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Enclosure:

- POSTER: Barratt J, Huang M, Hafkin J, et al. Presented at: NKF 2026 Spring Clinical Meetings (SCM26); May 7-10, 2026; New Orleans, LA, USA.

Evaluation of Immunoglobulin G Reduction and Infection Incidence in an Interim Analysis of the Phase 3 VISIONARY Trial of Sibeprenlimab in IgA Nephropathy

G-444

Jonathan Barratt,[1] Mai Huang,[2] Jeffrey Hafkin,[2] Emanuel Lohrmann,[2] Jing Xia,[2] Vinu George,[2] Vlado Perkovic[3]

[1]University of Leicester, Leicester, United Kingdom; [2]Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA; [3]University of New South Wales, Sydney, Australia

INTRODUCTION

- Immunoglobulin A (IgA) nephropathy is a progressive immune-mediated chronic kidney disease characterized by mesangial deposition of immune complexes containing pathogenic galactose-deficient immunoglobulin A1 (Gd-IgA1) and associated autoantibodies[1]
- Sibeprenlimab is a humanized immunoglobulin G2 (IgG2) monoclonal antibody that selectively blocks a proliferation-inducing ligand (APRIL), a key driver of IgA nephropathy pathogenesis[1,2]
- 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 on November 25, 2025[3]
- The ongoing Phase 3 VISIONARY trial (NCT05248646) evaluates the efficacy and safety of sibeprenlimab vs placebo in adults (aged ≥18 years) with IgA nephropathy[4]
  - In the prespecified interim analysis evaluating the primary endpoint, sibeprenlimab resulted in a significant placebo-adjusted reduction in 24-hour urine protein to creatinine ratio (uPCR-24h) of 51.2% (*P*<0.001) after 9 months of treatment[5]
    - Sibeprenlimab also led to a 54.3% (95% CI, 46.4-60.9) placebo-adjusted reduction in uPCR-24h at month 12[5]
  - The safety profile was comparable between sibeprenlimab and placebo[5]
  - At week 48, serum IgA levels had decreased in patients receiving sibeprenlimab by 68.8% (95% CI, 67.2-70.5), IgG levels had decreased by 35.0% (95% CI, 32.8 to 37.3), and IgM levels had decreased by 74.5% (95% CI, 73.1-75.9), all measured as secondary endpoints. Minimal changes were observed with placebo[5]
  - In clinical immunology practice, IgG reductions in adults are often classified as mild to moderate (300-600 mg/dL), significant (100-299 mg/dL), or profound (<100 mg/dL)[6]
  - As lower IgG levels can be associated with a higher incidence of recurrent and more severe infections,[6,7] we herein report further analyses of the effect of sibeprenlimab on IgG levels and infection incidence

RESULTS

- Treatment-emergent adverse events (TEAEs) in the Medical Dictionary for Regulatory Activities (MedDRA) v27.0 System Organ Class (SOC) of "Infections and infestations" occurred in 49.0% (127/259) of patients receiving sibeprenlimab vs 45.0% (113/251) with placebo
  - Rates of the most common infections were also comparable (**Table 1**)
  - In the placebo and sibeprenlimab arms, 10/251 and 8/259 patients, respectively, had dose interruptions due to infection. All infections in the sibeprenlimab arm were resolved without leading to permanent treatment discontinuation
- No patients had IgG <300 mg/dL, and 3.5% (9/258) of patients had an IgG level <400 mg/dL
  - Per protocol, all patients received a fixed dose of sibeprenlimab or placebo, and IgG levels were blinded throughout the study. Thus, there were no dose interruptions due to IgG levels
- There was no increase in incidence of infection in the lower IgG strata (**Table 2**)
  - Two of the 9 patients with an IgG level <400 mg/dL had adverse events (moderate COVID-19 in one and mild urinary tract infection in the other) that occurred during treatment and resolved without dose modification (**Table 2**)[5]
  - Serious infections occurred in 2 patients with IgG ≥600 mg/dL (including 1 severe infection in 1 patient), 1 patient with IgG 400-499 mg/dL, and no patients with IgG <400 mg/dL (**Table 2**)
  - All infections were resolved

Table 1. Most common treatment-emergent infection adverse event incidences based on MLG in the VISIONARY Phase 3 trial

	Sibeprenlimab (N=259) n (%)[a]	Placebo (N=251) n (%)[a]	Total (N=510) n (%)[a]	Risk difference[b] sibeprenlimab – placebo (95% CI)
COVID-19	28 (10.8)	19 (7.6)	47 (9.2)	3.2 (-1.8, 8.2)
Influenza	21 (8.1)	16 (6.4)	37 (7.3)	1.7 (-2.8, 6.2)
Nasopharyngitis	43 (16.6)	34 (13.5)	77 (15.1)	3.1 (-3.1, 9.3)
Respiratory tract infection	43 (16.6)	41 (16.3)	84 (16.5)	0.3 (-6.2, 6.7)

[a]Percentages are based on the number of patients who received ≥1 dose of sibeprenlimab; [b]Risk difference was calculated with 95% CI.
CI, confidence interval; COVID-19, coronavirus disease 2019; MLG, Medical Dictionary for Regulatory Activities labeling grouping.

Table 2. Incidence of treatment-emergent infection events by IgG group in the sibeprenlimab arm

Postbaseline IgG, mg/dL	n	Patients with treatment-emergent infection events, n (%)	Patients with treatment-emergent serious infection events, n (%)	Patients with treatment-emergent severe infection events, n (%)
<300	0	0 (0.0)	0 (0.0)	0 (0.0)
300-399	9	2 (22.2)	0 (0.0)	0 (0.0)
400-499	31	18 (58.1)	1 (3.2)	0 (0.0)
500-599	50	29 (58.0)	0 (0.0)	0 (0.0)
≥600	168	78 (46.4)	2 (1.2)	1 (0.6)
Total	**N=258[a]**	**127 (49.2)**	**3 (1.2)**	**1 (0.4)**

[a]259 patients received sibeprenlimab treatment; however, 1 patient did not have any postbaseline data on IgG level at the prespecified interim analysis cutoff.
IgG, immunoglobulin G.

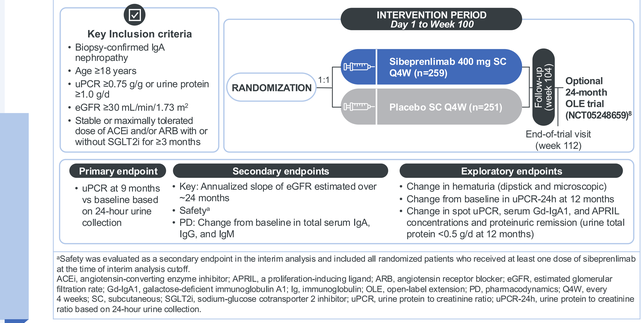
CONCLUSIONS

- In the interim analysis of VISIONARY
  - Incidence of infections was comparable between the sibeprenlimab and placebo treatment arms; all infections were resolved
  - In the sibeprenlimab arm, no patients had IgG <300 mg/dL, and reductions in IgG levels to <400 mg/dL were very infrequent
  - Reductions in IgG levels did not appear to increase the overall infection incidence, and serious infections were uncommon across all IgG strata
- These findings support a favorable infection safety profile for selective APRIL inhibition with sibeprenlimab, which will be further evaluated in the ongoing VISIONARY trial over a 24-month treatment period

METHODS

- VISIONARY is a randomized, multicenter, double-blind, placebo-controlled trial in patients with biopsy-confirmed IgA nephropathy (key inclusion criteria are listed in **Figure 1**)[5]
  - Patients with serum IgG values <600 mg/dL at screening were excluded from the trial
  - Eligible patients (N=510) were randomized 1:1 to sibeprenlimab or placebo every 4 weeks for 100 weeks[5]
- Incidence of infection with sibeprenlimab vs placebo was compared using MedDRA v27.0 "Infections and infestations" SOC and MedDRA Labeling Group categories
  - Risk differences between treatment arms were calculated along with 95% CIs
- Postbaseline IgG levels with sibeprenlimab were collected every 4 weeks in the first 3 months and then every 12 weeks and were stratified by immunoglobulin levels
  - Treatment-emergent infections were reported by seriousness and severity
  - Reductions in IgG levels were assessed at individual time points; therefore, the reported values may reflect transient observations rather than sustained decreases over time

Figure 1. VISIONARY trial design[5]



[a]Safety was evaluated as a secondary endpoint in the interim analysis and included all randomized patients who received at least one dose of sibeprenlimab at the time of interim analysis cutoff.
ACEi, angiotensin-converting enzyme inhibitor; APRIL, a proliferation-inducing ligand; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; Gd-IgA1, galactose-deficient immunoglobulin A1; Ig, immunoglobulin; OLE, open-label extension; PD, pharmacodynamics; Q4W, every 4 weeks; SC, subcutaneous; SGLT2i, sodium-glucose cotransporter 2 inhibitor; uPCR, urine protein to creatinine ratio; uPCR-24h, urine protein to creatinine ratio based on 24-hour urine collection.

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DISCLOSURES

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. **MH**, **EL**, **JX**, and **VG** are employees of Otsuka Pharmaceutical. **JH** is a former employee of Otsuka Pharmaceutical. **VP:** Consulting, advisory board, steering committee membership, scientific presentations: AstraZeneca, Bayer Healthcare, Biogen, Boehringer Ingelheim, Chinook Therapeutics, GlaxoSmithKline, Guard Therapeutics, Incyte Corporation, Janssen Global Services, Novartis Pharma, Novo Nordisk; Otsuka Pharmaceutical, Shaanxi Micot, Travere Therapeutics, Tricida, Vifor Pharma (fees paid to institution); Other (board director; holds share options): George Clinical.

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.

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