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Otsuka Announces FDA Acceptance and Priority Review of Biologics License Application (BLA) for Sibeprenlimab in the Treatment of Immunoglobulin A Nephropathy (IgAN)

Otsuka Pharmaceutical, Co. Ltd. (Otsuka) and Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) today announce the U.S. Food and Drug Administration (FDA) has accepted for review the Biologics License Application (BLA) for sibeprenlimab, an investigational monoclonal antibody that selectively inhibits the activity of APRIL (**A PR**oliferation-**I**nducing **L**igand) in adults with immunoglobulin A nephropathy (IgAN). APRIL plays a key role in the pathogenesis of IgAN as explained by the 4-hit process, in which pathogenic galactose-deficient IgA (Gd-IgA1) is produced, leading to the synthesis of autoantibodies against Gd-IgA1, immune complex formation, and deposition in the glomerular mesangium. Sibeprenlimab is a single-dose prefilled syringe for subcutaneous injection every four weeks intended for self-administration, providing patients the convenience of at-home delivery.

The BLA is supported by the Phase 3 VISIONARY clinical trial (NCT05248646), which met its primary endpoint at the prespecified interim analysis, and results from the Phase 2 ENVISION clinical trial (NCT04287985). Sibeprenlimab demonstrated a statistically significant and clinically meaningful reduction in 24-hour uPCR after nine months of treatment compared to placebo in the Phase 3 VISIONARY trial.[1]

The BLA has been granted priority review and a Prescription Drug User Fee Act (PDUFA) target action date of November 28, 2025.

“Over the past decade, Otsuka has consistently approached difficult-to-treat diseases in nephrology with scientific and clinical innovation, seeking to provide crucial advancements for underserved patients with complex conditions like IgA nephropathy,” said John Kraus, M.D., Ph.D., executive vice president and chief medical officer, Otsuka Pharmaceutical Development & Commercialization, Inc. “If approved, sibeprenlimab would enable individuals living with IgA nephropathy to self-inject once every 4 weeks. We are thankful to share a potential treatment that could offer important clinical benefits and convenience to those living with this disease.”

Sibeprenlimab has Breakthrough Therapy designation for the treatment of IgAN based on the favorable results from the Phase 2 (ENVISION) trial (NCT04287985).[2]
IgAN is a progressive, autoimmune, chronic kidney disease that can lead to end-stage kidney disease (ESKD) over the lifetime of most patients under current optimized standard care.[3]
Targeting APRIL represents a potential therapeutic strategy to disrupt IgAN's pathogenesis via the 4-hit process, which may reduce production of immune complexes, which can deposit into kidney tissue, and may lead to ESKD and the need for transplantation.[1,2,4,5]

About sibeprenlimab

Sibeprenlimab (formerly VIS649) was designed and engineered by Visterra, Inc., a wholly owned subsidiary of Otsuka. Pre-clinical and early-stage trials of sibeprenlimab were also conducted by Visterra.

Sibeprenlimab is an investigational monoclonal antibody that selectively binds to and inhibits the activity of APRIL and plays a key role in the 4-hit process. By binding and inhibiting APRIL, sibeprenlimab may help reduce the amount of immunoglobulin A (IgA) and Gd-IgA1 levels. Lower levels of Gd-IgA1 provide less substrate for immune complex formation, and may also result in reduced auto-antibody production. Decreased immune complex creation should result in diminished deposition in the kidney, and reduced proteinuria and kidney inflammation. By reducing the production of Gd-IgA1, sibeprenlimab may help slow kidney damage and progression toward ESKD.[2,4,5,6] By inhibiting APRIL, sibeprenlimab may help address one of the IgAN-specific drivers for nephron loss.

About IgAN and APRIL

IgAN is a progressive, autoimmune, chronic kidney disease that typically manifests in adults aged 20-40 years and leads to ESKD over the lifetime of most patients.[3,6,7]

IgAN is characterized by the accumulation of Gd-IgA1 complexes in the kidneys. IgAN can lead to progressive loss of kidney function and, eventually, ESKD, imposing a significant burden on patients.[6] Despite supportive care, there is an unmet need for treatments that address the root cause of the condition. Continued research in the disease remains crucial to uncovering opportunities for advancement in our understanding and treatment of patients.[8]

APRIL, a cytokine in the tumor necrosis factor (TNF) family, is integral to the pathogenesis and progression of IgAN. It promotes the survival and class switching of B cells to produce IgA, particularly the pathogenic Gd-IgA1 that forms immune complexes in the kidneys.[8]

About Otsuka

Otsuka Pharmaceutical Co., Ltd. is a total healthcare company that focuses on each individual's potential to enhance their well-being. Our medical-related business provides treatments and diagnostics for both physical and mental health. Our nutraceutical business supports daily health maintenance and improvement. Otsuka's unique products and services are based on scientific evidence, under the

guidance of our corporate philosophy: Otsuka-people creating new products for better health worldwide. For further information, please visit www.otsuka.co.jp/en/

References

1. Otsuka Pharmaceutical Development & Commercialization, Inc.Visionary Study: Phase 3 Trial of Sibeprenlimab in Immunoglobulin A Nephropathy (IgAN). Clinicaltrials.gov.
2. Mathur M, Barratt J, Suzuki Y, et al. Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of VIS649 (Sibeprenlimab), an APRIL-Neutralizing IgG2 Monoclonal Antibody, in Healthy Volunteers. Kidney Int Rep. 2022;7(5):993-1003.
3. Pitcher, D. Braddon, et. al Long-term outcomes in IGA nephropathy. Clinical journal of the American Society of Nephrology : CJASN. https://pubmed.ncbi.nlm.nih.gov/37055195/.
4. Mathur M, Barratt J, Chacko B, et al. A Phase 2 Trial of Sibeprenlimab in Immunoglobulin A Nephropathy Patients. NEJM. 2023 https://www.nejm.org/doi/full/10.1056/NEJMoa2305635
5. Chang S, Li XK. The Role of Immune Modulation in Pathogenesis of IgA Nephropathy (nih.gov)
6. Cheung, Chee Kay & Boyd, JKF & Feehally, J.. (2012). Evaluation and management of IgA nephropathy. Clinical Medicine. 12. s27-s30. 10.7861/clinmedicine.12-6-s27.
7. Lai K. Iga nephropathy. Nature reviews. Disease primers. 2016. https://pubmed.ncbi.nlm.nih.gov/27189177/.
8. 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. Frontiers in nephrology. February 1, 2024.