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P201

Effect of Sibeprenlimab on Hematuria in Adults With IgA Nephropathy: Interim Analysis of the VISIONARY Phase 3 Trial

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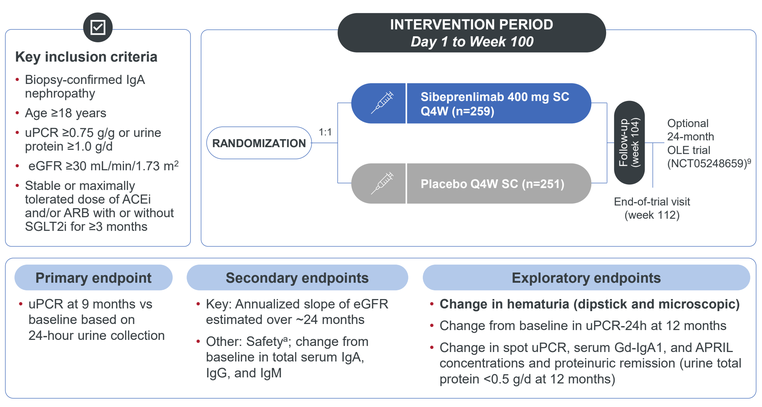
INTRODUCTION

- Immunoglobulin A (IgA) nephropathy is a progressive immune-mediated chronic kidney disease characterized by mesangial deposition of immune complexes containing pathogenic galactose-deficient IgA1 (Gd-IgA1) and associated autoantibodies[1]
- Sibeprenlimab is a fully humanized IgG2 monoclonal antibody that selectively blocks a proliferation-inducing ligand (APRIL), a key driver of IgA nephropathy pathogenesis[1-3]
- 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 urine protein to creatinine ratio (uPCR) based on 24-hour urine collection (uPCR-24h) of 51.2% (P<0.001) after 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[5]
- Here, we report the effect of sibeprenlimab on microscopic hematuria, building on the previously published dipstick hematuria data[3]
  - Hematuria is a hallmark of active glomerular injury in IgA nephropathy and a common clinical manifestation of IgA nephropathy[6-8]
  - Persistence of microscopic hematuria was shown to be associated with an increased risk of kidney function decline and poor prognosis, whereas hematuria remission is linked to improved renal outcomes[6-8]
  - Experimental data indicate that tubular exposure to hemoglobin and heme from lysed red blood cells (RBCs) can drive oxidative stress, tubulointerstitial inflammation, and fibrosis[6]
  - These findings support the consideration of microscopic hematuria both as a prognostic marker and as a potential indicator of disease modification following therapeutic intervention, alongside established endpoints such as proteinuria and estimated glomerular filtration rate (eGFR)[6-8]
- Evaluating hematuria in VISIONARY may provide additional biological evidence that APRIL inhibition is associated with attenuation of active glomerular inflammation and downstream tubular injury beyond its established effects on proteinuria[6,8]

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**)[3]

Figure 1. Study Design[3]



[a]Safety was evaluated as a secondary endpoint in the interim analysis, and included all randomized patients who received ≥1 dose of sibeprenlimab at the time of interim analysis cutoff.

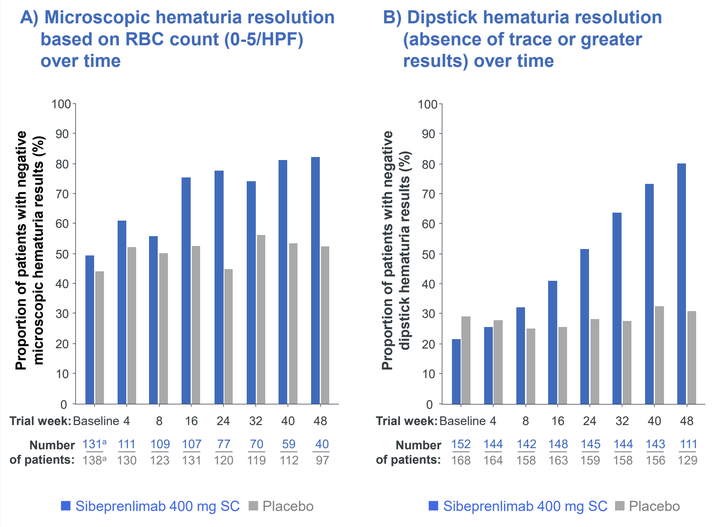
ACEi, angiotensin-converting enzyme inhibitor; APRIL, a proliferation-inducing ligand; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; Gd-IgA1, galactose-deficient immunoglobulin A1; Ig, immunoglobulin, OLE, open-label extension; Q4W, every 4 weeks; SC, subcutaneous; SGLT2i, sodium–glucose cotransporter 2 inhibitor; uPCR, urine protein to creatinine ratio; uPCR-24h, urine protein to creatinine ratio based on 24-hour urine collection.

- Eligible patients were randomized 1:1 to sibeprenlimab or placebo every 4 weeks for 100 weeks (**Figure 1**)[4]
- Change in hematuria over time was evaluated as an exploratory endpoint (**Figure 1**) in the interim analysis and was assessed in patients with ≥1 measure of uPCR-24h at baseline
  - Microscopic hematuria, quantified by automated microscopy of urinary sediment, was considered positive if RBC count was >5 per high-power field (HPF), and dipstick hematuria was defined as trace, 1+, 2+, and 3+
  - Kaplan–Meier methods estimated time to and probability of hematuria resolution (0-5/HPF; the absence of trace or greater dipstick results) by 12 months

RESULTS

- Of the 320 patients randomized and included in the interim analysis, 143 were positive (>5/HPF) for microscopic hematuria at baseline (sibeprenlimab: n=66/152; placebo: n=77/168) and 238 had a positive (trace, 1+, 2+, or 3+) dipstick hematuria test (sibeprenlimab: n=119/152; placebo: n=119/168)[3]
  - 51 patients lacked baseline urine RBC count data (sibeprenlimab: n=21/152; placebo: n=30/168)
- At week 48
  - 82.5% (n=33/40) of the sibeprenlimab group vs 52.6% (n=51/97) of the placebo group showed resolution of microscopic hematuria (0-5/HPF) (**Figure 2A**)
  - 80.2% (n=89/111) of the sibeprenlimab group vs 31.0% (n=40/129) of the placebo group showed resolution of dipstick hematuria (absence of trace or greater results)[3] (**Figure 2B**)

Figure 2. Change in hematuria based on RBC count (>5/HPF) and dipstick test (1+, 2+, 3+, and trace) over time

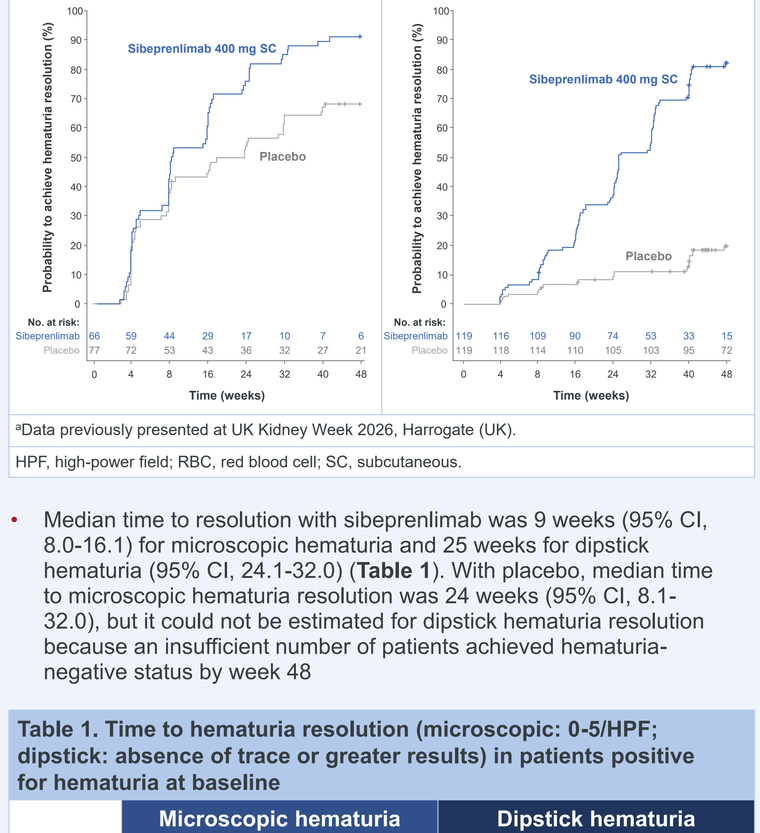


[a]The total number of patients at baseline excludes the patients who were lacking RBC count data at baseline (sibeprenlimab: n=21; placebo: n=30).

HPF, high-power field; RBC, red blood cell; SC, subcutaneous.

- Kaplan–Meier estimates showed that in patients with hematuria at baseline, the probability of achieving hematuria resolution was greater with sibeprenlimab than with placebo over 48 weeks
  - Probability of microscopic hematuria resolution (0-5/HPF) was 90.9% (95% CI, 82.5%-96.3%) in the sibeprenlimab group vs 68.1% (95% CI, 57.6%-78.2%) in the placebo group (**Figure 3A**)
  - Probability of dipstick hematuria resolution (absence of trace or greater results) was 82.1% (95% CI, 74.5%-88.5%) in the sibeprenlimab group vs 19.5% (95% CI, 13.3%-28.1%) in the placebo group (**Figure 3B**)

Figure 3. Probability of hematuria resolution based on RBC count (0-5/HPF) and dipstick test (absence of trace or greater results) in patients positive for hematuria at baseline



[a]Data previously presented at UK Kidney Week 2026, Harrogate (UK).

HPF, high-power field; RBC, red blood cell; SC, subcutaneous.

- Median time to resolution with sibeprenlimab was 9 weeks (95% CI, 8.0-16.1) for microscopic hematuria and 25 weeks for dipstick hematuria (95% CI, 24.1-32.0) (**Table 1**). With placebo, median time to microscopic hematuria resolution was 24 weeks (95% CI, 8.1-32.0), but it could not be estimated for dipstick hematuria resolution because an insufficient number of patients achieved hematuria-negative status by week 48

Table 1. Time to hematuria resolution (microscopic: 0-5/HPF; dipstick: absence of trace or greater results) in patients positive for hematuria at baseline

Time point	Microscopic hematuria		Dipstick hematuria	
	Placebo, % (95% CI) n=77	Sibeprenlimab 400 mg SC, % (95% CI) n=66	Placebo, % (95% CI) n=119	Sibeprenlimab 400 mg SC, % (95% CI) n=119
4 weeks	19.5 (12.2, 30.2)	18.2 (10.8, 29.8)	1.7 (0.4, 6.6)	3.4 (1.3, 8.7)
8 weeks	37.7 (27.9, 49.5)	42.4 (31.6, 55.2)	5.0 (2.3, 10.9)	10.9 (6.5, 18.1)
16 weeks	44.2 (34.0, 56.0)	60.6 (49.1, 72.3)	6.7 (3.4, 13.0)	25.3 (18.5, 34.2)
24 weeks	53.5 (42.8, 65.0)	75.8 (65.0, 85.3)	10.2 (5.9, 17.2)	39.8 (31.6, 49.2)
32 weeks	61.5 (50.8, 72.3)	84.8 (75.2, 92.2)	11.0 (6.6, 18.2)	59.3 (50.6, 68.2)
40 weeks	65.5 (54.8, 75.9)	89.4 (80.6, 95.3)	14.6 (9.4, 22.5)	74.7 (66.6, 82.1)
48 weeks	68.1 (57.6, 78.2)	90.9 (82.5, 96.3)	19.5 (13.3, 28.1)	82.1 (74.5, 88.5)

HPF, high-power field; SC, subcutaneous.

CONCLUSION

- Interim analysis of VISIONARY demonstrated greater resolution of microscopic and dipstick hematuria with sibeprenlimab than with placebo in patients with IgA nephropathy
  - Interpretation of hematuria outcomes is limited by nonstandardized testing, heterogeneous definitions (eg, RBC/HPF cutoffs, dipstick categories, remission thresholds), and variability in urine sample timing and handling, reducing comparability across studies[6]
  - Hematuria is not yet a validated surrogate endpoint and is therefore currently used only as an exploratory endpoint in clinical trials[6]
- These findings complement the observed effects of sibeprenlimab on Gd-IgA1 and proteinuria, supporting the potential for sibeprenlimab to act as a disease-modifying therapy in IgA nephropathy by selectively inhibiting APRIL, reducing pathogenic Gd-IgA1, and thereby reducing IgA-containing immune complex (IgA-IC) formation and IgA-IC–mediated glomerular injury[3]
- The ongoing VISIONARY trial will further evaluate its potential impact on kidney function preservation based on eGFR rate slope over a 24-month treatment period

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SCAN TO VIEW

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DISCLOSURES

HS: advisory role: Otsuka Pharmaceutical, Vera Therapeutics, Viatris; honoraria: Novartis, Alexion Pharma, Chugai, Otsuka Pharmaceutical, Viatris. **VJ:** scientific advisory board: AstraZeneca, Baxter, Boehringer Ingelheim; consultancy fees: GSK, Otsuka. **MW:** consultancy fees: Bayer, GSK, Hansa BioPharma, Latham Watkins /OBO Otsuka/Visterra; endpoint review committee: Novo Nordisk; provincial medical lead: Ontario Health. **JS:** nothing to disclose. **FN:** principal investigator in previous clinical trials: Travere, Otsuka, Bayer, Novartis, GSK. **YY:** nothing to disclose. **KDJ:** consultancy fees: Novartis, Otsuka, Calliditas, George Clinicals, Travere Therapeutics. **RD:** nothing to disclose. **LdV:** speaker fees: Vifor, AstraZeneca, Bayer, Amgen, Astellas; advisory board: Travere, Otsuka. **RV:** advisory board: Boehringer Ingelheim, Bayer, AstraZeneca; speaker bureau: Bayer, Boehringer Ingelheim, Globo Asiatico, Novartis. **LS:** Otsuka Pharmaceutical employee. **JX:** Otsuka Pharmaceutical employee. **CF:** Otsuka Pharmaceutical employee. **JH:** Otsuka Pharmaceutical employee. **MP:** consultancy fees: Alexion Pharmaceuticals, GSK, Novartis, Otsuka, Sobi, Travere Therapeutics.

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