Immunoglobulin-Directed Therapies for IgA Nephropathy

Draft Background and Scope

JULY 31, 2025

Background

IgA nephropathy (IgAN, known as Berger's disease) occurs when abnormal complexes of immunoglobulin A (IgA) are deposited in the glomeruli of the kidneys, resulting in inflammation of the glomeruli (glomerulonephritis) and damage. Some patients with IgAN note recurrent episodes of blood in the urine (gross hematuria), often coinciding with upper respiratory infections, while others are found to have the disorder when urine studies show protein in the urine and/or microscopic hematuria.[1] Presentations with gross hematuria are more common in children and young adults than in older adults.[1] Over time, kidney damage can progress to end-stage kidney disease (ESKD) where patients require dialysis or renal transplant. Although blood and urine tests can suggest IgAN, confirming the diagnosis requires a biopsy of the kidney. An estimated 200,000 individuals in the United States have IgAN, and in American cohorts IgAN is more than twice as common among males than females.[2,3] For many patients, either death or ESKD occurs within 15-20 years after IgAN diagnosis, although other reports suggest more than two-thirds still have functioning kidneys at 25 years.[4,5] Based on estimates of the prevalence of ESKD caused by IgAN, the current US population, and the cost of ESKD per year, we estimate that care for ESKD caused by IgAN costs $1.3 billion dollars annually.[4,6,7]

Current clinical treatment guidelines for IgAN include general measures for kidney protection in people with chronic kidney disease (CKD), including blood pressure control and the use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) in patients with substantial proteinuria. More recent management and pending guidelines include the use of dual endothelin and angiotensin receptor antagonist (DEARA) therapy and/or sodium-glucose cotransporter-2 inhibitor (SGLT2i) therapy in some patients.[8] General supportive care is also recommended, including smoking cessation, weight control, exercise, and reduction in salt intake. For patients with higher levels of protein loss and other poor prognostic markers, immunosuppressive drugs can be considered; side effects of these therapies can be substantial. Both the draft guidelines as well as our discussions with clinical experts suggest that new guidelines will emphasize the importance of simultaneously (1) reducing the production of IgA antibodies that eventually deposit in the kidneys as well as (2) protecting glomerular function in the kidneys once

deposition of pathogenic IgA has already occurred. Both novel and existing medications generally fit into one or the other of these clinical purposes.

Sibeprenlimab (Otsuka Holdings Co., Ltd.) is a monoclonal antibody that binds to and neutralizes a proliferation-inducing ligand (APRIL), which regulates immune cell activity and the production of IgA antibodies.[9] The drug is administered intravenously. The U.S. Food and Drug Administration granted priority review for sibeprenlimab on May 26, 2025 with a PDUFA date of November 28, 2025.[10] Atacicept (Vera Therapeutics, Inc.) is a recombinant fusion protein that can bind to and neutralize APRIL as well as B-cell Activating Factor (BAFF), another regulator of immune activity.[11] The manufacturer has announced plans to submit a BLA application in the fourth quarter of 2025 with a potential PDUFA date in 2026.[12] A specific formulation of budesonide (Calliditas Therapeutics AB) is an oral corticosteroid that was granted full approval on December 31, 2023.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patient advocacy groups, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Discussions with clinical experts emphasized the importance of evolving treatment paradigms for IgAN. Consistent with draft clinical guidelines, with a final version in development, some clinical experts anticipate that treatment for IgAN will involve simultaneously reducing the production of pathogenic IgA as well as protecting kidney function once deposition has occurred.[8] Given rapid development of new therapeutic options, clinical experts are currently reviewing and debating potential new therapeutic pathways. Clinical experts emphasized that given this emerging treatment paradigm, neither traditional (ACE/ARB) or novel (DEARA) inhibitors of the renin-angiotensin system like sparsentan are alternatives to inhibitors of APRIL and/or BAFF.

Discussions with clinical experts also emphasized the magnitude of unmet need for individuals with IgAN. Many patients are at high risk for developing ESKD over the course of years, even with lower levels of proteinuria.

Discussions with patient advocacy groups emphasized the difficulty of accessing care, particularly at earlier stages before dialysis is needed. Availability of nephrologists who have specific expertise in clinical management of glomerulopathies is limited and better access to expertise at an earlier stage of disease might improve patient outcomes. Patients prioritize avoiding dialysis, and burdens for family and caregivers increase when patients develop ESKD.

A Voice of the Patient Report for IgA Nephropathy highlighted the importance of measures including kidney function, rate of damage to kidney function (proteinuria/albuminuria), and the time to dialysis or transplant. Patients would be more enthusiastic about trying a novel medication that reduces proteinuria, slows deterioration in kidney function, or improves the way patients feel, function, or survive. Halting progression of disease and/or delaying need for dialysis were core hopes for any new therapies. Patients also note that trials should include children. Any requirement for annual kidney biopsies would reduce interest in trial enrollment. Conversely, patients expressed willingness to participate in clinical trials for many years and expressed high tolerance for risk given the expected trajectory of IgAN.[13]

Patients do not feel that their treatments adequately reduce important symptoms, including fatigue, anxiety/depression, or intolerance to heat/cold. Systemic steroids such as prednisone are commonly noted to have substantial side effects. Patients also report difficulties with social isolation, difficulty maintaining relationships, uncertainty about trajectory, and the ability to attend important recreational and life events.[13]

Report Aim

This project will evaluate the health and economic outcomes of treatments for IgAN that reduce pathogenic IgA deposits in the glomeruli. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of interest for this review is people with IgA nephropathy.

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

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

Interventions

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

- Sibeprenlimab (Otsuka Holdings Co., Ltd.)
- Atacicept (Vera Therapeutics, Inc.)
- Tarpeyo® (budesonide, Calliditas Therapeutics AB)

Comparators

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

Outcomes

The outcomes of interest are described in the list below.

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

Timing

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

Settings

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

Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.2. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
There is substantial unmet need despite currently available treatments.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on 10/24/2025. This scoping document provides early thoughts about the overall model structure.

Data-permitting, we will develop an economic model to separately assess the lifetime cost-effectiveness of sibeprenlimab, atacicept, and targeted budesonide (Tarpeyo®) versus placebo and systemic steroids or no specific immunomodulatory therapy. Both the treatment and comparators will be considered add-on therapies to supportive care (e.g., RASis, SGLT2is, ERAs, and lifestyle modification).

The model structure will be based in part on a literature review of prior published models of IgA nephropathy.[14,15] Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Societal impacts (e.g., patient and caregiver productivity, caregiver utilities) and other indirect costs will be considered in a separate modified societal perspective analysis. This analysis will be considered as a co-base case when (a) direct data on indirect costs are available, (b) the societal costs of care are large relative to direct health care costs, and (c) the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of sibeprenlimab, atacicept, and budesonide on

productivity (patient and caregiver) as well as certain other impacts (e.g., patient time in treatment).

The target population will reflect clinical trial populations. The model will consist of health states including chronic kidney disease (CKD) stage 1, CKD stage 2, CKD stage 3a and 3b, CKD stage 4, end-stage kidney disease (ESKD) with and without dialysis, post-kidney transplant, and death. A cohort of patients will transition between states during predetermined cycles of one month over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five, ten, and thirty years).

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using clinical trial evidence and, data-permitting, network meta-analyses.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of cases of dialysis avoided and transplants avoided, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per case of dialysis and transplant avoided. Analyses will incorporate a 3% discount rate for both costs and benefits.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by treatments that reduce the production of abnormal IgA complexes (e.g., need for dialysis and/or transplant), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of IgA Nephropathy beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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