Sibeprenlimab in patients with IgA nephropathy: a Phase 2 trial

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Executive summary

Immunoglobulin A nephropathy (IgAN) is the most common cause of primary glomerulonephritis worldwide[1,2]

Evidence suggests a key role for **A PR**oliferation-**I**nducing **L**igand (APRIL) in IgAN pathogenesis[3-9]

Data are reported from a Phase 2 study of sibeprenlimab – an antibody that binds and blocks APRIL

Sibeprenlimab treatment resulted in significant reductions in proteinuria, stabilization of estimated glomerular filtration rate (eGFR), and robust suppression of serum APRIL

1 Background

- Up to 40% of individuals with IgAN progress to kidney failure within 30 years of a kidney biopsy diagnosis[1]
- Multiple lines of evidence support a key role for APRIL in the pathogenesis of IgAN[3-9]
- Sibeprenlimab is a humanized IgG_2 monoclonal antibody that binds and blocks APRIL
- The first-in-human Phase 1 trial of sibeprenlimab concluded that sibeprenlimab was well tolerated, and reversibly suppressed APRIL and various immunoglobulins, without loss of antigen-specific vaccination response[10]

2 Methods

- A Phase 2, multicenter, randomized, double-blind, placebo-controlled, multiple-dose, parallel-group study (NCT04287985) was conducted in adults with IgAN at high risk of disease progression, despite standard-of-care treatment
- Eligible patients were aged ≥18 years, with biopsy-confirmed IgAN, 24-hour urine protein-to-creatinine ratio (uPCR) ≥0.75 g/g (or 24-hour urine protein ≥1.0 g/day), eGFR ≥30 mL/min/1.73 m^2, serum IgG levels ≥700 mg/dL, IgM ≥37 mg/dL, and IgA ≥70 mg/dL, and receiving stable, maximally-tolerated doses of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) for at least three months prior to screening
- Patients were randomized 1:1:1:1 to intravenous sibeprenlimab 2 mg/kg, 4 mg/kg, or 8 mg/kg, or placebo, administered monthly for 12 months as add-on to standard-of-care treatment. Randomization was stratified by region (Japan, rest-of-world), and rest-of-world was further stratified by 24-hour uPCR ≤2.0 g/g or >2.0 g/g at screening
- The primary endpoint was change from baseline in log-transformed 24-hour uPCR at Month 12
- Secondary/exploratory endpoints included change in 24-hour uPCR at Months 9 and 16, change in eGFR, pharmacodynamics, and safety/tolerability

3 Results

Patient characteristics

- In the randomized sample (n=155), baseline characteristics were generally similar between treatment groups (Table 1)
- The full treatment course (12 doses) was completed by 146 patients (94.2%)
- Median duration of follow-up was 16 months

Changes in proteinuria

- After 12 months of treatment, there was a statistically significant linear treatment effect for the primary endpoint of change from baseline in 24-hour uPCR (p=0.0002), with geometric mean ratio reduction of 47.2%, 58.8%, 62.0%, and 20.0% in the sibeprenlimab 2, 4, and 8 mg/kg and placebo groups (Figure 1; Table 2)
- Placebo adjusted uPCR reduction at Month 12 was 34.0% (2 mg/kg), 48.5% (4 mg/kg), and 52.5% (8 mg/kg)
- Reductions at Month 9 were maintained through Month 16 with sibeprenlimab 4 and 8 mg/kg

Changes in eGFR

- The annualized eGFR slope estimate was attenuated for all sibeprenlimab doses compared with placebo (Figure 2; Table 2)

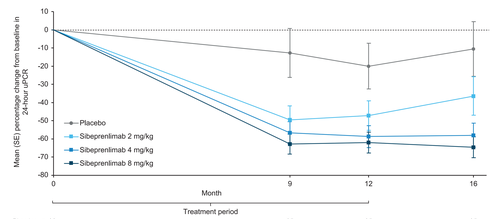
Pharmacodynamics

- With sibeprenlimab 4 and 8 mg/kg, reductions from baseline were observed in serum Gd-IgA_1 (Figure 3) and IgA (both by ~65%), IgG (~35% reduction), and IgM (~75% reduction)
- APRIL monitoring showed near complete and sustained suppression with sibeprenlimab 4 and 8 mg/kg at Month 12, which returned to baseline following treatment cessation (Figure 4)

Safety

- The incidence of treatment-emergent adverse events (TEAEs) was similar between treatment groups (Table 3)
- No increased risk of infection (MedDRA infections and infestations system organ class) was observed with pooled sibeprenlimab (49.6%) versus placebo (55.3%)

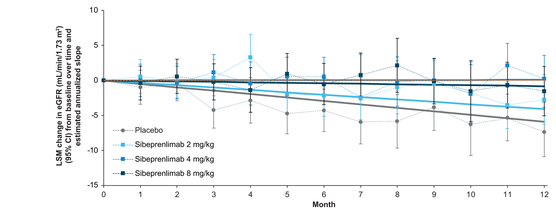
Figure 1: Percentage change from baseline in 24-hour uPCR



Placebo n=	38	35	35	35
Sibeprenlimab 2 mg/kg n=	38	35	35	35
Sibeprenlimab 4 mg/kg n=	41	40	38	38
Sibeprenlimab 8 mg/kg n=	38	36	37	37

SE=standard error; uPCR=urine protein-to-creatinine ratio

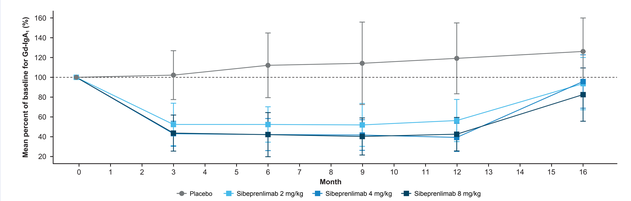
Figure 2: Change from baseline in eGFR



Placebo n=	38	36	36	37	36	36	34	36	34	36	34	35	36
Sibeprenlimab 2 mg/kg n=	38	38	36	38	38	33	36	35	35	35	35	31	34
Sibeprenlimab 4 mg/kg n=	41	41	41	41	41	40	40	41	41	41	40	40	39
Sibeprenlimab 8 mg/kg n=	38	37	38	38	38	35	38	35	33	37	37	37	36

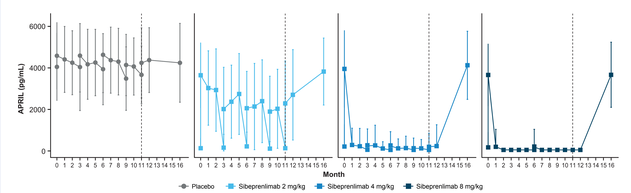
Solid lines represent regression slopes; dashed orange line marks a change of 0. for reference
CI=confidence interval; eGFR=estimated glomerular filtration rate; LSM=least squares mean

Figure 3: Percentage change from baseline in Gd-IgA_1



Gd-IgA,=galactose-deficient IgA,

Figure 4: APRIL levels



APRIL=A PRoliferation-Inducing Ligand

Table 1: Baseline demographic and clinical characteristics

	Sibeprenlimab 2 mg/kg (n=38)	Sibeprenlimab 4 mg/kg (n=41)	Sibeprenlimab 8 mg/kg (n=38)	Placebo (n=38)
Median age (range), years	41.0 (25–71)	39.0 (20–73)	41.5 (23–72)	36.5 (18–52)
Sex				
Female	16 (42.1)	15 (36.6)	12 (31.6)	24 (63.2)
Male	22 (57.9)	26 (63.4)	26 (68.4)	14 (36.8)
Race				
Asian	28 (73.7)	31 (75.6)	28 (73.7)	28 (73.7)
White	9 (23.7)	9 (22.0)	8 (21.1)	10 (26.3)
Other	1 (2.6)	1 (2.4)	2 (5.3)	0
Region				
Japan	5 (13.2)	5 (12.2)	5 (13.2)	4 (10.5)
Rest of world	33 (86.8)	36 (87.8)	33 (86.8)	34 (89.5)
BMI, mean (SD), kg/m^2	27.2 (4.5)	28.1 (6.4)	27.6 (5.8)	27.4 (6.7)
History of hypertension	29 (76.3)	31 (75.6)	28 (73.7)	24 (63.2)
Median days since diagnostic kidney biopsy	781.0	288.0	364.0	933.0
Receiving maximally-tolerated ACEI/ARB therapy	37 (97.4)	40 (97.6)	37 (97.4)	38 (100.0)
Geometric mean baseline 24-hour uPCR, g/g (GSE)	1.46 (0.12)	1.53 (0.12)	1.44 (0.14)	1.68 (0.17)
Baseline uPCR				
≤2.0 g/g	24 (63.2)	26 (63.4)	24 (63.2)	25 (65.8)
>2.0 g/g	9 (23.7)	10 (24.4)	9 (23.7)	9 (23.7)
Median baseline eGFR mL/min/1.73 m^2 (range)	58.0 (35.0–154.0)	64.0 (35.0–133.0)	56.0 (34.0–109.0)	68.5 (33.0–116.0)

Data are n (%) unless stated otherwise; randomized sample
ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; BMI=body mass index; eGFR=estimated glomerular filtration rate; GSE=geometric standard error; SD=standard deviation; uPCR=urine protein-to-creatinine ratio

Table 2: Primary endpoint and select secondary and exploratory endpoints

	Sibeprenlimab 2 mg/kg (n=38)	Sibeprenlimab 4 mg/kg (n=41)	Sibeprenlimab 8 mg/kg (n=38)	Placebo (n=38)
Geometric mean ratio reduction in 24-hour uPCR from baseline, % (SE)[a]				
Month 9	49.6 (7.7)	56.7 (6.2)	62.8 (5.5)	12.7 (13.4)
Month 12 (primary endpoint)	47.2 (8.2)	58.8 (6.1)	62.0 (5.7)	20 (12.6)
Month 16	36.5 (10.6)	58.0 (6.6)	64.6 (5.7)	10.6 (15.0)
Geometric mean uPCR reduction at Month 12 relative to placebo, % (SE)[b]	33.96 (13.7)	48.45 (10.4)	52.52 (9.7)	–
Geometric mean ratio change in uPCR from baseline to Month 12 (95% CI)				
Baseline uPCR ≤2.0 g/g	0.7 (0.5–0.9)	0.4 (0.2–0.7)	0.4 (0.3–0.6)	1.0 (0.7–1.4)
Baseline uPCR >2.0 g/g	0.5 (0.3–0.8)	0.6 (0.3–1.0)	0.5 (0.3–0.8)	0.8 (0.6–1.1)
LS mean eGFR (mL/min/1.73 m^2) change from baseline at Month 12 (SE)	−2.7 (1.8)	0.2 (1.7)	−1.5 (1.8)	−7.4 (1.8)
Treatment difference in eGFR (mL/min/1.73 m^2) relative to placebo, LSMD (95% CI)	+4.6 (−0.3–9.5)	+7.6 (2.8–12.3)	+5.8 (0.9–10.7)	–

Modified intent-to-treat sample
[a]GM ratio reduction is calculated as (1−exponentiated LSM)*100% and the corresponding SE is calculated as the exponentiated (LSM)*SE of LSM)*100%.
[b]GM ratio reduction difference is calculated as (1−exponentiated LSMD)*100% and the corresponding SE is calculated as the exponentiated (LSMD)*SE of LSMD)*100%
CI=confidence interval; eGFR=estimated glomerular filtration rate; GM=geometric mean; LS=least squares; LSM=least squares mean; LSMD=least squares mean difference; SE=standard error; uPCR=urine protein-to-creatinine ratio

Table 3: Summary of TEAEs

	Sibeprenlimab 2 mg/kg (n=38)	Sibeprenlimab 4 mg/kg (n=41)	Sibeprenlimab 8 mg/kg (n=38)	Pooled sibeprenlimab (n=117)	Placebo (n=38)
Any TEAE	28 (73.7)	33 (80.5)	31 (81.6)	92 (78.6)	27 (71.1)
TEAE with a maximum severity of:					
Mild	19 (50.0)	22 (53.7)	22 (57.9)	63 (53.8)	23 (60.5)
Moderate	7 (18.4)	9 (22.0)	8 (21.1)	24 (20.5)	3 (7.9)
Severe	2 (5.3)	2 (4.9)	1 (2.6)	5 (4.3)	1 (2.6)
TEAE related to study drug	7 (18.4)	7 (17.1)	4 (10.5)	18 (15.4)	5 (13.2)
Serious TEAE	2 (5.3)	2 (4.9)	1 (2.6)	5 (4.3)	2 (5.3)
TEAE leading to treatment interruption	5 (13.2)	1 (2.4)	3 (7.9)	9 (7.7)	0
TEAE leading to death	0	0	0	0	1 (2.6)
TEAEs with incidence ≥5% in pooled sibeprenlimab group					
COVID-19	11 (28.9)	11 (26.8)	13 (34.2)	35 (29.9)	16 (42.1)
Pyrexia	5 (13.2)	5 (12.2)	6 (15.8)	16 (13.7)	6 (15.8)
Nasopharyngitis	4 (10.5)	5 (12.2)	6 (15.8)	15 (12.8)	3 (7.9)
Upper respiratory tract infection	3 (7.9)	5 (12.2)	2 (5.3)	10 (8.5)	0
Headache	1 (2.6)	5 (12.2)	3 (7.9)	9 (7.7)	4 (10.5)
Hypertension	4 (10.5)	3 (7.3)	0	7 (6.0)	1 (2.6)
Diarrhea	0	4 (9.8)	2 (5.3)	6 (5.1)	1 (2.6)
Muscle spasms	1 (2.6)	4 (9.8)	1 (2.6)	6 (5.1)	1 (2.6)

Data are n (%)
TEAE=treatment-emergent adverse event

4 Discussion

- In patients with IgAN, 12 months of sibeprenlimab treatment resulted in significant reduction in proteinuria, stabilization of eGFR decline, and robust suppression of Gd-IgA_1, compared to placebo
- Of the available therapies for IgAN, none have demonstrated a sustained impact on eGFR stabilization of the magnitude observed in the present study
- Robust suppression of serum APRIL was also observed
- Sibeprenlimab was generally safe and well tolerated, without evidence of undesirable toxicity
- A Phase 3 trial is underway to investigate the efficacy and safety of sibeprenlimab in a larger population of patients with IgAN (NCT05248646; the Visionary study) – please scan the QR code for more information

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Disclosures

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