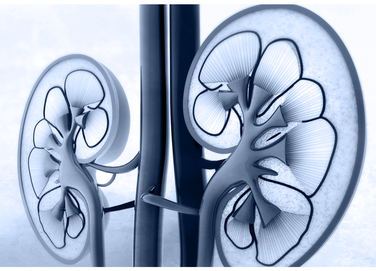
TH-PO991

Interim Analysis (IA) of a Global Phase 2 RCT of Sibeprenlimab (VIS649), an APRIL-Neutralizing Monoclonal Antibody, in IgA Nephropathy



Laura Kooienga,[1] Yusuke Suzuki,[2] Bobby Chacko,[3] Muh Geot Wong,[4] Jonathan Barratt,[5] Chris Oh,[6] Manisha Sahay,[7] Mohit Mathur,[8] Xiaofeng Wang,[9] Jill Yarbrough,[8] Brian Pereira[8]

[1]Colorado Kidney Care, Denver, CO, USA; [2]Juntendo University, Tokyo, Japan; [3]John Hunter Hospital, Newcastle, New South Wales, Australia; [4]University of Sydney, New South Wales, Australia; [5]University of Leicester, Leicester, England, UK; [6]Seoul National University, Seoul, Korea; [7]Osmania General Hospital, Hyderabad, India; [8]Visterra, Inc., Waltham, MA; [9]Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA

Introduction

- IgA nephropathy (IgAN; Berger's disease) is the most common primary glomerulonephritis worldwide with 30-40% of patients progressing to end-stage renal disease within 20 years of diagnosis[1]
- Current therapies include renin-angiotensin aldosterone system blockers and blood pressure control[2,3]. The life expectancy of patients with IgAN may be reduced by up to 10 years[4]
- The cytokine, A PRoliferation-Inducing Ligand (APRIL), is an important B cell growth factor that mediates immunoglobulin production and class switching, and plays a key role in the pathogenesis of IgAN[5,6]
- APRIL and Gd-IgA1 levels are elevated in patients with IgAN and correlate with disease severity[7]
- Sibeprenlimab (VIS649), a humanized IgG2 monoclonal antibody that blocks APRIL, is being developed as a treatment for IgAN. It binds and blocks the biological actions of APRIL, leading to the reduced production of IgA and galactose-deficient (Gd) IgA1 in healthy subjects[8]

Objective

- Evaluate the safety and efficacy of intravenously (IV) administered sibeprenlimab at the 9-month interim analysis (IA) in participants with IgAN

Methods

- This poster presents the protocol-specified IA, conducted when 72 participants completed Month 9 of the 12-month study
- The study was a phase 2 multicenter, randomized, double-blind, placebo-controlled, multiple-dose study. Participants were randomized (1:1:1:1) to sibeprenlimab 2, 4, or 8 mg/kg or placebo (**Figure 1**)
- Study treatment was administered as 12 monthly IV infusions starting on Day 1

Key inclusion criteria

- Adults (aged ≥18 years) with IgAN diagnosis confirmed by biopsy
- Receiving optimized supportive treatment for IgAN (stable and maximally tolerated doses of either angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, as per local standard of care and applicable guidelines) for ≥3 months preceding screening
- Estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73 m^2 by Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI, 2009)
- Screening proteinuria ≥1.0 g/day or urine protein creatinine ratio (uPCR) ≥0.75 g/g

Key exclusion criteria

- Secondary IgAN (e.g., Henoch-Schönlein purpura [IgA vasculitis], infection-associated IgAN, or IgAN associated with hepatic cirrhosis)
- Co-existing chronic kidney disease, other than from IgAN
- Evidence of additional pathological findings in the kidney biopsy (with the exception of hypertensive vascular changes)
- Presence of nephrotic syndrome, acute or chronic infectious disease, history of organ transplantation or bone marrow/stem cell transplantation
- Systemic steroids or other systemic immunosuppressive agents within 16 weeks of screening

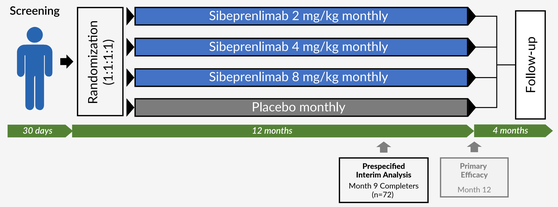
Interim analysis of efficacy and safety

- Change from baseline in 24-hour uPCR (measured on natural log scale) at Month 9
- Change from baseline in mean eGFR over time
- Safety of sibeprenlimab

Analyses

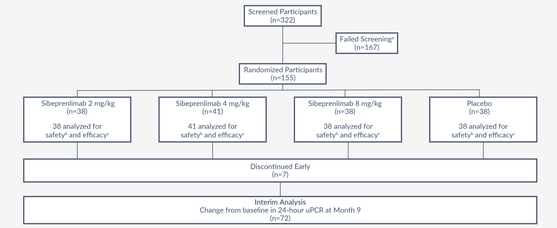
- Efficacy data shown are for the pooled sibeprenlimab participants
- Participants were not divided by treatment assignment to avoid the risk of unblinding
- Statistical analysis was not performed during IA and therefore *P* values were not calculated

Figure 1: Study design



Results

Figure 2: Participant disposition at the time of data cutoff for the IA



[a]Participants failed screening if they did not meet a uPCR ≥0.75 g/g measured from a 24-hour urine and not having an eGFR ≥45 mL/min/1.73m^2. [b]All randomized participants who receive any amount of study intervention. [c]All randomized participants who receive at least 1 dose of study intervention.
IA, interim analysis; uPCR, urine protein creatinine ratio.

Table 1: Participant demographics

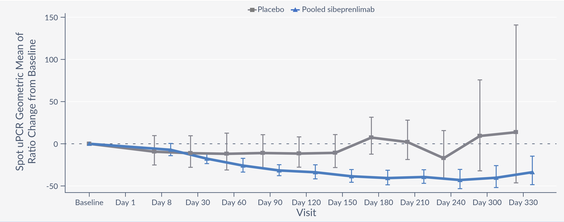
	Overall (N=155)
Age (years), mean (SD)	40.7 (11.65)
Sex, n (%)	
Male	88 (56.8)
Female	67 (43.2)
Race	
White	36 (23.2)
Black or African American	1 (0.6)
Asian	115 (74.2)
American Indian or Alaska Native	1 (0.6)
Other	2 (1.3)
Region	
Japan	19 (12.3)
Rest of World	136 (87.7)

SD, standard deviation.

Figure 3a: Change from baseline in 24-hour uPCR at Month 9

uPCR, urine protein creatinine ratio.

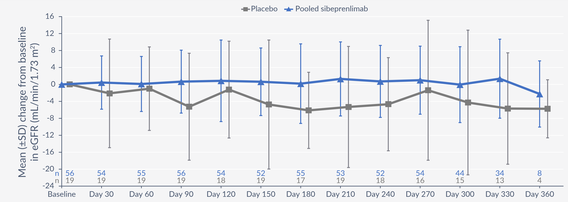
Figure 3b: Spot uPCR geometric mean of ratio change from baseline over time



uPCR, urine protein creatinine ratio.

- Among pooled sibeprenlimab recipients, there was a 43% placebo-adjusted reduction from baseline in 24-hour uPCR values at Month 9 (**Figure 3a**)
- Spot uPCR measurements (collected monthly in the clinic) validate the observed Month 9, 24-hour urine collection uPCR reduction, and provide insight into the time course of proteinuria reduction (**Figure 3b**)

Figure 4: Mean eGFR change from baseline over time



eGFR, estimated glomerular filtration rate; SD, standard deviation.

- Mean eGFR measured monthly was stable over 330 days in the pooled sibeprenlimab recipients (**Figure 4**), while this parameter declined among placebo recipients
- In subjects who completed ≥9 months in the study, the modeled annualized eGFR slope was stable (+1.2 mL/min/1.73m^2/year) in the pooled sibeprenlimab recipients versus declining (-6.5 mL/min/1.73m^2 /year) in the placebo group, with a slope difference of +7.7 mL/min/1.73m^2/year (95% confidence interval 1.32 to 14.01)
- There was immediate and sustained neutralization of APRIL, with robust reduction in IgA and Gd-IgA1 levels and relatively modest reduction in IgG levels (data not shown)

Table 2: Pooled treatment-emergent adverse events

	Overall (N=155)
At Least 1 TEAE	102 (65.8)
TEAE with a Maximum Severity of:	
Mild	80 (51.6)
Moderate	18 (11.6)
Severe	4 (2.6)
TEAE Related to Study Drug	27 (17.4)
TEAE Related to Study Drug with a Maximum Severity[a] of:	
Mild	26 (16.8)
Moderate	1 (0.6)
Severe	0
Serious TEAE	6 (3.9)
Serious TEAE Related to Study Drug	0
TEAE Leading to Study Drug Interruption	7 (4.5)
TEAE Leading to Discontinuation of Study Drug	1 (0.6)
TEAE Leading to Death	1 (0.6)

[a]A participant is only counted once for the maximum severity experienced among their TEAEs.
TEAE, treatment-emergent adverse event.

- Eleven serious adverse events were reported in 6 participants
- No serious adverse events were considered study drug-related, and most adverse events were mild or moderate in severity
- Five data safety monitoring board meetings have been held thus far, and the decision after each was to continue the trial without any changes

Conclusions

- In this interim analysis from the ENVISION study, a global Phase 2 trial, APRIL neutralization with sibeprenlimab resulted in robust proteinuria reduction at Month 9 of treatment with stable or improving eGFR over time, in marked contrast to placebo
- These preliminary data also point to an acceptable safety and tolerability profile
- These results provide preliminary validation for sibeprenlimab as a precision therapeutic agent for the treatment of IgAN
- The global phase 3 VISIONARY Study (NCT05248646) is currently recruiting patients with IgAN

References

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Disclosures

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Conflict of Interest
LK has nothing to disclose. **YS** reports advisory role: Novartis, Visterra/Otsuka, Chinook, Travere/Retrophin, Morphosys, Argenx, Kyowa Kirin; honoraria: Kyowa Kirin, Mitsubishi Tanabe, Daiichi Sankyo, Novartis, Chugai; research grants: Visterra, Moderna, Travere/Retrophin, Chinook, Kyowa Kirin, Argenx, Purespring, Pfizer, Novartis. **BC** reports advisory/leadership role: Boehringer Ingelheim and Eli Lilly; speakers bureau: Boehringer Ingelheim and Eli Lilly, AstraZeneca. **MGW** reports executive steering committee/medical advisor: TESTING, PROTECT, and DUPRO trials, Travere, Otsuka, Eledon, Kira, CSL-Behring, Chinook; honoraria: AstraZeneca, Amgen, Baxter. **JB** reports consulting/speaker fees: Alnylam, Argenx, Astellas, BioCryst, Calliditas, Chinook, Dimerix, Galapagos, Novartis, Omeros, Travere, Vera, Visterra; grant support: Argenx, Calliditas Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere, Visterra. **CO** [need]. **MS** [need]. **XZ** is an employee of Otsuka. **MM**, **JY**, **BP** are employees of Visterra.

For additional information please contact Dr. Laura Kooienga, lkooienga@cokidneycare.com