States. *Clin Nephrol*. 2025;103(1):19-25. doi:10.5414/CN111489. Link

18. Sim JJ, Chen Q, Cannizzaro N, et al. Incidence of Adult Primary Immunoglobulin A Nephropathy among a Racially/Ethnically Diverse Population in the United States. *Am J Nephrol*. 2025;56(2):172-177. doi:10.1159/000541869. Link
19. Caster DJ, Abner CW, Walker PD, et al. Clinicopathological Characteristics of Adult IgA Nephropathy in the United States. *Kidney Int Rep*. 2023;8(9):1792-1800. Published 2023 Jun 28. doi:10.1016/j.ekir.2023.06.016. Link
20. Ollendorf DA, Chapman RH, Pearson SD. Evaluating and Valuing Drugs for Rare Conditions: No Easy Answers. *Value Health*. 2018;21(5):547-552. doi:10.1016/j.jval.2018.01.008. Link
21. Lee D, McCarthy G, Saeed O, Allen R, Malottki K, Chandler F. The Challenge for Orphan Drugs Remains: Three Case Studies Demonstrating the Impact of Changes to NICE Methods and Processes and Alternative Mechanisms to Value Orphan Products. *Pharmacoecon Open*. 2023;7(2):175-187. doi:10.1007/s41669-022-00378-8. Link
22. National Institute for Health and Care Excellence (NICE). NICE health technology evaluation topic selection: the manual. NICE Process and Methods (MPG37). Published January 31, 2022. Link.
23. Orphan Drug Act – Relevant Excerpts. U.S. Food and Drug Administration. Updated August, 2014. Link

January 14, 2026

Institute for Clinical and Economic Review (ICER)
14 Beacon St, Suite 800
Boston, MA 02108
publiccomments@icer.org

Re: Public Comment on Draft Evidence Report – B-Cell Directed Therapies for IgA Nephropathy: Effectiveness and Value

Vera Therapeutics (Vera) appreciates the opportunity to engage with ICER on the IgA Nephropathy (IgAN) assessment evaluating systemic glucocorticoids (SGCs), Nefecon, sibeprenlimab, and atacicept. We recognize the complexity of evaluating a chronic, heterogeneous disease such as IgAN and commend ICER for the breadth of analyses undertaken as outlined in the draft evidence report on B-Cell Directed Therapies for IgA Nephropathy: Effectiveness and Value (December 10, 2025). We thank you for the consideration given to the input provided by Vera during the scoping and model analysis plan phases.

At the same time, we have several concerns about the current approach and its implications for the comparative value of available and emerging therapies. Our comments focus on issues that, in our view, materially affect conclusions and will be important for payers, clinicians, and most importantly patients living with IgAN.

IgAN is a chronic, B-cell–mediated autoimmune kidney disease characterized by progressive nephron loss, high lifetime risk of kidney failure, and substantial morbidity and mortality despite best supportive care. Emerging disease-modifying therapies targeting upstream immunologic drivers have the potential to fundamentally alter the clinical trajectory of IgAN. Atacicept, a dual BAFF/APRIL inhibitor, is designed to modulate pathogenic B-cell activity by reducing production of galactose-deficient IgA1 and corresponding autoantibodies that form nephritogenic immune complexes. In clinical studies, atacicept has demonstrated sustained reductions in proteinuria accompanied by stabilization of eGFR over extended follow-up,[i,ii] suggesting a capacity to slow long-term disease progression rather than produce transient effects. In a disease where even modest reductions in eGFR slope can translate into years of dialysis-free survival,[iii] therapies capable of durable kidney function preservation represent a potentially transformative advance for patients, clinicians, and health systems. Importantly, the value of such disease-modifying therapies is driven by durable stabilization of eGFR slope over time, an outcome that may be systematically underrepresented in the ICER IgAN cost-effectiveness model in which long-term benefits are calibrated primarily through short-term or mean eGFR changes.

Implausible time to ESKD due to overestimation of atacicept eGFR decline

Under representation of eGFR stabilization. It is important to highlight a broader internal inconsistency in the model outputs that materially affects the interpretation of atacicept's value. In the base-case results (Draft Evidence Report, Table 4.3), atacicept is associated with a mean time to end-stage kidney disease (ESKD) of 15.2 years. Given the modeled population characteristics and observed clinical data, this estimate appears implausibly low. As described in the model inputs, the simulated cohort is predominantly composed of patients with CKD stages 2, 3a, and 3b, with no patients starting in CKD stages 4 or 5. In this population, a time to ESKD of 15.2 years implies an effective eGFR decline on the order of approximately 2–3 mL/min/1.73 m² per year, which is several-fold faster than the annualized eGFR slope observed in clinical trials and long-term extension data for atacicept.[i,ii,iv]

This disconnect suggests that the model has overestimated the rate at which patients transition through worsening CKD stages despite treatment. As a consequence, the model thereby truncates the disease-modifying benefit of atacicept demonstrated through sustained eGFR stabilization. When compounded over time, these aggressive progression assumptions materially limit modeled time to ESKD and downstream life-year gains. Absent such aggressive transition assumptions, it is difficult to envision a clinical scenario in which a disease-modifying therapy that demonstrates sustained eGFR stabilization would yield only a modest delay (e.g., 4 years versus SGC, Table 4.3) to ESKD in a predominantly CKD stage 2–3 population.

Approach to systemic glucocorticoids lacks face validity

Over-reliance on a subset from the TESTING trial for lifetime SGC benefit. ICER's decision to rely on the reduced-dose TESTING cohort as the basis for lifetime SGC treatment effects is concerning because these results define the base-case comparator arm of the model. The data selected come from a subset of a single study resulting from a trial that was halted due to safety concerns and subsequently restarted under a revised protocol. Roughly 95% of participants were enrolled in China or other Asian countries, thus substantially limiting generalizability to the modeled US population. The rationale for using this cohort from a single trial as the sole basis of evidence for this important comparator, modeled over a lifetime horizon, is unclear, especially as the trial itself shows that eGFR and proteinuria benefits are largely front-loaded and diminish over time as acknowledged by the study authors.[v,vi,vii]

In addition, other randomized SGC trials (e.g., STOP-IgAN[viii] and earlier studies) do not demonstrate consistent, durable renoprotective benefit, and this broader evidence base does not appear to be fully incorporated or reflected in the assumed long-term effect of SGCs in the model. Importantly, the apparent long-term benefit attributed to SGCs in the model is not supported by how these therapies are used in real-world IgAN care. SGCs are typically administered as short-course interventions and are not intended to provide durable disease modification or sustained eGFR stabilization. In real-world IgAN care, SGCs are not prescribed as chronic maintenance therapy.

Modeling a chronic SGC paradigm is not simply an uncertainty, it is a clinically implausible construct that does not reflect how steroids are used in practice and should not serve as the cornerstone comparator for long-term value conclusions.[ix] Modeling short-course steroid effects as providing persistent lifetime benefit likely overstates their ability to reduce the risk of progression to kidney failure. When such overstated durability is applied to steroids but not to therapies designed for chronic disease modification, the resulting comparisons risk understating the long-term clinical and economic value of B-cell modulators such as atacicept.

Choice of base-case comparator. The draft report deviates from the original model analysis plan by reporting SGCs as the only base-case comparator, with "no specific immunomodulatory therapy" or best supportive care (BSC) relegated to supplemental scenarios. Using chronic SGC maintenance (up to 9 months on therapy) assuming a durable clinical benefit well beyond treatment discontinuation (as described above) as the implicit reference framework is fundamentally flawed for IgAN and creates a structural bias in the model: it anchors long-term comparisons to a 'standard of care' that is not clinically plausible. This implicitly treats SGCs as the default standard of care, despite substantial uncertainty about their role and the fact that many patients in practice do not stay on therapy because of contraindications, prior toxicity, or preference.[ix,x] This modeling decision is particularly consequential because SGCs are not routinely used as chronic therapy in IgAN, given well-recognized safety limitations, and therefore do not represent a clinically plausible long-term comparator for therapies intended to deliver disease-modifying benefit through sustained eGFR stabilization. Moreover, comparing SGCs with precision B-cell modulators as if they represent comparable long-term treatment strategies conflates fundamentally different therapeutic intents: systemic glucocorticoids are episodic, broadly immunosuppressive interventions, whereas atacicept is a precision B-cell modulator targeting IgAN-specific drivers through dual BAFF/APRIL inhibition. Treating these approaches as interchangeable within the base-case framework introduces structural bias that disadvantages novel therapies whose value lies in durable disease modification rather than short-term suppression.

Asymmetric handling of treatment duration for SGCs. ICER's stated rationale for selecting SGCs as the base-case comparator is that they were dominant to BSC in preliminary model analyses. This assumption effectively treats SGCs as chronic maintenance therapies while simultaneously constraining other short-course or disease-modifying therapies to time-limited benefit, despite comparable or more durable clinical signals. Of concern, this conclusion appears to be driven by the assumptions used to model eGFR slope, specifically treating SGCs, which are short-term interventions, as providing a continuous long-term benefit. In contrast, ICER assumes a time-limited, 24-month benefit for Nefecon. The rationale for modeling two steroid treatments so differently is unclear, and this asymmetrical approach leads to counterintuitive results. For example, time to end-stage kidney disease (ESKD) is 6.17 years for BSC, 7.1 years for Nefecon, and 11.23 years for SGCs (Section E5, Table 4.3). Applying different durability assumptions for Nefecon and SGCs results in a 4.1-year longer time to ESKD with SGCs versus Nefecon, and consequently a dominant cost-effectiveness result with SGCs costing less and providing better outcomes.

The handling of off-treatment transitions appears central to this issue. After 24 months, Nefecon is forced back onto the BSC curve based on NefIgArd Part B data, while SGCs maintain a treatment-specific trajectory indefinitely. These modeled results are difficult to reconcile with the underlying trials, which show qualitatively similar short-term eGFR and proteinuria profiles for methylprednisolone and Nefecon (both short steroid courses with waning benefit over time).[xiii,v] Given that the SGC arm currently serves as the sole base-case comparator, it is especially important that SGCs are modeled in a way that realistically reflects the totality of the evidence and is clinically plausible. In practice, the clinical distinction between methylprednisolone and Nefecon is not one of durability but of formulation and safety profile; both are administered as finite steroid courses with waning effects, making the modeled divergence in long-term outcomes difficult to justify.

Modeled population and progression rates are not aligned with real-world IgAN

Baseline population comparability and treatment-effect modifiers. The draft report states that the model assumes the same baseline population characteristics for each treatment arm, based on an assumption of broad similarity across pivotal IgAN studies. However, baseline characteristics across the source trials show meaningful differences in variables known to influence disease progression, including CKD stage, proteinuria or urine protein-creatinine ratio (UPCR), race and ethnicity, and SGLT2 inhibitor use in the more contemporary trials.[i,ii,xi,xii,xiii] Failure to account for these differences may also introduce implicit bias into comparative estimates, particularly when newer trials enroll patients with more contemporary background therapy and different baseline risk profiles. While age and sex are often used as default covariates, as described by ICER's Clinical Trial Diversity Rating (CDR) tool,[xiv] evidence suggests that these alone are insufficient predictors of IgAN progression. Notably, CKD stage, proteinuria, and race are important clinical predictors of eGFR decline and treatment response in IgAN.[iii,xv] Assuming an identical baseline model population for all interventions, without adjusting for these differences or exploring them in sensitivity analyses, risks distorting comparative outcomes. Ignoring the importance of these factors has potential equity implications, particularly when some populations are systematically under or overrepresented. We acknowledge that the current evidence base limits the analytic levers available to fully resolve these between-trial differences; therefore, the report should explicitly acknowledge this limitation and interpret comparative findings accordingly.

Baseline natural history and speed of progression. In the current model, the "no specific immunomodulatory therapy" arm progresses to ESKD in roughly six years on average, which is notably faster than many natural-history and registry data would suggest for a broad IgAN population.[iii,xv] This accelerated progression is especially influential because it magnifies the apparent benefit of therapies assumed to have sustained effects. When modeled, rapid early transitions amplify this effect, further disadvantaging therapies whose benefit accrues through longer-term stabilization rather than early separation. This baseline is derived from an "evidence-based transition matrix" submitted during the data request period, but the draft report does not clearly describe the underlying data sources or transition probabilities. Because this matrix underpins the calibration for all treatments, understanding its construction and testing alternative

assumptions are critical. This is extremely important for eGFR slope. For IgAN, sustained differences in annualized eGFR slope are the most clinically meaningful determinant of time to kidney failure. Even modest slope preservation (e.g., ~0.5 mL/min/1.73 m² per year) can translate into multiyear delays in ESKD, with nonlinear downstream effects on dialysis initiation, transplantation, and healthcare costs. Therapies whose benefit manifests through eGFR slope stabilization, such as atacicept, are therefore particularly sensitive to modeling choices that rely on mean change rather than time-dependent, slope-based extrapolation.

Cross-trial calibration and transportability of treatment effects. Beyond baseline differences, the calibration strategy forces all therapies onto a single shared "no immunomodulatory therapy" progression curve and then uses forward and backward multipliers to approximate each trial's eGFR effect. The exception appears to be the SGC arm which follows its own trajectory. This implicitly assumes that relative treatment effects are fully transportable across meaningfully different trial populations, including differences in geography, race and ethnicity, baseline risk, and background therapy. The draft report does not fully describe the eGFR calibration process, such as how specific time points and slopes were chosen as targets or why some modeled differences (for example, in Table E2.2) diverge from the headline trial results and from each other. For therapies such as atacicept, whose value is driven by durable stabilization of eGFR slope rather than large early mean changes, this calibration approach compresses true differences and underrepresents long-term benefit. Because transportability cannot be empirically verified with the current evidence base, ICER should explicitly describe resulting structural uncertainty and avoid framing the calibrated outputs as definitive comparative estimates. This concern is heightened if long-term extension data are down weighted or excluded from calibration targets.

To address these considerations, we recommend that ICER:

- **Remove the chronic SGC maintenance paradigm from the base-case framework** by either:
  (a) **using best supportive care/no specific immunomodulatory therapy as the base-case comparator**, or
  (b) **modeling SGCs as a short-course strategy with waning benefit and clinically realistic discontinuation**, and presenting SGCs only as a scenario analysis.
  (Rationale: chronic SGC maintenance is not clinically plausible in IgAN and structurally biases the model results.)
- **Reassess base-case progression assumptions that underrepresent atacicept's disease-modifying benefit by overestimating eGFR decline and CKD stage transitions**, and conduct slope-based scenario analyses anchored to observed annualized eGFR stabilization where available (including long-term extension data).
- **Harmonize durability and off-treatment assumptions across short-course therapies and disease-modifying therapies**, including consistent approach to **treatment duration, waning, and off-treatment transitions associated with a SGC formulations**, to avoid asymmetry that can drive dominance conclusions.
- **Explicitly acknowledge between-trial heterogeneity and limited ability to fully adjust for it** and transparently reflect this structural uncertainty in the main report interpretation (not only supplements), including sensitivity bounds that show how conclusions change under plausible alternative assumptions.

Thank you again for the opportunity to provide comments. We would welcome the chance to engage further with ICER staff to discuss these issues and to support refinement of the model so that it more closely reflects the totality of the clinical evidence and the real-world experiences of people living with IgA nephropathy.

Sincerely,

Jay Jackson, PharmD, MPH

Executive Director, Health Economics & Outcomes Research

Vera Therapeutics

jay.jackson@veratx.com

[i] Lafayette R et al. A phase 2b, randomized, double-blind, placebo-controlled, clinical trial of atacicept for treatment of IgA nephropathy. Kidney Int. 2024 Jun;105(6):1306-1315. doi: 10.1016/j.kint.2024.03.012. Epub 2024 Mar 27. PMID: 38552841.

[ii] Lafayette R et al. ORIGIN Phase 3 Trial Investigators. A Phase 3 Trial of Atacicept in Patients with IgA Nephropathy. N Engl J Med. 2025 Nov 6. doi: 10.1056/NEJMoa2510198. Epub ahead of print. PMID: 41196369.

[iii] Pitcher D, Braddon F, Hendry B, Mercer A, Osmaston K, Saleem MA, Steenkamp R, Wong K, Turner AN, Wang K, Gale DP, Barratt J. Long-Term Outcomes in IgA Nephropathy. Clin J Am Soc Nephrol. 2023 Jun 1;18(6):727-738. doi: 10.2215/CJN.0000000000000135. Epub 2023 Apr 13. PMID: 37055195; PMCID: PMC10278810.

[iv] Barratt J, Barbour SJ, Brenner RM, Cooper K, Wei X, Eren N, Floege J, Jha V, Kim SG, Maes B, Phoon RKS, Singh H, Tesař V, Lafayette R; ORIGIN Phase 2b Investigators. Long-Term Results from an Open-Label Extension Study of Atacicept for the Treatment of IgA Nephropathy. J Am Soc Nephrol. 2025 Apr 1;36(4):679-687. doi: 10.1681/ASN.0000000541. Epub 2024 Oct 26. PMID: 39462308; PMCID: PMC7616790.

[v] Kim D, Lv J, Hladunewich M, et al. The Efficacy and Safety of Reduced-Dose Oral Methylprednisolone in High-Risk Immunoglobulin A Nephropathy. Kidney International Reports. 2024;9(7):2168-2179. Supplemental Figure S1 & S2.

[vi] Lv J, Zhang H, Wong MG, et al. Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. JAMA. 2017;318(5):432-442. doi:10.1001/jama.2017.9362.

[vii] Lv J, Wong MG, Hladunewich MA, et al. Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. *JAMA*. 2022;327(19):1888-1898. doi:10.1001/jama.2022.5368.

[viii] Rauen T, Wied S, Fitzner C, Eitner F, Sommerer C, Zeier M, Otte B, Panzer U, Budde K, Benck U, Mertens PR, Kuhlmann U, Witzke O, Gross O, Vielhauer V, Mann JFE, Hilgers RD, Floege J; STOP-IgAN Investigators. After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy. Kidney Int. 2020 Oct;98(4):1044-1052. doi: 10.1016/j.kint.2020.04.046. Epub 2020 May 22. PMID: 32450154.

[ix] Pesce G, Patel M, Gusto G, Kadambi A, Chandak A, Madison T. Real-world challenges associated with the use of four common systemic glucocorticoids in a United States IgAN cohort. *Front Nephrol*. 2025;5:1574239. Published 2025 Apr 24. doi:10.3389/fneph.2025.1574239.

[x] Rovin BH, Barratt J, Cook HT, et al. KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV). Kidney Int. Oct 2025;108(4s):S1-s71.

xi Mathur M, et al. A phase 2 trial of sibeprenlimab in patients with IgA nephropathy. N Engl J Med. 2024;390(1):20-31. doi:10.1056/NEJMoa2305635.

xii Perkovic V, Trimarchi H, Tesar V, et al. VISIONARY Trial Investigators Group. Sibeprenlimab in IgA Nephropathy - Interim Analysis of a Phase 3 Trial. N Engl J Med. 2025 Nov 8. doi: 10.1056/NEJMoa2512133. Epub ahead of print. PMID: 41211929.

xiii Lafayette R, et al. Efficacy and safety of a targeted-release formulation of budesonide in primary IgA nephropathy (NefIgArd): 2-year, randomized phase 3 results. Lancet. 2023;402(10405):859-870. doi:10.1016/S0140-6736(23)01554-4.

[xiv] Agboola, F. and Wright, A.C., 2024. A Framework for Evaluating the Diversity of Clinical Trials. Journal of Clinical Epidemiology, p.111299. https://doi.org/10.1016/j.jclinepi.2024.111299

xv Sim JJ, Chen Q, Cannizzaro N, Fernandes AW, Pinto C, Bhandari SK, Chang J, Schachter AD, Mathur M. CKD progression, kidney failure, and mortality among US patients with IgA nephropathy. Nephrol Dial Transplant. 2025 Oct 30;40(11):2104-2117. doi: 10.1093/ndt/gfaf084. PMID: 40307873; PMCID: PMC12559788.

I wanted to take a moment to share my thoughts regarding your recent ICER report on B-Cell-Directed Therapies for IgA Nephropathy. As someone living with IgA Nephropathy, the most important thing for me and many others is to protect our kidney function for as long as we can. We all want to avoid going on dialysis or needing a transplant if at all possible. It's tough enough managing the ups and downs of our condition without adding the stress of those major interventions! I appreciate your efforts in researching this area, but I wanted to point out that relying on systemic steroids as a long-term solution may not be realistic for most of us. They come with some serious side effects and, honestly, many of us struggle to stay on them for a long time. What I find really exciting is the new treatments being developed. They focus on addressing the root cause of the disease, which gives us hope for a more stable kidney function over time. It's refreshing to see options that could potentially lead to a better quality of life and help us maintain our independence. I do worry, though, that some models predicting how quickly our kidney function declines might not reflect what we actually experience. If those models underestimate the benefits of new treatments, it could undermine the hope we have for improvements in our lives. Even the smallest gains in kidney preservation can mean a big difference for us—more time without dialysis, fewer hospital visits, and just an overall better life experience. In the end, it's crucial that studies and evaluations focus on what really matters to us as patients. We want to see outcomes that reflect our day-to-day realities.

Stuart Miller

Director of Strategic Partnerships

IGA Nephropathy Foundation

Response Letter on ICER Draft Evidence Report: IgA Nephropathy (IgAN)
Submitted by: NephCure (with input from the community including patients and clinical and economic experts in IgAN)
Stakeholder Category: Patient Advocacy Organization
Date: January 14, 2026

Executive Summary

NephCure is a patient advocacy organization dedicated to ensuring that all individuals with rare kidney disease (RKD) have timely and equitable access to the care and treatments that offer them the best kidney health outcome possible. It is the only kidney organization squarely focused on nephrotic syndrome, FSGS, IgAN, and other rare, protein-spilling kidney diseases. In 2025, NephCure partnered with multiple stakeholders, including other advocacy organizations and industry, to form the IgAN Alliance to be a unified voice advocating for the community to help patients address access barriers to care and to receive earlier and accurate diagnosis.

In addition to representing the patient voice and experience, NephCure's comments embody perspectives of leading clinical experts in IgAN and our health economics and outcomes research advisors. We appreciate the opportunity to provide feedback on ICER's efforts to present a balanced and thorough preliminary assessment of emerging therapies for IgAN.

Overall Perspective

While the overall report is generally balanced within the constraints of currently available data, the current evidence base remains immature, with limited glomerular filtration rate (GFR) outcomes, short follow-up durations, and evolving real-world data. The evidence limits the ability to fully assess long-term kidney preservation, dialysis avoidance, and transplant delay. [1,2] In addition, several drugs have been recently approved to treat CKD, including SGLT2is, which have also shown efficacy specifically in IgAN. This limit in current evidence is compounded by the fact that IgAN is a rare disease, with a high degree of heterogeneity across subpopulations. **It is essential that this report be clearly framed as an interim assessment subject to meaningful revision as phase 3 and open-label extension (OLE) data mature.**

While cost-effectiveness remains challenging for novel agents, patients urgently need treatment options beyond systemic prednisone. Multiple publications document significant toxicity even with short-term and low-dose exposure, limited durability of response, and declining evidence of efficacy outside of Asian populations.[3,4] Patients consistently report the burden of repeated steroid courses, cumulative side effects, and the uncertainty associated with disease progression. [3,4]

While the report appropriately acknowledges uncertainty in comparative effectiveness, comparative framing against systemic steroids risks overstating their real-world clinical value while underestimating patient harm. **Therapeutic decisions in IgAN must remain between**

patients and their care team, and they should be informed by evolving evidence, individual risk tolerance, and patient-centered outcomes.

Given the heterogeneous disease trajectory of IgAN across racial, ethnic, and socio-economic groups, ICER assessments should consider health equity beyond what exists in the current report to ensure that cost-effectiveness and clinical recommendations reflect the real-world experience of all patients, including historically underserved populations.[5,1]

As new data emerge, particularly definitive GFR outcomes for B-cell modulators and long-term extension data, it will be critical for ICER to reassess the value framework to fully capture the long-term clinical, quality-of-life, and societal benefits of disease-modifying therapies.[6,7,8]

Key Issues for ICER Consideration:

- Importance of patient-centered decision-making in partnership with their care team
- Underestimation of productivity loss and caregiver burden
- Absence of GFR outcome data for B-cell modulators
- Short duration of follow-up across all therapies
- Steroid toxicity, limited durability, and real-world burden
- Limitations of systemic steroids as a comparator
- Limitations in capturing IgAN heterogeneity and disease trajectory

Comments on Evidence Report

1. **Evidence Maturity and Interim Nature of the Report:**
   The drugs under review have all been approved under the accelerated approval pathway. Therefore, the absence of GFR outcome data for B-cell modulators represents a major limitation of the current existing evidence.[6,7,8] In a progressive and rare disease such as IgAN, proteinuria reduction is a surrogate endpoint, while long-term preservation of kidney function is the clinically meaningful outcome.[1,2] Coupled with short follow-up durations across trials, the current assessment should be explicitly framed as an interim evaluation that will require revision once phase 3 GFR data and OLE data become available.[6,7,8]

   From a health economics perspective, the lack of mature GFR outcomes introduces significant uncertainty into long-term modeling assumptions related to dialysis avoidance, transplant delay, healthcare utilization, productivity, and survival. The slow and heterogeneous progression of IgAN introduces substantial uncertainty when extrapolating long-term outcomes from short-duration clinical trials. Additionally, current trial populations underrepresent key racial and ethnic groups, limiting confidence in generalizing outcomes.[5]

2. **Steroids as a Base Case Comparator: Real-World and Evidence-Based Limitations:**
   While systemic steroids are historically used in IgAN, multiple publications document significant toxicity even with short-term and low-dose exposure.[3,4] Furthermore, treatment

durability is limited, often requiring repeated courses with cumulative risk. Outside of Asian populations, evidence supporting steroid efficacy is substantially weaker. Thus, framing steroids as a dominant comparator with both comparative effectiveness and cost-effectiveness risks overstating their real-world clinical value and underestimating patient harm.

From an evidence-based standpoint, systemic steroids were never evaluated under modern regulatory standards and rely on discordant and outdated trial data. In the report, only one study used systemic steroids as the comparator. Serious infections observed in the TESTING trial (the study was halted due to a death of a patient) required dose reduction. Higher-dose regimens may carry substantially greater toxicity than is reflected in the model.[3] The choice of steroids as the primary comparator strongly influences cost-effective outcomes and warrants careful reconsideration.

3. **Targeted Budesonide as a Distinct Therapeutic Category:**
   As acknowledged in the report, targeted budesonide is more convincingly cost effective, abstract presentations support the safety and efficacy of at least a second course, and it is likely that they are relatively gentler in side effects and serious risks for steroid complications. Analyses should treat it separately from systemic steroids as a distinct therapeutic category, because its impact on side effects, healthcare use, and patient quality of life is considerably less severe.

4. **B-Cell Modulators and Long-Term Disease Modification**
   Once definitive GFR data are available for B-cell modulators, the benefits of delaying CKD progression, dialysis, and transplantation may be substantial. These downstream benefits are not currently captured in the economic model but have profound implications for quality of life, employment, caregiver burden, and societal costs.[6,7,8,1,2]

5. **Patient Experience and Decision-Making**
   While the report appropriately acknowledges uncertainty in comparative effectiveness, patient experience is not fully captured in current trial data and is rarely systematically measured. Treatment burden, adverse effects, and quality of life are central to therapeutic decision-making in a chronic disease such as IgAN.[3,4] Patient-centered outcomes may also differ across communities. Consideration needs to be given to how social determinants and structural barriers influence real-world uptake of therapies to ensure equitable evaluation of value. **Ultimately, therapeutic decisions must remain between patients and their care teams, informed by evolving evidence and individual risk tolerance.**

   Patients consistently prioritize preserving kidney function, avoiding dialysis, maintaining independence, remaining employed, and minimizing treatment toxicity. Productivity loss and caregiver burden occur long before kidney failure and are not adequately reflected in current economic models.[2,10]

+++

Key Recommendations:

- Explicitly label the report as an interim assessment.
- Further acknowledge cost impact, productivity loss and caregiver burden into societal value assessments in regard to disease progression.
- Reframe systemic steroids as a limited and toxic comparator.
- Distinguish targeted budesonide as a distinct therapeutic category notable for both its clinical role and long-term therapeutic value (confirmed from real-world evidence).
- Acknowledge that B+ evidence ratings for newer agents may outweigh historical steroid data once GFR outcomes mature.
- Improve transparency around model assumptions, durability extrapolations, and heterogeneity.
- Commit to a formal reassessment upon availability of phase 3 and OLE GFR data.
- Incorporate health equity and population heterogeneity into model assumptions, subgroup analyses, and societal value assessments, ensuring that recommendations reflect the diverse experiences and needs of all patients.

Thank you again for the opportunity to provide comments. We would welcome the chance to engage further with ICER staff to help refine the model, so it can reflect the full real-world experience and clinical evidence of those impacted by IgAN.

Sincerely,
Josh Tarnoff
Chief Executive Officer
NephCure
jtarnoff@nephcure.org

References

1. Pitcher D, Braddon F, Hendry B, Mercer A, Osmaston K, Saleem MA, Steenkamp R, Wong K, Turner AN, Wang K, Gale DP, Barratt J. Long-Term Outcomes in IgA Nephropathy. Clin J Am Soc Nephrol. 2023 Jun 1;18(6):727-738. doi: 10.2215/CJN.0000000000000135. Epub 2023 Apr 13. PMID: 37055195; PMCID: PMC10278810.
2. Sim JJ, Chen Q, Cannizzaro N, Fernandes AW, Pinto C, Bhandari SK, Chang J, Schachter AD, Mathur M. CKD progression, kidney failure, and mortality among US patients with IgA nephropathy. Nephrol Dial Transplant. 2025 Oct 30;40(11):2104-2117. doi: 10.1093/ndt/gfaf084. PMID: 40307873; PMCID: PMC12559788.
3. Pesce G, Patel M, Gusto G, Kadambi A, Chandak A, Madison T. Real-world challenges associated with the use of four common systemic glucocorticoids in a United States IgAN cohort. *Front Nephrol*. 2025;5:1574239. Published 2025 Apr 24. doi:10.3389/fneph.2025.1574239.
4. Lv J, Zhang H, Wong MG, et al. Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. JAMA. 2017;318(5):432-442. doi:10.1001/jama.2017.9362.

5. Agboola, F. and Wright, A.C., 2024. A Framework for Evaluating the Diversity of Clinical Trials. Journal of Clinical Epidemiology, p.111299. https://doi.org/10.1016/j.jclinepi.2024.111299
6. Lafayette R et al. ORIGIN Phase 3 Trial Investigators. A Phase 3 Trial of Atacicept in Patients with IgA Nephropathy. N Engl J Med. 2025 Nov 6. doi: 10.1056/NEJMoa2510198. Epub ahead of print. PMID: 41196369.
7. Mathur M, et al. A phase 2 trial of sibeprenlimab in patients with IgA nephropathy. N Engl J Med. 2024;390(1):20-31. doi:10.1056/NEJMoa2305635.
8. Perkovic V, Trimarchi H, Tesar V, et al. VISIONARY Trial Investigators Group. Sibeprenlimab in IgA Nephropathy - Interim Analysis of a Phase 3 Trial. N Engl J Med. 2025 Nov 8. doi: 10.1056/NEJMoa2512133. Epub ahead of print. PMID: 41211929.
9. Lafayette R, et al. Efficacy and safety of a targeted-release formulation of budesonide in primary IgA nephropathy (NefIgArd): 2-year, randomized phase 3 results. Lancet. 2023;402(10405):859-870. doi:10.1016/S0140-6736(23)01554-4.
10. NephCure. 2025. Unpublished survey conducted by SmithSolve on IgAN Community Experiences.

###