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Patient Baseline Characteristics in the Ongoing Phase 3 VISIONARY Trial: A Randomized, Placebo-Controlled Study of Sibeprenlimab for Immunoglobulin A Nephropathy

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Executive Summary

APRIL plays a key role in the immune-related pathogenesis of **immunoglobulin A nephropathy** (IgAN)[1–3]

Sibeprenlimab has demonstrated **significant reduction in proteinuria** and **stabilization of estimated glomerular filtration rate (eGFR)** in patients with IgAN[4]

The Phase 3 **VISIONARY** trial is the **largest in adult patients with IgAN** to date

The VISIONARY trial enrolled a **broad, diverse population** of patients with IgAN who are at **high risk of disease progression**

Background

- Immunoglobulin A nephropathy (IgAN) is a progressive, autoimmune, chronic kidney disease that typically manifests in adults aged 20–40 years and leads to end-stage kidney disease within the lifetime of most patients[5–7]
- IgAN, clinically characterized by proteinuria and a progressive decline in kidney function, is the most common primary glomerulonephritis worldwide[8–10]
- The annual global incidence of IgAN is 2.5 cases per 100,000 persons; however, this varies by region and ethnicity[8,11]
  - Regional disparities in the incidence of IgAN, ranging from 0 to 10.7 per 100,000/year, highlight a need for a global trial that reflects the diverse global patient population[11]
- A PRoliferation-Inducing Ligand (APRIL) plays a key role in the immune-related pathogenesis of IgAN[1–3]
- Sibeprenlimab is a humanized immunoglobulin G2 monoclonal antibody that targets and blocks APRIL[3]
- In the recently completed Phase 2 ENVISION trial, sibeprenlimab demonstrated significant reduction in proteinuria and stabilization of estimated glomerular filtration rate (eGFR), with a favorable safety profile in patients with IgAN[4]

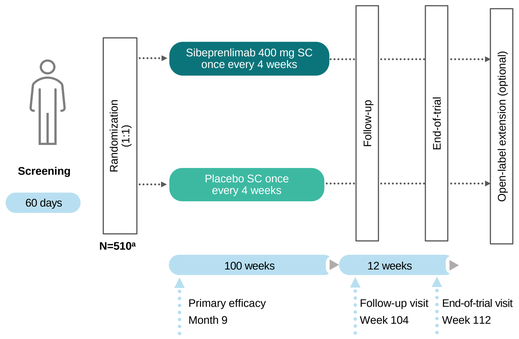
Objective

- To report the baseline clinical characteristics of patients enrolled in the VISIONARY trial, a Phase 3 study of sibeprenlimab administered subcutaneously (SC) in adult patients with IgAN (NCT05248646)

Methods

- VISIONARY is an ongoing multicenter, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of sibeprenlimab SC in patients with IgAN
- Patients were randomized 1:1 to receive sibeprenlimab 400 mg or placebo administered SC once every 4 weeks for 26 doses (**Figure 1**)
  - Patients who complete trial treatment will have the opportunity to enter the rollover open-label extension trial to continue access to sibeprenlimab for long-term safety and efficacy evaluation

Figure 1: VISIONARY Study Design



[a]An additional exploratory cohort of approximately 20 patients with IgAN and an eGFR of 20 to 29 mL/min/1.73 m^2 was enrolled and randomized with equal allocation (1:1) to sibeprenlimab or placebo in this cohort.
eGFR, estimated glomerular filtration rate; SC, subcutaneous.

- The primary efficacy endpoint is the relative change from baseline in the urinary protein to creatinine ratio based on 24-hour urine collections (uPCR-24h) after 9 months of treatment
- The key secondary efficacy endpoint is the annualized slope of eGFR estimated over the course of approximately 24 months
- Patients were on a stable and maximally tolerated renin-angiotensin system (RAS) inhibitor, with or without sodium-glucose cotransporter-2 inhibitor (SGLT2i) background therapy
- Key inclusion and exclusion criteria are shown in **Table 1**
- Demographics, baseline characteristics, and baseline kidney biopsy data were summarized using descriptive statistics

Table 1: Eligibility Criteria

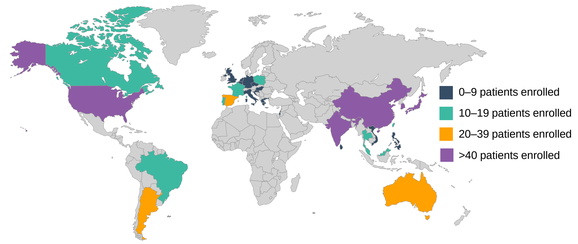
Key Inclusion Criteria
Adults ≥18 years of age
Biopsy-confirmed IgAN
On a stable and maximally tolerated dose of authorized ACEI and/or ARB therapy for ≥3 months prior to screening[a]
If on SGLT2i therapy for IgAN, must be on a stable dose for ≥3 months prior to screening
At screening, uPCR ≥0.75 g/g or urine protein excretion ≥1.0 g/24h[b]
At screening, eGFR ≥30 mL/min/1.73 m^2
Key Exclusion Criteria
IgAN secondary to another condition or IgA vasculitis
Chronic kidney disease other than IgAN
On systemic immunosuppression currently or within 16 weeks prior to randomization
Uncontrolled hypertension (defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg)
Uncontrolled Type 2 diabetes (defined as hemoglobin A1c >8%)
History of serious and/or unstable cardiovascular, respiratory, gastrointestinal, hematologic, autoimmune, or blood dyscrasias disorder

[a]Patients who are unable to tolerate ACEI and/or ARB therapy may be eligible for participation in the trial if their overall management of IgAN, including blood pressure control, is as per local SOC and guidelines. [b]uPCR and urine protein excretion were measured from 24-hour urine samples.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SOC, standard of care; uPCR, urine protein:creatinine ratio.

Results

- Patients were recruited across 5 continents: North America, South America, Europe, Asia, and Australia (**Figure 2**)
  - The countries with the highest patient enrollment were South Korea (n=54), India (n=52), United States (n=49), and China (n=42)

Figure 2: VISIONARY Geographic Footprint



- Of the 510 patients randomized, median age was 42 years (range, 18–83 years), and 58.8% were male (**Table 2**)
- The majority of patients were Asian (59.0%); 36.7% were White, 0.8% were Black or African American, and 0.2% were American Indian or Alaska Native

Table 2: Demographics and Baseline Characteristics

	All patients (N=510)
Demographics	
Age, years, median (range)	42 (18–83)
Sex, n (%)	
Male	300 (58.8)
Female	210 (41.2)
Race, n (%)	
Asian	301 (59.0)
White	187 (36.7)
Black or African American	4 (0.8)
American Indian or Alaska Native	1 (0.2)
Other	17 (3.3)
Ethnicity, n (%)	
Not Hispanic or Latino	433 (84.9)
Hispanic or Latino	58 (11.4)
Other	18 (3.5)
Unknown	1 (0.2)
Geographic region, n (%)	
East Asia	160 (31.4)
South/South-East Asia	132 (25.9)
Europe	113 (22.2)
North America	65 (12.7)
South America	40 (7.8)
Clinical Characteristics	
BMI, kg/m^2, mean (SD)	27.1 (5.5)
Blood pressure, mmHg, mean (SD)	
Systolic	123.7 (11.7)
Diastolic	78.5 (8.5)
uPCR-24h (g/g), mean (SD)	1.5 (0.9)
uPCR-24h (g/g), median (range)	1.3 (0.5–7.8)
Screening uPCR-24h, n (%)	
≤2.0 g/g	402 (78.8)
>2.0 g/g	108 (21.2)
Urinary protein excretion-24h (g/24h), mean (SD)	2.1 (1.3)
eGFR, mL/min/1.73 m^2, median (range)[a]	60.0 (25.0–134.0)
Background regimen at randomization, n (%)	
RAS blockade[b]	499 (97.8)[c]
SGLT2i[d]	230 (45.1)
Kidney Biopsy Characteristics[e]	
Duration from initial biopsy to randomization, years, median (range)	1.4 (0.0–34.0)
M1: Mesangial hypercellularity in ≥50% of glomeruli, n (%)	292 (57.3)
E1: Endocapillary proliferation hypercellularity in any glomeruli, n (%)	144 (28.2)
S1: Presence of segmental glomerulosclerosis in any glomeruli, n (%)	392 (76.9)
T1: Tubular atrophy/interstitial fibrosis 25%–50%, n (%)[f]	193 (37.8)
C1: Crescents in <25% of glomeruli, n (%)[g]	117 (22.9)
IgA score on IF 3–4, n (%)	285 (55.9)
Complement C3 score 3–4, n (%)	81 (15.9)

[a]Calculated by the CKD-EPI 2021 equation using serum creatinine. [b]RAS blockade includes patients on an ACEI and/or ARB. [c]Patients who were unable to tolerate ACEI and/or ARB therapy were eligible for participation in the trial if overall management of IgAN, including blood pressure control, was as per local SOC and applicable guidelines. [d]Here, SGLT2i includes patients on ACEI and/or ARB and SGLT2i, and SGLT2i only. [e]The method used for biopsy interpretation was reported as MEST score (12.2%), MEST-C score (70.0%), or descriptive method (14.3%). [f]Two patients had T2 (tubular atrophy/interstitial fibrosis >50%). [g]No patients had C2 (crescents in ≥25% of glomeruli).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; RAS, renin-angiotensin system; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SOC, standard of care; uPCR, urine protein:creatinine ratio.

- At baseline, the mean uPCR-24h (SD) was 1.5 g/g (0.9), with 21.2% of patients having a uPCR-24h >2.0 g/g at screening
- Mean baseline urine protein excretion (SD) was 2.1 g/24h (1.3), and mean spot uPCR (SD) was 1.4 (1.0)
- At baseline, median eGFR was 60.0 mL/min/1.73 m^2 (range, 25.0–134.0 mL/min/1.73 m^2)
- RAS blockade and SGLT2i use were reported in 97.8% and 45.1% of patients, respectively

Conclusion

- The Phase 3 VISIONARY trial evaluating sibeprenlimab SC has recruited patients globally with biopsy-confirmed IgAN who are at high risk of disease progression
  - This cohort reflects a broad population including those with reduced kidney function and elevated proteinuria
  - Nearly all patients were on RAS blockade and approximately half were on SGLT2i therapy
  - Patients were optimally managed at the time of enrollment based on blood pressure control and use of recommended supportive care
  - With 510 patients enrolled and randomized, VISIONARY is the largest trial in adult patients with IgAN to date
- Similar to the Phase 2 ENVISION study, VISIONARY successfully enrolled a diverse patient population across key demographics reflective of the clinical and histological heterogeneity observed in IgAN patients with high-risk disease and allows for evaluation of sibeprenlimab treatment across a spectrum of patients with IgAN
  - Recruited population was global and reflective of the disease epidemiology with predominance of male and Asian patients, comparable with ENVISION
  - Sex and regional location are consistent with the epidemiology of IgAN
  - Enrollment in VISIONARY extended global representation beyond that of ENVISION
- In the Phase 2 ENVISION and ongoing Phase 3 VISIONARY trials, patients have the opportunity to rollover into an open-label extension to continue receiving sibeprenlimab
- An additional exploratory cohort of approximately 20 patients with IgAN and an eGFR of 20 to 29 mL/min/1.73 m^2 was enrolled and randomized with equal allocation (1:1) to sibeprenlimab or placebo in this cohort
- The completed VISIONARY trial (NCT05248646) evaluating efficacy and safety of the novel anti-APRIL treatment for IgAN, sibeprenlimab, will report clinical results at a future date

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Disclosures

For author disclosures, please scan the QR code.

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