August 20, 2025

Submitted electronically to: mbooth@icer.org
Sarah K. Emond, MPP
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14 Beacon Street, 8th Floor
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RE: ICER's Draft Scoping Document for Immunoglobulin A Nephropathy (IgAN)

Dear ICER Review Team,

Calliditas Therapeutics and Veloxis Pharmaceuticals, Asahi Kasei companies, appreciate the opportunity to participate in ICER's evaluation of Tarpeyo®, which is a targeted release form of budesonide, for the treatment of immunoglobulin A nephropathy (IgAN).

IgAN is a chronic, progressive, immune-mediated kidney disease that can lead to kidney failure or premature death, often within 10-15 years of diagnosis.[1,2] IgAN mostly affects young individuals in their most productive years and may be asymptomatic at early stages.[1,3] About 50% of US patients >30 years of age are diagnosed at advanced stages of the disease when renal damage has already occurred.[2] There is an urgency for early intervention to help preserve kidney function and improve clinical and economic outcomes. Approximately 30% of patients with IgAN will go on to lose kidney function and require a kidney transplant or lifelong dialysis.[4] Although kidney transplantation is the treatment of choice for patients with kidney failure, about 19-28% of these patients experience disease recurrence within 10 years since IgAN is an autoimmune disease that originates outside of the kidney.[5] Until recently, treatment for IgAN consisted primarily of supportive care and off-label immunosuppressants. These treatments lack disease-modifying potential, and some are associated with serious adverse events.[3,6]

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.[7,8] 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.[8,9] In addition, the draft 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guideline supports Tarpeyo as the only FDA-approved treatment shown to reduce levels of pathogenic forms of IgA and IgA immune complexes, key drivers of one out of two IgAN-specific pathogenic pathways leading to nephron loss. The beneficial effects of Tarpeyo on pathogenic forms of IgA and proteinuria and rate of eGFR decline support Tarpeyo as the first approved potentially disease-modifying treatment for IgAN.[10]

We provide the following recommendations and clarifications to ICER's draft scope.

Tarpeyo is the first FDA-approved Potentially Disease-Modifying Therapy Designed to Target the Source of the Disease

Tarpeyo is a targeted-release formulation of budesonide indicated to reduce the loss of kidney function in adults with IgAN who are at risk for disease progression. Tarpeyo was designed to deliver the active ingredient to the ileum mucosal cells where IgAN is thought to originate. The Tarpeyo capsule is coated with an enteric coating layer that is designed to dissolve when it encounters the pH level of the distal ileum, where the Peyer's patches are located.[11-13] Peyer's patches are lymphoid follicles found in highest concentration in the distal ileum, where locally active budesonide can modulate mucosal B-cell numbers and activity to reduce production of pathogenic galactose-deficient IgA1 (Gd-IgA1).[a,14] Targeting IgAN at a source by modulating a key pathogenic biomarker like pathogenic Gd-IgA1 supports a potential disease-modifying approach to treatment.[10,13] Tarpeyo is the only formulation of oral budesonide that reliably targets the distal ileum and per the FDA orange book, it cannot be substituted with generic budesonide.[11,15] In addition, the high first-pass metabolism of budesonide limits the amount of active budesonide that is systemically available, which may limit some systemic side effects otherwise associated with the use of systemic glucocorticoids, which have not been specifically approved for treatment of IgAN.[16]

Tarpeyo's efficacy and safety have been demonstrated in a Phase 2b study (NEFIGAN) and a large multicenter Phase 3 randomized controlled trial (NefIgArd) in patients at high risk of disease progression maintained on optimized supportive care. In the NEFIGAN trial in which all patients received optimized renin-angiotensin system inhibition (RASi), 9 months of treatment with Tarpeyo resulted in reduction of proteinuria and stabilization of estimated glomerular filtration rate (eGFR) decline versus placebo.[17] These results were consistent with the NefIgArd phase 3 randomized placebo-controlled trial, in which 9-month treatment period was followed by a 15-month observational follow-up period off drug.[13] Tarpeyo plus RASi led to statistically significant and clinically meaningful benefits for up to 24 months on eGFR and proteinuria endpoints compared to placebo plus RASi. eGFR was stabilized during the 9-month treatment period in patients that received Tarpeyo and the eGFR treatment benefit vs placebo was maintained during the 15-month off-treatment follow-up period.[18] In an open-label extension study, 45 patients that completed NefIgArd received a second 9 month treatment course that yielded similar efficacy and safety results.[19]

The clinical benefit in eGFR and proteinuria observed after 9 months of treatment that was maintained over 15 months off treatment follow-up indicate that Tarpeyo has the potential to modify IgAN disease course by reducing the loss of kidney function. This reduction in loss of kidney function has the potential to delay onset of kidney failure as supported by modelling approaches. A recent modeling study using datasets from the NefIgArd trial, a long-term Leicester General Hospital patient registry, and a published meta-analysis estimated that Tarpeyo can delay onset of clinical outcomes by 12.8 years.[20] The results suggest that through 10-12 years, fewer patients treated with Tarpeyo are expected to have a clinical outcome event versus optimized supportive care alone.[b]

Tarpeyo has an Established Safety Profile

In the NefIgArd trial, the safety profile was consistent with that of a locally acting treatment with low systemic exposure of budesonide (peripheral edema, hypertension, muscle spasms, acne). Some clinical events typically seen with systemic corticosteroids were generally limited.[c,7,13] Most adverse events were mild to moderate and resolved within 3 months of treatment cessation.[d] No clinically relevant differences between treatment groups in blood pressure, body weight, or HbA1c were observed, and incidence of infections was comparable between the treatment groups.[13]

Tarpeyo is a Cost-Effective Treatment Option

Economic modeling suggests that Tarpeyo is expected to be cost-effective as a 9-month course of treatment every 2 years. In a peer-reviewed, published economic model,[21] 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. 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 14.92 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.

eGFR is the Most Accurate and Clinically Relevant Overall Measure of Kidney Function and Monitoring Kidney Disease

eGFR levels determine the stage of chronic kidney disease (CKD) and for tracking progression over time. eGFR is considered the most useful overall measure of kidney function and eGFR decline is associated directly with a worse renal prognosis in patients with IgAN.[1] We agree with ICER's proposed plan to use CKD-based health states in the economic model. The relationship between eGFR and CKD can be used to inform health state transitions in ICER's economic model. In contrast, current evidence is not sufficient to determine how changes in biomarkers such as Gd-IgA1 impact outcomes and should not be included in the evaluation or economic model. In addition, surrogate endpoints such as proteinuria should not be included in the evaluation or model in place of eGFR, which is a validated endpoint in clinical trials.[22,23]

Tarpeyo is the only FDA-approved therapy within the proposed evaluation scope that has been proven to stabilize kidney function while on therapy and reduce the loss of kidney function during the 15-month off-treatment follow-up period. These benefits observed in the robust clinical trial program and supported by modeling approaches, highlight Tarpeyo's potential as a disease-modifying therapy that may help improve long-term outcomes for patients at risk of progression. We look forward to continued engagement with ICER throughout this review.

Sincerely,

Lobat Hashemi

Global Head, HEOR
Veloxis Pharmaceuticals

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[a] It has not been established to what extent the efficacy of Tarpeyo is mediated via local effects in the ileum vs. systemic effects.
[b] The effect of Tarpeyo on the long-term rate of kidney function decline is unknown.
[c] Tarpeyo prescribing information includes corticosteroid class warnings regarding risk of hypercorticism and adrenal axis suppression, immunosuppresion and increased risk of infection, and other corticosteroid effects.
[d] The most common adverse reactions with Tarpeyo (occurring in ≥5% of Tarpeyo treated patients, and ≥2% higher than placebo) were peripheral edema (17%), hypertension (12%), muscle spasms (12%), acne (11%), headache (10%), upper respiratory tract infection (8%), face edema (8%), weight increased (7%), dyspepsia (7%), dermatitis (6%), arthralgia (6%), and white blood cell count increased (6%).

Otsuka

Otsuka: people creating new products for better health worldwide

August 20, 2025

Submitted electronically to publiccomments@icer.org

RE: ICER Draft Background and Scope: Immunoglobulin-Directed Therapies for IgA Nephropathy

Otsuka America Pharmaceutical, Inc. (Otsuka) appreciates the opportunity to submit comments on the Institute for Clinical and Economic Review's (ICER's) draft scoping document for its review of immunoglobulin-directed therapies for IgA nephropathy (IgAN).

We offer the following questions and comments on each section of the Draft Scoping Document below.

Background and Stakeholder Input

We appreciate ICER's acknowledgement of the severity of IgAN and the substantial burden it imposes on patients, caregivers, and the healthcare system. The IgAN patient advocacy community is robust and will be able to offer guidance to ICER during the course of their review.

Scope of Evidence Review

Interventions:

Since ICER's focus is on disease-modifying therapies, Otsuka recommends inclusion of Fabhalta® (iptacopan, Novartis). Fabhalta targets the inflammation pathway in IgAN and received FDA approval in August 2024 for this indication.[1]

Otsuka also questions whether Tarpeyo® (budesonide) should be included in the review. As a corticosteroid, Tarpeyo is not recommended for long-term use and has a recommended maximum treatment duration of nine months. According to the Tarpeyo Prescribing Information, while the effect on kidney function that was seen during the 9-month treatment period persisted following completion of treatment, the long-term rate of kidney function decline was not altered by Tarpeyo.[2] Therefore, Otsuka questions whether Tarpeyo is truly a disease modifying agent for chronic/maintenance use for patients with IgAN, and whether it should be assessed in this review.

Comparators:

Otsuka also recommends the removal of oral corticosteroids as a comparator in this review. Steroids are short-term, acute therapy, and not recommended for use longer than 6-9 months per the KDIGO 2024 draft guidelines.[3] The drugs included in the scope of this review are meant as maintenance therapy. Comparing long-term disease-modifying agents to short-term steroid therapy is inappropriate and risks misleading conclusions.

Outcomes:

- Under ***Patient-Important Outcomes***, Otsuka recommends that dialysis and kidney transplantation be assessed separately, as they have distinct economic implications and quality-of-life impacts.
- Otsuka also recommends including workforce-related productivity outcomes (e.g., absenteeism, presenteeism, and short-term disability) under ***Patient-Important Outcomes*** since IgAN is often diagnosed during a person's working years.
- Fatigue (mental and physical) is also another ***Patient-Important Outcome*** that should be captured, as it has negative impacts on quality of life.[4,5]
- Otsuka recommends capturing the costs and burden of adherence to a REMS program under the ***Adverse Events*** outcomes section, as comparators in this review may have a REMS program required for accessing the therapy.

Scope of Comparative Value Analysis

Otsuka has two main concerns regarding the economic model comparators.

1. Comparison to placebo: None of the therapies included in the review conducted placebo-controlled trials. All trials were conducted vs. standard of care such as renin-angiotensin system inhibitors (RASis), angiotensin-converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARB) or sodium-glucose cotransporter 2 inhibitors (SGLT2i). Modeling against placebo may yield results of limited relevance and should be reconsidered.
2. Comparison to steroids: As noted above, systemic steroids are acute, non-maintenance therapy and are not appropriate comparators for chronic disease-modifying treatments.

Another overarching issue is the valuation of rare diseases and their treatments. Many countries have removed or amended cost effectiveness thresholds from decisions regarding orphan and ultra-orphan treatments.[6] The National Institute for Health and Care Excellence (NICE) and Sweden have adopted significantly higher willingness to pay thresholds (WTP) thresholds and allow for greater levels of uncertainty in the review of treatment for rare diseases, recognizing the challenges in generating an evidence base that is robust enough to bring these products to market.[6,7,8] Value determinations for orphan drugs in other countries including Canada, Germany, France and the Netherlands do not include assessments of cost effectiveness at all.[6]

A 2022 literature review of economic modeling for rare disease found that many data points for the models were limited, including efficacy and safety profiles, direct and indirect cost burden, and potential economic benefits of treatment, which prevent accurate estimates of benefits in relation to cost. The authors suggest approaches that can address these challenges, including the use of patient and/or clinician feedback to inform model assumptions, using data from disease analogues, and other epidemiological techniques, such as matching-adjusted indirect comparison.[9]

Many of these data concerns will also be a factor in ICER's review of the IgAN treatments, including incomplete efficacy and safety information and potential long term economic benefits of the treatments. We therefore recommend that ICER adopt disease severity and disease rarity-based WTP thresholds and adopt some alternate approaches to modeling for rare disease that recognize the societal desire to help patients with devastating orphan diseases.

Identification of Low Value Services

There is evidence that longer nephrology care before ESRD is associated with better health care utilization[10,11] improved quality of life, attenuation of cardiovascular and renal complications, delayed ESRD onset, and reduced mortality on dialysis.[12] A recent study quantified the direct health economic benefits of novel interventions for patients with IgAN and the spillover benefits of these treatments on the US kidney transplant system. The model estimated that new IgAN interventions reduced annual kidney transplant demand by 33.4%, saving an average of 669 kidneys per year and reduced the overall waitlist size by 2138 candidates within 5 years. This reduction in waitlist size decreased the average transplant wait time by 25 days (0.070 years) per waitlist candidate, which in turn generated 0.087 QALYs (monetized benefit US$13,116) per waitlist candidate. Per treated patient with IgAN, novel interventions generated 1.772 QALYs, 23.1% (0.410 QALYs) of which were attributable to spillover benefit.[13] Otsuka recommends that the spillover benefits of these new treatments for IgAN be incorporated into the economic model, as they are an important societal benefit of treatment.

Lastly, there has been a recent focus on the carbon footprint of dialysis. Dialysis facilities use large quantities of water, with up to 60% being discarded. Energy demands of the facilities and transportation of people to the facilities also produce carbon emissions. Waste production, particularly plastic waste, poses additional environmental challenges.[14] While environmental concerns are often not considered in the societal viewpoint in economic modeling, ICER may wish to take some of these points into consideration as well.

* * * * *

Conclusion

Otsuka appreciates the opportunity to comment on ICER's draft scope for the IgAN review. We respectfully recommend that ICER refine its intervention list, comparator selection, and modeling framework to reflect clinical practice, and the unique challenges of rare disease evaluation.

If you have any questions about these comments, please contact: Heidi Waters, PhD, Senior Director Policy Research, at Heidi.Waters@otsuka-us.com.

Sincerely,

Kaan Tunceli

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August 20, 2025

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Re: Public Comment on Draft Scoping Document – Immunoglobulin-Directed Therapies for IgA Nephropathy

Vera Therapeutics (Vera) welcomes the opportunity to comment on the Draft Scoping Document for the recently announced assessment of treatments for IgA nephropathy (IgAN). Vera is a clinical-stage biotechnology company who is committed to advance treatments that target the source of immunologic diseases to change the standard of care for patients.

IgAN is an autoimmune B-cell driven disorder characterized by the production of both an autoantigen (galactose-deficient IgA1 [Gd-IgA1]) and an autoantibody (anti-Gd-IgA1), which form pathogenic immune complexes that deposit in the glomeruli, driving inflammation, progressive nephron loss, and chronic kidney damage. Targeting B-cell activity is therefore a foundational disease-modifying strategy. B cells are regulated by the cytokines B-cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL), both of which bind to the transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) receptor. Atacicept, a rationally designed TACI-Fc fusion protein, functions as a soluble receptor that binds BAFF and APRIL with nanomolar potency, modulating B-cell activity at its source. Clinical evidence supports the disease-modifying potential of this approach. In IgAN trials, atacicept achieved sustained reductions in Gd-IgA1, resolution of hematuria (reflecting glomerular inflammation), robust reductions in proteinuria (the regulatory endpoint for accelerated approval), and stabilization of kidney function as measured by eGFR (an unprecedented outcome in biopsy-proven progressive kidney disease).[1,2,3]

IgAN is predominantly diagnosed in young adults and represents a critical challenge in nephrology due to its unrelenting progressive nature and associated burden, significant lifelong risk of kidney failure, and impact on life expectancy and life quality.[4,5] Given this impact, it is essential that health technology assessments fully reflect the pathophysiology of IgAN, patient priorities, and the unique, disease-modifying potential of therapies like atacicept.

Following review of ICER's draft scoping document, Vera is aligned with many of the preliminary scoping choices. However, Vera offers several recommendations for ICER to consider in the Revised Scoping Document to improve clarity, interpretation, and specificity of the planned assessment. Recommendations are organized by Draft Scope section.

Background

To ensure consistent descriptions of each intervention, ICER should update the description of atacicept to include the self-administered, at-home, subcutaneous route of administration. Additionally, as the assessment includes both investigational and approved interventions, ICER is encouraged to describe the U.S. Food and Drug Administration's (FDA) established accelerated and full approval pathways for treatments in IgAN. Specific mention should be made of regulatory authority–mandated

manufacturer restrictions that may limit disclosure of certain trial results and represents an important limitation for this assessment.

Population
ICER should clearly define important clinical and demographic characteristics to stratify the base-case analysis, given the influence of these factors on both clinical and economic outcomes. Specifically, the analysis should be risk-stratified by baseline proteinuria (e.g., ≤1 g/day vs >1 g/day) and baseline eGFR, due to the strong effect-modification risks these variables pose for both clinical and modeling endpoints. ICER should also account for geographic and ethnic heterogeneity in any comparisons to ensure analyses are more clinically realistic, given differential progression risks and trial population characteristic mixes, as part of the primary analysis population.[6]

Comparators
Caution is warranted when comparing therapies whose benefits are primarily reflected in short-term proteinuria changes without evidence of durable eGFR preservation. Such comparisons may be misleading and undervalue therapies like atacicept with demonstrated long-term stabilization of kidney function. ICER's plan to compare each intervention to systemic steroids, to each other, and to no specific immunomodulatory therapy also assumes that "all groups would be expected to receive renal protective therapies that may include renin-angiotensin system inhibitors (RASi), sodium-glucose cotransporter 2 (SGLT2) inhibitors, and/or endothelin receptor antagonists (ERAs), as well as lifestyle modification." This general approach aligns with evolving treatment guidelines that recommend simultaneous management of existing nephron loss and IgAN-specific causes of nephron loss.[7]

However, ICER should carefully consider which comparisons are appropriate given the evolving therapeutic landscape over the timeframe of included clinical trials. Importantly, each trial differed in design, eligibility criteria, demographics/ethnicities, baseline progression risk categories, rates of concomitant treatment, follow-up duration, measures, and endpoint definitions. Network meta-analysis methods may not adequately address these variations, given their influence on target outcomes of interest. As such, direct comparisons of the interventions will be difficult to interpret and have limited utility.

Patient-Important Outcomes
For patients, the most critical outcome is stabilization of kidney function, as measured by long-term eGFR trajectory. Atacicept's 96-week Phase 2b results demonstrated both sustained proteinuria reduction and eGFR stabilization, underscoring its potential to alter disease progression. We recommend ICER elevate long-term eGFR stabilization as a primary "Patient-Important Outcome." ICER should also include proteinuria under "Patient-Important Outcomes." Along with delaying time to dialysis or transplant, patients consistently report these as the most relevant measures of their IgAN experience.[8,9] We encourage ICER to fully consider the limitations of proteinuria as a more immediate but surrogate endpoint in isolation and to recognize the prognostic value of sustained eGFR stabilization, which eGFR is the measure used by nephrologists to determine whether a patient needs to prepare for end-stage supportive therapy with dialysis or transplantation. ICER should also clarify the definition of "symptomatic chronic kidney disease" to avoid redundancy with other listed outcomes.

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We further recommend that ICER add:

- **Hematuria** – a common manifestation of IgAN and an independent risk factor for progression to kidney failure.[10] Persistent hematuria is linked to greater declines in kidney function, whereas resolution is associated with slower progression.[11,12]
- **Metabolic and musculoskeletal side effects** – particularly relevant when systemic steroids are used as a comparator, given their known adverse effect profile.[8,13]

Finally, while patient-reported symptoms and quality of life are important to capture, there are currently no established fit-for-purpose IgAN-specific patient reported outcome measures appropriate to determine treatment effects.[14,15] Accordingly, treatment effects on IgAN-related fatigue or health-related quality of life have not been the focus of interventional trials. However, these effects can be indirectly captured in economic models using established health utility values associated with model outcomes like proteinuria and kidney function.[16]

Model Structure

Vera encourages ICER to include and align to prior published models in chronic kidney diseases beyond IgA Nephropathy. Multiple modeling approaches (e.g., Markov, simulation, decision tree, hybrid models) have been used to project long-term outcomes and cost-effectiveness while incorporating treatment effects on eGFR decline and other clinically important endpoints.[17] The model should incorporate kidney preservation and value with cost avoidance associated with delaying or preventing ESKD, dialysis, and transplantation.

Budget Impact Modeling

To support transparency, ICER should clearly describe all assumptions in the budget impact model, including the prevalent population included (e.g., all biopsy-confirmed vs indicated population vs high-risk population) and key parameters such as annual treatment adherence and discontinuation rates. This distinction is important to ensure appropriate utilization impact.

In conclusion, this review comes at a critical time in the IgAN treatment landscape, with significant innovation on the horizon. We support ICER's goal of evaluating therapies rigorously and transparently. Accordingly, we encourage ICER to fully incorporate the significant unmet need in IgAN and potential clinical value of these innovations in its assessment framework. Regardless of risk categorization, patients are still at risk of progression to kidney failure during their lifetime due to lack of eGFR stabilization with currently approved standard of care treatment. Therapies that target the underlying disease mechanisms hold promise for meaningfully altering disease course and improving quality of life for those affected.

Sincerely,

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