Provisional Translation (as of December 2025) *

Points to Consider for the Efficacy Evaluation of Drug for IgA Nephropathy (Early Consideration)

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Pharmaceuticals and Medical Devices Agency
Office of New Drug I

1. Introduction

IgA nephropathy is a primary glomerulonephritis characterized by persistent hematuria and proteinuria, with granular deposition of immunoglobulin A (IgA) predominantly in the mesangial region of the renal glomeruli, in the absence of underlying diseases that could cause this condition. It has been reported that approximately 40% of patients progress to end-stage renal disease (ESRD) within 20 years of diagnosis, indicating that IgA nephropathy is a serious disease[1)]. In Japan, IgA nephropathy is a designated intractable disease, and the number of patients based on the specific medical expense (designated intractable disease) recipient certificate holders was reported to be 14,333 in fiscal year 2023[2)].

Currently, dilazep hydrochloride hydrate is approved in Japan with an indication for IgA nephropathy (reduction of urinary protein in IgA nephropathy with mild to moderate renal dysfunction); however, its effect on suppressing the progression of renal dysfunction with long-term administration remains unclear[1)]. While renin-angiotensin system inhibitors, corticosteroids, and immunosuppressants are also used for IgA nephropathy, their effects on improving renal prognosis in IgA nephropathy have not been verified, and standard treatment has not been established[1)]. The situation is similar overseas, and development of new therapeutic drugs for IgA nephropathy has been progressing globally.

The established endpoint for clinical evaluation of chronic kidney disease (CKD) is ESRD necessitating renal replacement therapy[3)]. However, because clinical trials with ESRD as the primary endpoint require a long period, the possibility of using estimated glomerular filtration rate (eGFR) change from baseline, eGFR slope, urine protein-to-creatinine ratio (UPCR), etc. as surrogate endpoints has been explored domestically and internationally[3), 4), 5), 6)]. The "Guideline for Clinical Evaluation of Drugs for Early Chronic Kidney Disease" ("Guideline for Clinical Evaluation of Early CKD") in Japan[6)] defines early CKD as CKD with eGFR ≥30 mL/min/1.73m^2, and states that in

* This English version of the Japanese Early Consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

clinical trials targeting patients with early CKD, eGFR slope may be used as a surrogate endpoint depending on the study population, and discusses the observation period for eGFR slope and the clinically meaningful magnitude of effect in such cases. In addition to eGFR slope, the Guideline for Clinical Evaluation of Early CKD also discusses the possibility of using reduction in albuminuria or proteinuria as a surrogate endpoint.

In clinical trials for patients with IgA nephropathy, patients with relatively early CKD corresponding to eGFR ≥30 mL/min/1.73m^2 (mild to moderate renal dysfunction) are often included. The Guideline for Clinical Evaluation of Early CKD, based on the results of a meta-analysis of randomized controlled trials in IgA nephropathy[7], notes that early reduction in UPCR may potentially be used as a surrogate endpoint.

In fact, there are cases of Phase III trials in patients with IgA nephropathy that have been planned and conducted with UPCR at 9 months or other timepoints as the primary endpoint, aiming to verify the 2-year eGFR slope or change in eGFR from baseline[8, 9]. In the United States, since the approval of budesonide for IgA nephropathy in 2021, multiple drugs have been approved either through accelerated approval (based on UPCR results) or full approval following accelerated approval (based on eGFR results).

The purpose of this "Points to Consider" document is to present basic considerations for efficacy evaluation in the development of drugs for IgA nephropathy in order to promote such development in Japan. Based on the recommendation that Japan should participate in global clinical trials without delay to promote the development of drugs for IgA nephropathy in Japan, this document presents basic considerations for efficacy evaluation of drugs for IgA nephropathy, particularly regarding eGFR and UPCR. However, specific clinical trial designs for individual drugs should be determined based on the characteristics of the drug and its clinical positioning, and it is strongly recommended to utilize consultations with Pharmaceuticals and Medical Devices Agency (PMDA). Please note that the considerations presented in this document may change based on newly obtained knowledge in the future.

2. Points to Consider for Efficacy Evaluation

Considering the Guideline for Clinical Evaluation of Early CKD and other clinical evaluation guidelines in Japan[3, 6], it is recommended that clinical trials for IgA nephropathy with mild to moderate renal dysfunction set eGFR slope or change in eGFR from baseline based on an observation period of at least 2 years as the primary endpoint. The eGFR slope should be the total slope from the start of drug administration.

On the other hand, based on the status of planning and implementation of Phase III trials in Japan and overseas as described above, the results of discussions in the clinical evaluation guidelines in Japan[3, 6], and published literature[7, 10], when the magnitude of effect on UPCR based on observation

periods such as 9 months, the eGFR slope or change in eGFR from baseline based on the observation period up to that timepoint can reasonably predict that the results of eGFR slope or change in eGFR from baseline based on an observation period of 2 years or more will show a clinically meaningful magnitude of effect, it may be possible to demonstrate a certain level of efficacy of the investigational drug.

Considering that treatment for IgA nephropathy is not established at present, when clinical trial results are determined to demonstrate a certain level of efficacy and safety of the investigational drug, the conditional approval system for drugs as described in the "Handling of Conditional Approval of Drugs" (PSEHB/PED Notification No. 0831-2 dated August 31, 2020; partially revised on October 23, 2024, by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare; "the Director's Notification") may potentially be applicable. For consultations regarding the application of this system, please utilize PMDA's consultation system in accordance with the Director's Notification.

[Reference]

1) AMED Research Project on Intractable Diseases - Research Group on Intractable Kidney Diseases. Evidence-based Clinical Practice Guideline for IgA Nephropathy 2020
2) https://www.nanbyou.or.jp/wp-content/uploads/2024/11/koufu20241.pdf (last accessed: December 23, 2025)
3) AMED Research on Regulatory Science of Pharmaceuticals and Medical Devices - Research Group on Clinical Evaluation Guidelines for Chronic Kidney Disease. Guideline for Clinical Evaluation of Chronic Kidney Disease. Nihon Jinzo Gakkai Shi 2018; 60: 67-100
4) Baigent C, et al.; KDIGO Controversies Conference on Challenges in the Conduct of Clinical Trials in Nephrology Conference Participants. Challenges in conducting clinical trials in nephrology: conclusions from a Kidney Disease-Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2017; 92: 297-305
5) Levey AS, et al. Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of CKD: A Scientific Workshop Sponsored by the National Kidney Foundation in Collaboration With the US Food and Drug Administration and European Medicines Agency. Am J Kidney Dis 2020; 75: 84-104
6) Japanese Society of Nephrology. Guideline for Clinical Evaluation of Drugs for Early Chronic Kidney Disease. http://jsn.or.jp/academicinfo/report/suttogate-endpoint_guideline_20230222.pdf (last accessed: December 23, 2025)
7) Inker LA, et al. Association of Treatment Effects on Early Change in Urine Protein and Treatment Effects on GFR Slope in IgA Nephropathy: An Individual Participant Meta-analysis. Am J Kidney Dis 2021; 78: 340-9

8) Lafayette R, et al. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomized phase 3 trial. Lancet 2023; 402: 859-70
9) Perkovic V, et al. Alternative Complement Pathway Inhibition with Iptacopan in IgA Nephropathy. N Engl J Med 2025; 392: 531-43
10) Thompson A, et al. Proteinuria Reduction as a Surrogate End Point in Trials of IgA Nephropathy. Clin J Am Soc Nephrol 2019; 14: 469-81