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Enclosure:

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Impact of SGLT2i Use on Sibeprenlimab Outcomes in IgA Nephropathy (IgAN): Subgroup Analysis From the Phase 3 VISIONARY Trial Interim Analysis

G-488

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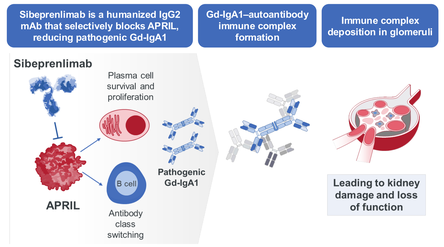
INTRODUCTION

- 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 (**Figure 1**)[1,2]

Figure 1. Sibeprenlimab mechanism of action[1-5]



APRIL, a proliferation-inducing ligand; Gd-IgA1, galactose-deficient immunoglobulin A1; IgG2, immunoglobulin G2; mAb, monoclonal antibody.

- The ongoing phase 3 VISIONARY trial (NCT05248646) evaluates the efficacy and safety of sibeprenlimab vs placebo in adults with IgA nephropathy[3]
  - 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 and 54.3% after 12 months of treatment[4]
- Sibeprenlimab was granted accelerated approval by the US Food and Drug Administration for the reduction of proteinuria in adults with primary IgA nephropathy at risk for disease progression on November 25, 2025[5]
- Based on its use in the broader chronic kidney disease population, sodium-glucose cotransporter 2 inhibitor (SGLT2i) use is recommended by the 2025 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as add-on therapy to manage generic response to IgAN-induced nephron loss and was used in 44.7% of patients (n/N=228/510) in the VISIONARY trial at randomization[4,6]
  - In a prespecified subgroup analysis, the effects of sibeprenlimab on uPCR-24h were consistent for patients with and without background SGLT2i use, with 52.9% and 50.0% reduction at 9 months, respectively[4]
- The current post hoc analysis evaluated the impact of background SGLT2i use on 24-hour proteinuria reduction, spot proteinuria change over time, safety, and pharmacodynamics (PD) of sibeprenlimab

CONCLUSIONS

- In this post hoc interim analysis of the Phase 3 VISIONARY trial, sibeprenlimab led to a similar clinically, statistically significant proteinuria reduction of ~50% regardless of background SGLT2i use, suggesting no additive benefit of SGLT2i use on outcomes
- The safety profile was comparable between the sibeprenlimab and placebo groups regardless of background SGLT2i use
- Sibeprenlimab use was associated with a notable reduction in serum Gd-IgA1 over time regardless of background SGLT2i use, supporting the notion that sibeprenlimab targets the specific drivers of disease alongside SGLT2is to manage generic drivers of disease, and supporting use of sibeprenlimab independent of SGLT2i therapy
- VISIONARY will continue to evaluate the safety and efficacy of sibeprenlimab, including effects on estimated glomerular filtration rate, beyond 12 months. The ongoing VISIONARY open-label extension will also monitor the effects of long-term combined use of sibeprenlimab with SGLT2is

RESULTS

- Of 320 patients included in the interim analysis population, 39.4% (n=126) reported SGLT2i use at randomization (sibeprenlimab: n=54; placebo: n=72; **Table 1**)
- Median baseline uPCR-24h was similar (1.22-1.29 g/g) between groups at baseline

Table 1. Baseline patient demographics and disease characteristics

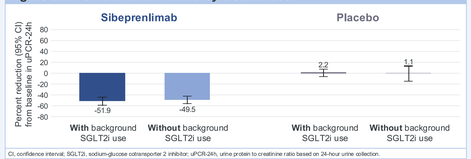
	Sibeprenlimab		Placebo	
	With SGLT2i use (n=54)	Without SGLT2i use (n=98)	With SGLT2i use (n=72)	Without SGLT2i use (n=96)
Age, median (range), years	41.5 (21.0-75.0)	42.0 (18.0-74.0)	42.5 (19.0-68.0)	44.0 (18.0-83.0)
Male, n (%)	36 (66.7)	64 (65.3)	47 (65.3)	53 (55.2)
Region, n (%)				
North America	8 (14.8)	14 (14.3)	6 (8.3)	15 (15.6)
South America	2 (3.7)	9 (9.2)	5 (6.9)	10 (10.4)
Europe	13 (24.1)	17 (17.3)	24 (33.3)	12 (12.5)
East Asia	17 (31.5)	26 (26.5)	19 (26.4)	29 (30.2)
South/Southeast Asia	14 (25.9)	32 (32.7)	18 (25.0)	30 (31.3)
Baseline disease characteristics				
Systolic blood pressure, mm Hg	122.5 (11.8)	125.6 (10.9)	119.6 (11.2)	125.8 (10.9)
Diastolic blood pressure, mm Hg	77.4 (7.5)	78.1 (8.4)	76.9 (8.2)	80.0 (7.6)
Time from initial biopsy to randomization, median (range), years	1.80 (0.20-9.90)	1.05 (0.10-23.70)	2.35 (0.10-23.00)	1.75 (0.00-34.00)
Baseline uPCR-24h, median (range), g/g	1.23 (0.49-4.86)	1.22 (0.51-6.69)	1.26 (0.50-5.46)	1.29 (0.52-4.85)
Baseline eGFR, median (range)	56.5 (25.0-131.0)	59.5 (29.0-125.0)	55.0 (27.0-117.0)	60.5 (27.0-129.0)
Positive baseline dipstick hematuria, n (%)	41 (75.9)	78 (79.6)	53 (73.6)	66 (68.8)
Prior immunosuppressive drug use, n (%)	3 (5.6)	3 (3.1)	2 (2.8)	4 (4.2)
Use of ACEi and/or ARB, n (%)	53 (98.1)	96 (98.0)	69 (95.8)	94 (97.9)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter 2 inhibitor; uPCR-24h, urine protein to creatinine ratio based on 24-hour urine collection.

Proteinuric response

- SGLT2i use did not alter the magnitude of uPCR-24h reduction at 9 months (**Figure 2**)

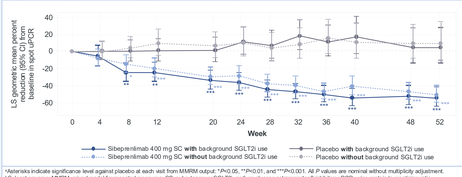
Figure 2. uPCR-24h at 9 months by SGLT2i use



CI, confidence interval; SGLT2i, sodium-glucose cotransporter 2 inhibitor; uPCR-24h, urine protein to creatinine ratio based on 24-hour urine collection.

- Background SGLT2i use did not affect the trajectory of spot urine protein to creatinine ratio (uPCR) for sibeprenlimab or placebo over the course of 12 months (**Figure 3**)

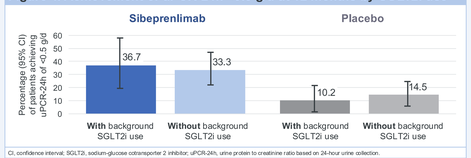
Figure 3. Spot uPCR (g/g) over time by SGLT2i use[a]



[a]Asterisks indicate significance level against placebo at each visit from MMRM output: *P<0.05, **P<0.01, and ***P<0.001. LS, least-squares; MMRM, mixed model for repeated measures; SC, subcutaneous; SGLT2i, sodium-glucose cotransporter 2 inhibitor; uPCR, urine protein to creatinine ratio.

- Rates of achieving proteinuria response thresholds at 12 months were comparable for SGLT2i use and nonuse (**Figure 4**), with approximately one-third of sibeprenlimab patients attaining 24-hour urine total protein <0.5 g/d regardless of background SGLT2i status
- At 12 months, most patients receiving sibeprenlimab attained uPCR-24h reduction of ≥50% regardless of SGLT2i use
  - 70.0% (21/30) of patients receiving sibeprenlimab and SGLT2i and 52.2% (36/69) receiving sibeprenlimab without SGLT2i attained uPCR-24h reduction of ≥50%, compared with 8.2% (4/49) of patients receiving placebo and SGLT2i and 18.8% (13/69) receiving placebo without SGLT2i
  - 80.0% (24/30) of patients receiving sibeprenlimab and SGLT2i and 63.8% (44/69) of those receiving sibeprenlimab without SGLT2i achieved ≥40% uPCR-24h reduction vs 8.2% (4/49) of patients receiving placebo and SGLT2i and 21.7% (15/69) receiving placebo without SGLT2i

Figure 4. Achievement of uPCR-24h <0.5 g/d at 12 months by SGLT2i use

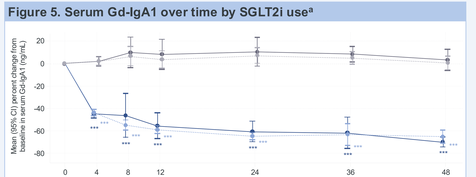


CI, confidence interval; SGLT2i, sodium-glucose cotransporter 2 inhibitor; uPCR-24h, urine protein to creatinine ratio based on 24-hour urine collection.

PD markers

- Serum levels of Gd-IgA1 were unaffected by background SGLT2i status (**Figure 5**)
- Similar results were observed for other PD markers, including APRIL, IgA, IgG, and IgM

Figure 5. Serum Gd-IgA1 over time by SGLT2i use[a]



[a]Asterisks indicate significance level against placebo at each visit: *P<0.05, **P<0.01, and ***P<0.001. Gd-IgA1, galactose-deficient immunoglobulin A1; SC, subcutaneous; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Safety

- Safety outcomes were comparable across groups (**Table 2**)
- Treatment-emergent adverse events (TEAEs) occurring in ≥5% of patients were similar by background SGLT2i status, namely, back pain; COVID-19; diarrhea; influenza; injection site erythema, pain, or swelling; nasopharyngitis; and upper respiratory tract infection
  - Cough and pyrexia were reported in ≥5% of patients with background SGLT2i use
  - Injection site irritation was reported in ≥5% of patients without background SGLT2i use
  - Genitourinary infection was reported in <5% of patients regardless of background SGLT2i use

Table 2. TEAEs by SGLT2i use

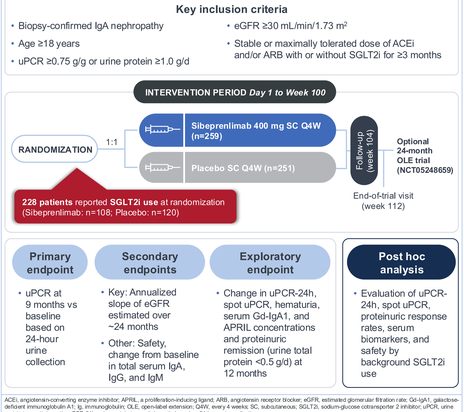
	Sibeprenlimab		Placebo	
	With SGLT2i use (n=108)	Without SGLT2i use (n=151)	With SGLT2i use (n=120)	Without SGLT2i use (n=131)
Any TEAE	81 (75.0%)	111 (73.5%)	103 (85.8%)	103 (78.6%)
Treatment-related TEAE	32 (29.6%)	43 (28.5%)	30 (25.0%)	37 (28.2%)
Any serious TEAE	7 (6.5%)	2 (1.3%)	3 (2.5%)	8 (6.1%)
TEAE leading to discontinuation	0 (0.0%)	1 (0.7%)	0 (0.0%)	4 (3.1%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

SGLT2i, sodium-glucose cotransporter 2 inhibitor; TEAE, treatment-emergent adverse event.

METHODS

- VISIONARY is a Phase 3, randomized, multicenter, double-blind, placebo-controlled trial in adults with biopsy-confirmed IgA nephropathy (**Figure 6**)[3,4]
  - Eligible patients were randomized 1:1 to sibeprenlimab or placebo every 4 weeks for 100 weeks and stratified by screening uPCR-24h, estimated glomerular filtration rate, and SGLT2i use[3,4]
- Here we report on a post hoc analysis using the interim analysis population from the main cohort (sibeprenlimab: n=152; placebo: n=168; data cutoff September 4, 2024)
  - Observed data were used to assess uPCR-24h reduction from baseline at 9 and 12 months and proteinuric remission at 12 months
  - uPCR-24h at 9 months was analyzed by ANCOVA
  - A mixed model for repeated measures was used to assess spot uPCR
  - Observed mean percent change from baseline was calculated for serum biomarkers
  - Safety was evaluated for all randomized patients who received ≥1 dose of sibeprenlimab at the time of interim analysis cutoff

Figure 6. VISIONARY trial design[3,7]



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; 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

DVR: Research support: Calliditas Therapeutics, Dimerix, LaRoche, Novartis, Otsuka Pharmaceutical, Sanofi, Takeda, Travere Therapeutics, Vertex Pharmaceuticals, Vera Therapeutics; Consulting fees: BioCryst, Biogen, Calliditas Therapeutics, Chugai, Climb Bio; Emerald Clinical (George Clinical), Jade Biosciences, LaRoche, Novartis, Otsuka Pharmaceutical, Timberlyne Therapeutics, Vera Therapeutics; Honoraria: Alpine Immune Science, Argenx, BioCryst, Calliditas Therapeutics, GSK, Novartis, Otsuka Pharmaceutical, Vera Therapeutics; Ownership: Reliant Glycosciences LLC. **KDJ:** Founder and co-president of the American Society of Onco-Nephrology; Consulting: Secretome Therapeutics, George Clinical, PMV Pharmaceuticals, Calliditas Therapeutics; Honoraria: American Society of Nephrology, International Society of Nephrology, UpToDate.com; Editorial board: *American Journal of Kidney Diseases*, *CJASN*, *Clinical Kidney Journal*, *Journal of Onconephrology*, *Kidney International*, *Nephrology Dialysis Transplantation*; Editor-in-Chief: *ASN Kidney News*; Section editor: Onconephrology for *Nephrology Dialysis Transplantation*. **BW** does not have any conflicts of interest to disclose. **JH** and **CF** are former employees of Otsuka Pharmaceutical Development & Commercialization, Inc. **LS** and **ZZ** are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. **RL:** Research support: Alexion, Calliditas Therapeutics, Chinook Therapeutics, National Institutes of Health, Omeros, Otsuka Pharmaceutical, Travere Therapeutics, University of Michigan, Vera Therapeutics; Consulting: Alexion, Calliditas Therapeutics, Chinook Therapeutics, Omeros, Otsuka Pharmaceutical, Travere Therapeutics, Vera Therapeutics. **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, Novo Nordisk, Otsuka Pharmaceutical, Shaanxi Micot, Travere Therapeutics, Tricida, Vifor Pharma (fees paid to institution); Other (board director; holds share options): George Clinical.

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