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Enclosure:

- POSTER: Zhang H, Liew A, Wong MG, et al. Presented at: ISN World Congress of Nephrology 2026 (WCN'26); March 28-31, 2026; Yokohama, Japan.

Evaluating Sibeprenlimab in Patients With IgA Nephropathy: Results From an Interim Analysis of the China Cohort of the Phase 3 VISIONARY Trial

P230

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INTRODUCTION

- Immunoglobulin A (IgA) nephropathy is a progressive immune-mediated chronic kidney disease with a global annual incidence rate of 2.5/100,000 persons[1-3]; in mainland China, the estimated incidence ranges from 6.3% to 24.7% among patients undergoing renal biopsy[4]
  - IgA nephropathy accounts for 30%-53% of primary glomerular diseases in the Chinese population,[5,6] in whom the disease follows a more aggressive course[7]
  - Despite supportive therapy, up to 24% of Chinese patients remain at risk for progression to kidney failure within 6 years[8]
- Sibeprenlimab is a fully humanized IgG2 monoclonal antibody that selectively blocks a proliferation-inducing ligand (APRIL), a key driver of IgA nephropathy pathogenesis[3]
- The safety and efficacy of sibeprenlimab are being evaluated in the ongoing VISIONARY trial (NCT05248646) in a global cohort of adults with IgA nephropathy[9]
- In a prespecified interim analysis (IA), sibeprenlimab met its primary endpoint, demonstrating a statistically significant placebo (PBO)-adjusted reduction in urine protein to creatinine ratio (uPCR) based on 24-hour urine collection (uPCR-24h) at 9 months[3]
- 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[10]
- An open-label trial (NCT05248659) to evaluate the long-term safety and efficacy of sibeprenlimab is currently enrolling patients who completed the VISIONARY trial without safety concerns[11]
- Here, we report the IA results of the antiproteinuric effects and safety of sibeprenlimab for the mainland China cohort

RESULTS

- 42 patients from the mainland China cohort were included in the China IA (sibeprenlimab, n=25; PBO, n=17)
- Demographic and baseline characteristics were generally balanced between treatment groups in the mainland China and global cohorts (**Table 1**)
  - Across all treatment groups, the mainland China cohort was younger (median age, 36 vs 42 years), included a higher percentage of women (52% vs 38%), and had more sodium-glucose cotransporter 2 inhibitor use (45% vs 39%) compared with the global cohort[3]

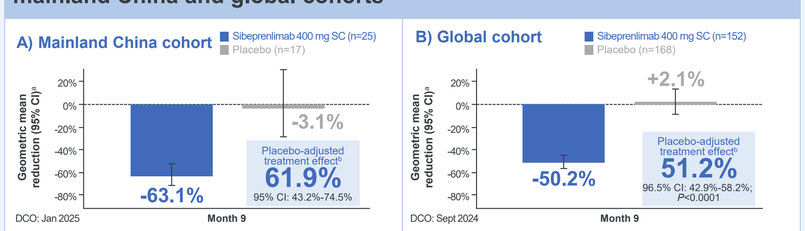
Table 1. Baseline demographic and clinical characteristics (mainland China and global cohort IA)

	Mainland China cohort		Global cohort	
Characteristic	**Sibeprenlimab (n=25)**	**Placebo (n=17)**	**Sibeprenlimab (n=152)**	**Placebo (n=168)**
Age, y				
Median (range)	35 (23-48)	40 (23-58)	42 (18-75)	43 (18-83)
Sex at birth, n (%)				
Male	8 (32.0)	12 (70.6)	100 (65.8)	100 (59.5)
Female	17 (68.0)	5 (29.4)	52 (34.2)	68 (40.5)
Screening uPCR-24h, n (%)				
≤2.0 g/g	21 (84.0)	14 (82.4)	123 (80.9)	137 (81.5)
>2.0 g/g	4 (16.0)	3 (17.6)	29 (19.1)	31 (18.5)
Screening eGFR, n (%)				
30-44 mL/min/1.73 m^2	2 (8.0)	0 (0.0)	37 (24.3)	43 (25.6)
≥45 mL/min/1.73 m^2	23 (92.0)	17 (100)	115 (75.7)	125 (74.4)
SGLT2i use, n (%)				
Yes	12 (48.0)	7 (41.2)	54 (35.5)	72 (42.9)
No	13 (52.0)	10 (58.8)	98 (64.5)	96 (57.1)
Time from initial biopsy to randomization, y				
Median (range)	1.0 (0.0-10.0)	2.5 (0.1-12.0)	1.3 (0.1-23.7)	1.9 (0.0-34.0)

eGFR, estimated glomerular filtration rate; IA, interim analysis; SGLT2i, sodium-glucose cotransporter 2 inhibitor; uPCR-24h, 24-hour urine protein to creatinine ratio.

- At 9 months (week 40), a reduction from baseline in uPCR-24h was observed in patients treated with sibeprenlimab (63.1%; 95% CI, 52.1% to 71.6%) vs PBO (3.1%; 95% CI, −31.0% to 28.3%), corresponding to a PBO-adjusted reduction in uPCR-24h of 61.9% (95% CI, 43.2% to 74.5%) (**Figure 1A**)
  - The antiproteinuric effect was consistent with (and numerically greater than) that of the global cohort (**Figure 1B**)

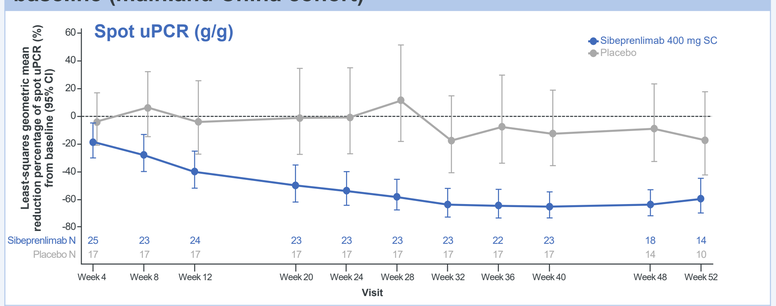
Figure 1. Change from baseline uPCR-24h (g/g) at month 9: mainland China and global cohorts



[a]The percentage reduction of uPCR-24h at month 9 is compared with baseline using ANCOVA.
[b]The percentage reduction for treatment effect was calculated as (1 – ratio of GM of uPCR-24h ratio for sibeprenlimab over placebo estimated from ANCOVA model) x 100%. The 95% CI corresponds to the treatment-specific reductions. The 96.5% CI corresponds to the between-treatment difference.
ANCOVA, analysis of covariance; DCO, date of cutoff; GM, geometric mean; SC, subcutaneous; uPCR-24h, 24-hour urine protein to creatinine ratio.

- Consistent with the global cohort, sibeprenlimab led to rapid and sustained reductions in spot uPCR in the mainland China cohort, evident at week 4 and maintained through week 52. At 9 months, the mean reduction from baseline was 65.2% (95% CI, 54.7% to 73.2%) with sibeprenlimab vs 12.5% (95% CI, −19.1% to 35.8%) with PBO, corresponding to a PBO-adjusted reduction of 60.2% (95% CI, 40.3% to 73.4%) (**Figure 2**)

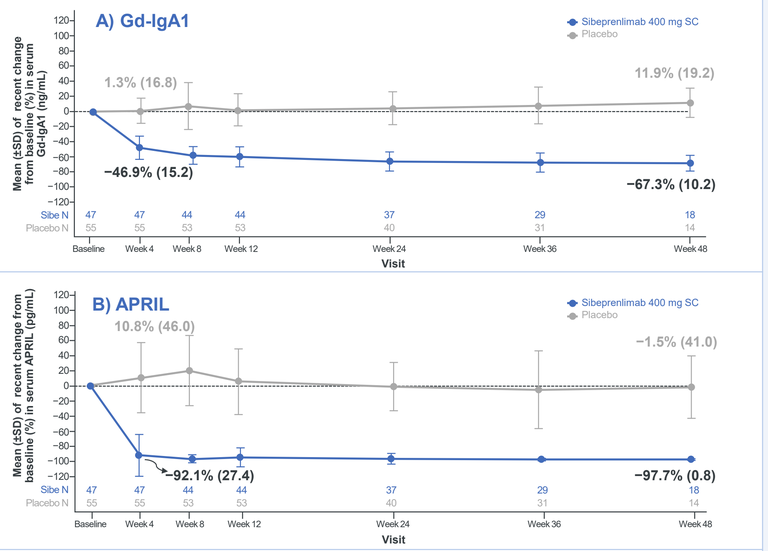
Figure 2. Least-squares geometric mean change in spot uPCR from baseline (mainland China cohort)



SC, subcutaneous; uPCR, urine protein to creatinine ratio.

- At week 48, sibeprenlimab achieved mean (SD) percent reductions of 67.3% (10.2) in serum galactose-deficient IgA1 (**Figure 3A**) and near complete suppression of APRIL levels, with reductions of 97.7% (0.8) (**Figure 3B**). Minimal changes were observed with PBO

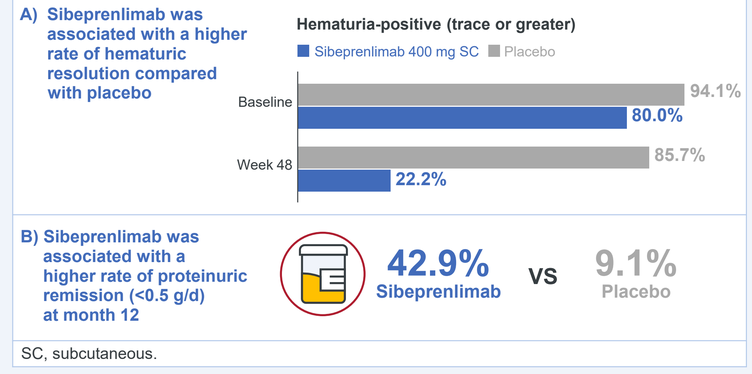
Figure 3. Mean percent change from baseline in Gd-IgA1 and APRIL levels by visit (mainland China cohort, PD set)



APRIL, a proliferation-inducing ligand; Gd-IgA1, galactose-deficient immunoglobulin A1; PD, pharmacodynamics; SC, subcutaneous; Sibe, sibeprenlimab.

- At week 48, sibeprenlimab also reduced serum IgA (−67.1%), IgG (−32.0%), and IgM (−74.4%) levels compared with PBO
- Consistent with the global cohort,[3] resolution of hematuria at week 48 (**Figure 4A**) and higher rates of proteinuric remission (total urine protein of <0.5 g/d at 12 months) were observed among patients treated with sibeprenlimab vs PBO in the mainland China cohort (**Figure 4B**)

Figure 4. Hematuric resolution and proteinuric remission with sibeprenlimab compared with baseline (mainland China cohort)



SC, subcutaneous.

- Treatment-emergent adverse event (TEAE) incidence was comparable across the sibeprenlimab and PBO groups, and consistent with the global cohort,[3] with no deaths reported (**Table 2**).

Table 2. TEAEs (mainland China cohort, safety set)

TEAEs	Sibeprenlimab, n (%) (n=47)	Placebo, n (%) (n=55)
Any TEAE	37 (78.7)	40 (72.7)
Treatment-related TEAE	10 (21.3)	9 (16.4)
TEAEs occurring in ≥5% of patients in either treatment group		
Upper respiratory tract infection	14 (29.8)	10 (18.2)
Hyperuricemia	4 (8.5)	3 (5.5)
Diarrhea	3 (6.4)	2 (3.6)
Injection site pain	3 (6.4)	2 (3.6)
Pyrexia	3 (6.4)	4 (7.3)
Influenza	3 (6.4)	3 (5.5)
Hyperlipidemia	3 (6.4)	3 (5.5)
Hepatic function abnormal	2 (4.3)	4 (7.3)
Cough	2 (4.3)	5 (9.1)
Weight increased	1 (2.1)	5 (9.1)
Any serious TEAE	2 (4.3)	3 (5.5)
Deaths	0 (0.0)	0 (0.0)

TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Baseline demographic and clinical characteristics were comparable across treatment groups in both cohorts
- At 9 months, results from the mainland China cohort were consistent with the previously published global interim analysis, with sibeprenlimab achieving a 61.9% PBO-adjusted reduction in uPCR-24h (95% CI, 43.2%-74.5%), along with proteinuric remission (at 12 months), biomarker reductions, and hematuria resolution by week 48
- Sibeprenlimab was well tolerated in the mainland China cohort, with a safety profile that was generally consistent with the global cohort, without additional clinically relevant safety findings
- Safety and the key secondary efficacy endpoint (estimated glomerular filtration rate slope) will be assessed at 24 months

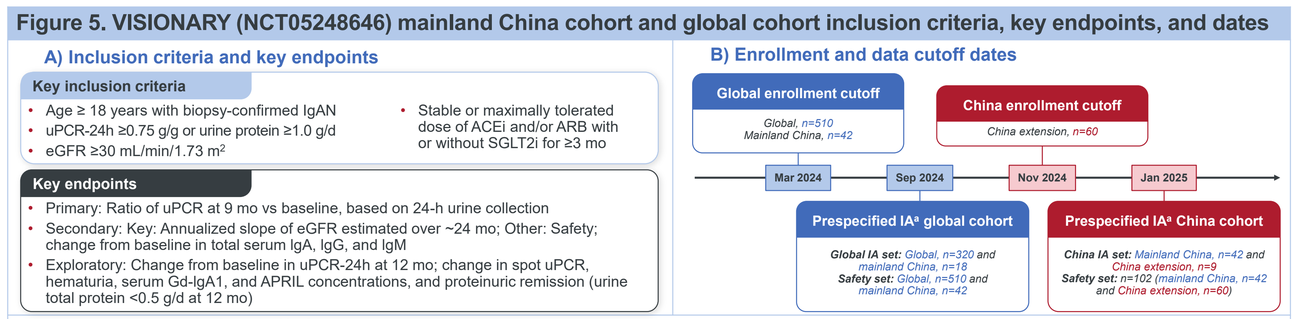
Limitations

- Initiation of the mainland China cohort occurred later than the global cohort IA, resulting in a small sample size relative to the global cohort; the current findings are based on an IA, and longer follow-up (up to 24 months) is required to fully characterize treatment effects

METHODS

- VISIONARY, a Phase 3, double-blind, PBO-controlled trial in adults with biopsy-confirmed IgA nephropathy, is being conducted at 240 sites across 31 countries,[3] including 25 trial sites in China
- Eligibility criteria and clinical endpoints were the same for the mainland China and global cohorts (**Figure 5A**)
- At the time of the China IA cutoff (January 2025), 42 patients from the mainland China cohort (included in this analysis) and 9 from the China extension had had the opportunity to complete the 9-month uPCR-24h assessment (**Figure 5B**)

Figure 5. VISIONARY (NCT05248646) mainland China cohort and global cohort inclusion criteria, key endpoints, and dates



[a]IA was conducted when the first 62.5% of randomized participants had the opportunity to complete the 9-month uPCR-24h assessment in the global cohort; IA for mainland China cohort comprised up to 51 patients from mainland China (at least 15% of the global cohort) who had the opportunity to complete the 9-month uPCR-24h assessment.
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; IA, interim analysis; Ig, immunoglobulin; IgAN, IgA nephropathy; SGLT2i, sodium-glucose cotransporter 2 inhibitor; uPCR, urine protein to creatinine ratio; uPCR-24h, 24-hour urine protein to creatinine ratio.

- The safety set included all randomized patients who received ≥1 dose of sibeprenlimab in the mainland China and global cohorts (**Figure 5B**)
- Analysis of the mainland China cohort followed the statistical analysis plan and the methodology of the global cohort IA
  - Statistical analyses included analysis of covariance (uPCR-24h), mixed model for repeated measures (spot uPCR), logistic-regression model (proteinuric remission), and descriptive statistics (demographic and baseline characteristics, safety, and pharmacodynamic markers)

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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 Himkusha Thakur, PhD (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

HZ: Consultancy and/or honoraria: Alexion/AstraZeneca, Alpine Immune Sciences/Vertex, Biogen, Calliditas Therapeutics, Chinook Therapeutics, Everest Medicines, George Clinical, Novartis, Omeros, Otsuka, Roche, Vera; **AL:** Consultancy and/or honoraria: Alexion/AstraZeneca, Biogen, Emerald Clinical Trials, Novartis, Otsuka, Takeda, Vera, Jade BioSciences, Climb Bio, Biohaven, Precision for Medicine, Vantive Healthcare, Fresenius Medical Care, Boehringer-Ingelheim, Candid Therapeutics, Sitala, Timberlyne; **MGW:** Consultancy and/or honoraria: AstraZeneca, Amgen, Baxter, Boehringer Ingelheim, George Clinical via Travere Therapeutics, Biohaven, Cadid Therapeutic, Alpine Pharma, Eledon Pharma, and Kira Pharma; Steering committee member: Alpine Pharma, CSL Behring, Eledon Pharmaceuticals, Kira Pharma, Travere Therapeutics, Otsuka Pharmaceuticals, and TESTING trials; Data safety monitoring boards: ARGX-133 and HFpEF Polypill trials; **DX:** None; **CW:** None; **WL:** Clinical research award: Clinical Research Award of The First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF-CRF-2022-029); **GL:** none; **JX:** Employee, Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ, USA; **CF:** Employee, Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ, USA; **JH:** Employee, Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ, USA; **JL:** Grants: China National Funds for Distinguished Young Scientists, Capital's Funds for Health Improvement and Research. Consultancy fee or research funding: Otsuka, Novartis, Everest Medicines and AstraZeneca Pharmaceuticals outside the submitted work.

SCAN TO VIEW

Presented at: ISN World Congress of Nephrology 2026 (WCN'26); March 28-31, 2026; Yokohama, Japan