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Enclosure:

- POSTER: Cheung CK, Barratt J, Roberts I, et al. Presented at: ISN World Congress of Nephrology 2026 (WCN'26); March 28-31, 2026; Yokohama, Japan.

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VISOR: An Ongoing Clinical Trial Assessing Changes in Kidney Histology Through Repeat Kidney Biopsies in Adults With IgA Nephropathy Treated With Sibeprenlimab

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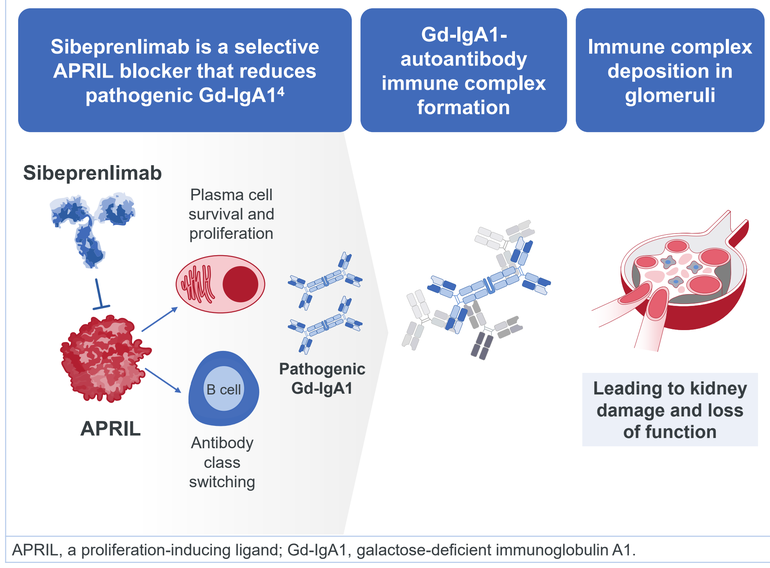
INTRODUCTION

- Immunoglobulin A (IgA) nephropathy is an immune-mediated kidney disease and the most common type of primary glomerulonephritis worldwide, with a global annual incidence rate of 2.5/100,000 persons[1,2]
  - It is characterized by mesangial deposition of immune complexes containing pathogenic galactose-deficient immunoglobulin A1 (Gd-IgA1) and associated autoantibodies[1]
- Sibeprenlimab is a fully humanized IgG2 monoclonal antibody that selectively blocks a proliferation-inducing ligand (APRIL), a key driver of IgA nephropathy pathogenesis (**Figure 1**)[1,3]

Figure 1. Sibeprenlimab mechanism of action[1,3]



APRIL, a proliferation-inducing ligand; Gd-IgA1, galactose-deficient immunoglobulin A1.

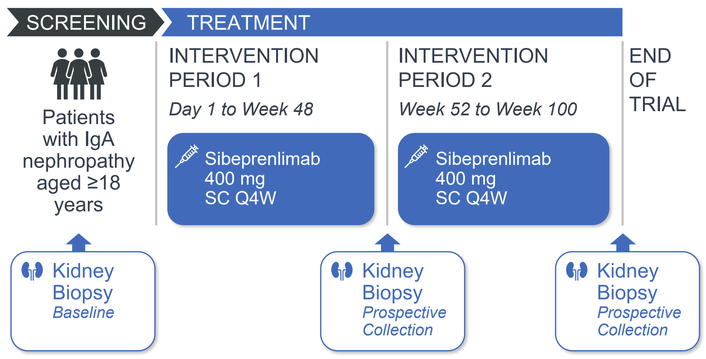
- In the Phase 2 ENVISION trial (NCT04287985), sibeprenlimab reduced proteinuria, stabilized estimated glomerular filtration rate (eGFR), suppressed serum APRIL, and decreased Gd-IgA1 levels in people with IgA nephropathy[5]
- In a prespecified interim analysis of the ongoing VISIONARY pivotal Phase 3 clinical trial (NCT05248646), sibeprenlimab led to a 51.2% (*P*<0.001) placebo-adjusted reduction in urine protein to creatinine ratio based on 24-hour urine collections at 9 months and markedly reduced Gd-IgA1 and APRIL compared with placebo at 48 weeks[4]
  - Resolution of hematuria (dipstick; positive=1+, 2+, 3+, and trace) occurred in 80.2% (n=89/111) vs 31.0% (n=40/129) of patients in the sibeprenlimab and placebo groups, respectively, over 48 weeks[4]
- Sibeprenlimab was granted accelerated approval for the reduction of proteinuria in adults with primary IgA nephropathy at risk for disease progression by the US Food and Drug Administration[6]
- Sibeprenlimab's potential impact on kidney tissues remains to be characterized

OBJECTIVE

- With an innovative protocol, VISOR (NCT06740526) aims to evaluate the anti-APRIL effect of sibeprenlimab on glomerular IgA deposition and immune-mediated drivers of disease activity in pre- and post-treatment kidney biopsies[7]

METHODS

Figure 2. Study design



Key Inclusion Criteria[a]

- Men and women ≥18 years of age
- Biopsy-proven IgA nephropathy
- eGFR >45 mL/min/1.73 m²

Key Exclusion Criteria[a]

- Coexisting chronic kidney disease other than IgA nephropathy
- Serum IgG value <600 mg/dL at screening
- History of nephrotic syndrome
- Currently receiving or has received systemic corticosteroids or immunosuppression within 24 weeks prior to the first dose of sibeprenlimab[b]
- Uncontrolled hypertension (>140/90 mm Hg)
- Weight <50 kg
- Type 1 diabetes; uncontrolled type 2 diabetes

[a]No proteinuria-related or MEST-C score inclusion or exclusion criteria are applied.

[b]The use of nonimmunosuppressant background therapy for IgA nephropathy (eg, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, mineralocorticoid receptor antagonists, sodium-glucose cotransporter 2 inhibitor, and endothelin receptor antagonists) is permitted at the discretion of the investigators.

eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; IgG, immunoglobulin G; MEST-C, mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and crescents (C); Q4W, every 4 weeks; SC, subcutaneous.

- VISOR is a Phase 2b, multicenter, open-label, repeat kidney biopsy, single-arm trial of sibeprenlimab in adults (aged ≥18 years) with IgA nephropathy (key inclusion and exclusion criteria are listed in **Figure 2**)
  - Eligible patients will receive sibeprenlimab 400 mg subcutaneously every 4 weeks for up to 2 years (**Figure 2**)
  - If adequate tissue is available from a diagnostic biopsy sample collected within 24 weeks of the anticipated start of treatment with sibeprenlimab, the diagnostic biopsy may serve as the baseline biopsy; alternatively, a baseline research biopsy may be performed. Repeat protocol biopsies are performed at week 52 and, for patients continuing into year 2, week 104
- **The VISOR trial is currently enrolling**
- Approximately 50 patients will be enrolled across approximately 18 global sites
- The primary endpoint of the trial occurs at week 52, when patients complete the repeat research kidney biopsy (**Table 1**)
- Exploratory objectives include evaluating additional changes in kidney tissue and immune activation, as well as blood and urine disease biomarkers (**Table 2**)

Table 1. Primary and secondary endpoints

Primary endpoint	Secondary endpoint
Changes in glomerular IgA deposition by immunofluorescence in kidney tissue from baseline to week 52	Incidence of TEAEs graded by severity, clinical laboratory tests, vital sign measurements, physical examinations, and injection site reactions

IgA, immunoglobulin A; TEAE, treatment-emergent adverse event.

Table 2. Exploratory endpoints

Source	Exploratory endpoint[a]
Kidney tissue	Change in **MEST-C component scores**
Kidney tissue	Change in **glomerular abundance of CD68+ cells** by immunohistochemistry
Kidney tissue	Change in deposition of **complement markers** including C3, C4d, C5b9, and C1q
Kidney tissue	Change in **single-cell resolution gene expression patterns** in glomerular cells
Kidney tissue	Change in immunoglobulins including **Gd-IgA1, IgA, IgG, and IgM,** and in **fibrosis markers**
Blood and urine	Change in biomarkers including **immune complexes** in blood, **urinary epidermal growth factor,** and **urinary membrane attack complex (C5b-9)**
Blood and urine	Changes in bulk and **cell-type–specific gene expression patterns** in blood and urine
Kidney tissue vs blood and urine	Changes in **eGFR, proteinuria** (first void/spot uPCRs), and **hematuria in relation to histologic changes**

[a]Timing: Baseline to week 52 and week 104.

C, complement component; CD68+, cluster of differentiation 68; eGFR, estimated glomerular filtration rate; Gd-IgA1, galactose-deficient immunoglobulin A1; Ig, immunoglobulin; MEST-C, mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and crescents (C); uPCR, urine protein to creatinine ratio.

DISCUSSION

- VISOR will explore the histologic and cellular changes following sibeprenlimab treatment in adults with IgA nephropathy
- These findings are expected to expand our mechanistic understanding of the effect of APRIL inhibition on histopathological changes in IgA nephropathy and help evaluate whether upstream targeting of the IgA nephropathy–specific immune cascade can modify disease progression by preserving nephrons and slowing kidney function decline[8]
- Additionally, the study of longitudinal biopsy samples collected over a 2-year period, in combination with assessments in blood and urine, will provide a unique opportunity to identify minimally invasive biomarkers that could predict improvement in disease activity in kidney tissues[8-10]

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FUNDING/ACKNOWLEDGMENTS

This study is funded by Otsuka Pharmaceutical Development & Commercialization, Inc. (Princeton, NJ, USA). Medical writing assistance was provided by Costanza Martelli, MSc (Syneos Health Medical Communications), funded by Otsuka Pharmaceutical Development & Commercialization, Inc. (Princeton, NJ, USA). The authors thank the trial participants, their families, and the investigators and research teams for their invaluable contributions to this work.

DISCLOSURES

CKC: Consulting/speaker fees: Alexion, Boehringer Ingelheim, Calliditas, CSL Vifor, Dimerix, Emerald Clinical, Novartis, Otsuka Pharmaceutical, Roche, Stada, Travere Therapeutics, Vera Therapeutics, Vertex; Research funding: Travere Therapeutics. **JB:** Consulting, speaker fees, grant support: Argenx, Calliditas Therapeutics, Chinook Therapeutics, Galapagos, Novartis, Omeros, Travere Therapeutics, Visterra/Otsuka; Consulting, speaker fees: Alnylam Pharmaceuticals, Astellas Pharma, BioCryst, Dimerix, Vera Therapeutics; Grant support: GlaxoSmithKline. **IR:** No competing interests to disclose. **MS:** Advisory boards: Vera, Travere Therapeutics, Novartis, Biogen, Otsuka, Relay TX, Merida Biosciences, Medibeacon; Safety monitoring: Alpine Immune Sciences/Vertex; Speaking agreements: TD Cowen, ReachMD/Medintelligence, Curio. **MW:** Consulting/speaker fees: Bayer, GSK, Hansa BioPharma, Latham Watkins /OBO Otsuka/Visterra; End Point Review Committee: Novo Nordisk; Provincial Medical Lead: Ontario Health. **HT:** Personal fees: Calliditas Therapeutics, Chinook Therapeutics, Novartis, Omeros. **AQ:** No competing interests to disclose. **YS:** Consulting fees: Alexion Pharmaceuticals, Alpine Immune Sciences, Argenx, BioCryst, Chinook Therapeutics, Novartis, Otsuka/Visterra, Renalys Japan; Payment/honoraria: AstraZeneca, Daiichi Sankyo, Kyowa Kirin, Mitsubishi Tanabe, Novartis; Grants/contracts: Argenx, Aurinia Pharmaceuticals, Chinook Therapeutics, Kyowa Kirin, Moderna, Pfizer, Rona Bioscience, Teijin Pharma, Travere Therapeutics. **HS:** Advisory role: Otsuka Pharmaceutical, Vera Therapeutics, Viatris; Honoraria: Novartis, Alexion Pharma, Chugai, Otsuka Pharmaceutical, Viatris. **LK:** Principal investigator: AstraZeneca, Boehringer Ingelheim, Cara Therapeutics, Chinook Therapeutics, ClimbBio, CSL Behring, Dimerix, Galderma, Novartis, Omeros Co., Otsuka Pharmaceuticals, Reata Pharmaceuticals, Travere Therapeutics, Vera Therapeutics, Vertex Therapeutics, Visterra, Walden Biosciences. Medical advisor role: Novartis, Vertex Therapeutics, Vera Therapeutics. **JH:** Otsuka Pharmaceutical employee. **GH:** Otsuka Pharmaceutical employee. **LS:** Otsuka Pharmaceutical employee. **DVR:** Ownership: Reliant Glycosciences LLC; Consultancy: Angion Biomedica, Calliditas Therapeutics (Pharmalink), Chinook Therapeutics, George Clinical, Novartis, Otsuka/Visterra, Roche, Vera Therapeutics; Research funding: Achillion Pharmaceuticals, Calliditas Therapeutics (Pharmalinks), Chinook Therapeutics, Otsuka/Visterra, Pfizer, Reata Pharmaceuticals, Travere Therapeutics (Retrophin), Vera Therapeutics; Honoraria: Angion Biomedica, Calliditas Therapeutics, George Clinical, Novartis, Otsuka/Visterra; Advisory/leadership role: Calliditas Therapeutics, Eledon Pharmaceuticals, George Clinical, Novartis, Otsuka/Visterra.

Presented at: ISN World Congress of Nephrology 2026 (WCN'26); March 28-31, 2026; Yokohama, Japan. The poster was also presented at the Mayo Clinic 2026 congress; February 13-15, 2026; Scottsdale, AZ.