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Safety, tolerability, and efficacy of mezagitamab (TAK-079) as add-on to standard-of-care therapy in individuals with primary IgA nephropathy: week 96 data from an open-label phase 1b study

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Introduction

- Immunoglobulin A nephropathy (IgAN) is the most prevalent form of primary glomerulonephritis. It is associated with a poor prognosis, as it can often result in reduced quality of life, kidney failure, or premature death.[1,2]
- Despite recent approvals of drugs for IgAN, there is an unmet need for tolerable therapies with durable effects and long-term preservation of kidney function.
- Mezagitamab is a fully human, anti-CD38 monoclonal antibody that depletes plasma cells, plasmablasts, and natural killer cells expressing high levels of CD38.[3,4]
  - Mezagitamab may deplete plasma cells that produce the galactose-deficient IgA1 (Gd-IgA1) and autoantibodies against Gd-IgA1.[3,5]
  - Depletion of these pathogenic plasma cells has the potential to produce sustained reductions in proteinuria and to stabilize kidney function.

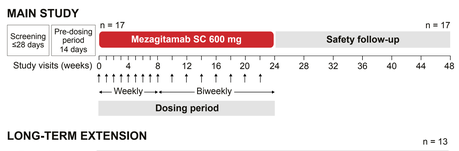
Objective

- To report results up to week 96 from a phase 1b study evaluating the safety, tolerability, and efficacy of mezagitamab in combination with stable background therapy in participants with primary IgAN.

Methods

- Open-label, single-arm, phase 1b, multicenter study (NCT05174221) (**Figure 1**).

Figure 1. Study design



Primary endpoint

- Percentage of participants with AEs including grade ≥3 AEs and serious AEs up to week 96

Secondary and exploratory endpoints

- Serum Gd-IgA1, IgA, and IgG levels
- Percent change from baseline in UPCR
- Change from baseline in eGFR
- Resolution of hematuria*

Main inclusion criteria

- Stable background therapy (ACEi and/or ARB) for ≥12 weeks
- Diagnosis of IgAN supported by biopsy within 10 years
- Proteinuria: UPCR ≥1 g/g or UPE ≥1 g/day, by 24-h urine collection
- eGFR ≥45 mL/min/1.73 m²

Main exclusion criteria

- Secondary IgAN, nephrotic syndrome, active extrarenal IgA vasculitis, or concomitant renal disease on kidney biopsy
- Immunosuppressant use within 6 months or systemic corticosteroid use within 4 months of screening

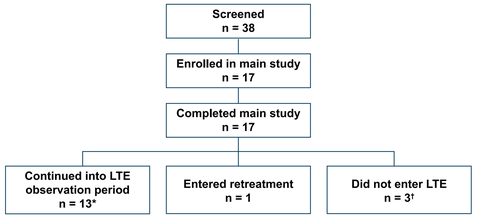
ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; Gd-IgA1, galactose-deficient immunoglobulin A1; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IgG, immunoglobulin G; SC, subcutaneous; UPCR, urine protein to creatinine ratio; UPE, urine protein excretion.
*Defined as negative or trace hematuria in participants who had hematuria at baseline and nonmissing hematuria data for the corresponding visit.

- In the main study, 17 participants received subcutaneous mezagitamab 600 mg once weekly for 8 weeks, then 600 mg every 2 weeks for 16 weeks, followed by a 24-week safety follow-up.
- 13 of the 17 participants completed the subsequent 48-week observation period in the long-term extension part of the study and 1 went directly into retreatment.
- Data are reported through the week 96 visit.

Results

- This analysis was performed when the 13 participants had completed the week 96 visit (**Figures 1** and **2**); data during retreatment not shown.

Figure 2. Participant disposition



LTE, long-term extension.
*One participant enrolled in the LTE retreatment period at week 96.
†Reasons for discontinuation: safety, lack of efficacy, patient decision.

Table 1. Baseline demographics and clinical characteristics

	Total (N = 17)
Demographics	
Age, years	
Mean (SD)	40.8 (13.6)
Range	20–68
Sex, n (%)	
Male	8 (47.1)
Female	9 (52.9)
Race, n (%)	
Asian	12 (70.6)
White	5 (29.4)
BMI, kg/m²	
Mean (SD)	27.1 (4.2)
Range	19.2–33.0
Background therapy, n (%)	
ACE inhibitor	4 (23.5)
ARB	13 (76.5)
SGLT2 inhibitor	6 (35.3)
Corticosteroids in prior 6 months, n (%)	0
Time since last biopsy, years	
Mean (SD)	2.7 (2.9)
Range	0.2–9.4
Years since IgAN diagnosis	
Mean (SD)	4.6 (7.4)
Range	0.1–28.6

	Total (N = 17)
Baseline characteristics	
24-h UPCR, mg/mg	
Mean (SD)	1.5 (0.7)
Range	0.6–3.0
24-h UPE, g/day	
Mean (SD)	2.0 (0.9)
Range	0.7–4.1
eGFR, mL/min/1.73 m²	
Mean (SD)	74.0 (21.0)
Range	42–122
Serum creatinine, µmol/L	
Mean (SD)	99.8 (26.3)
Range	58–149
Gd-IgA1, mg/L	
Mean (SD)	6.6 (3.4)
Range	1.5–14.9
IgA, g/L	
Mean (SD)	3.1 (1.0)
Range	1.4–5.0
IgG, g/L	
Mean (SD)	10.7 (2.1)
Range	7.9–14.1
Hematuria, n (%)	13 (76.5)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; Gd-IgA1, galactose-deficient immunoglobulin A1; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IgG, immunoglobulin G; SGLT2, sodium-glucose cotransporter-2; UPCR, urine protein to creatinine ratio; UPE, urine protein excretion.

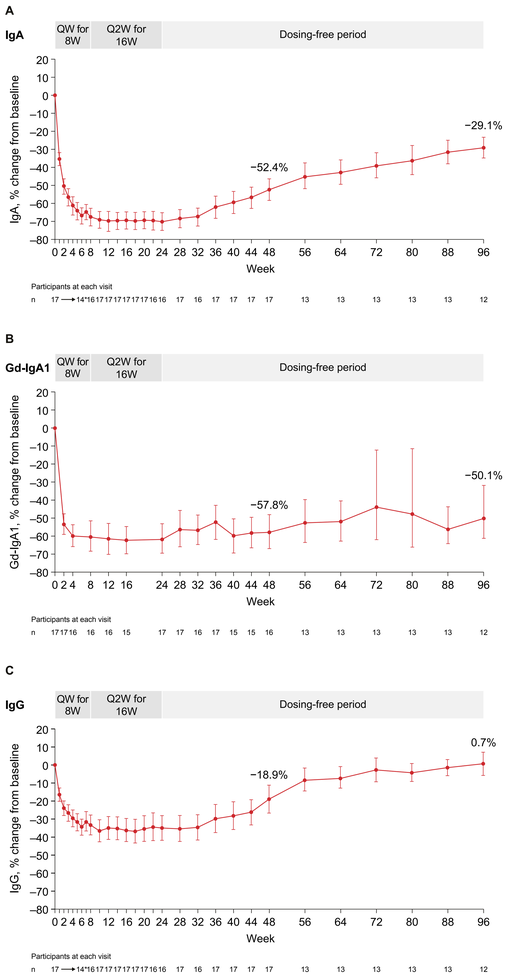
Table 2. Summary of safety in the main study and long-term observation period

	Total (N = 17)
Any AE, n (%)	16 (94.1)
AE related to study drug, n (%)	11 (64.7)
Grade ≥3 AE, n (%)	3 (17.6)
Grade ≥3 AE related to study drug, n (%)	1 (5.9)
Serious AE, n (%)	0
Infection-related AE, n (%)	14 (82.4)
Grade ≥3 infection-related AE, n (%)	0
Study discontinuations due to AE, n (%)	0

AE, treatment-emergent adverse event; n, number of participants experiencing the event.
The most frequently occurring AEs were upper respiratory tract infection (n = 8; 47.1%), pyrexia (n = 4; 23.5%), and oropharyngeal pain (n = 4; 23.5%).

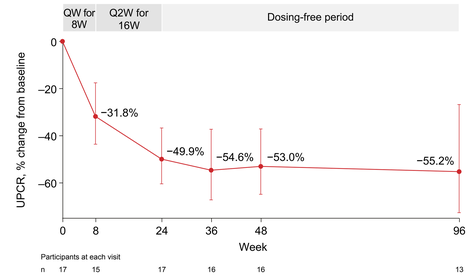
- No serious adverse events, grade ≥3 infections, or opportunistic infections were observed (**Table 2**). No new safety concerns were identified after long-term follow-up.

Figure 3. Rapid reductions in serum (A) IgA, (B) Gd-IgA1, and (C) IgG, with partial recovery in IgA, sustained reductions in Gd-IgA1, and complete recovery in IgG by week 96. Mean and 95% CI are shown



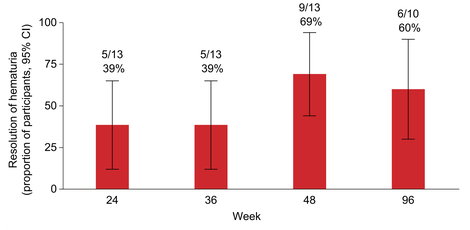
Gd-IgA1, galactose-deficient immunoglobulin A1; IgA, immunoglobulin A; IgG, immunoglobulin G; Q2W, every 2 weeks; QW, every week; W, week.
*n = 17 at week 6 and n = 14 at week 7 for IgA and IgG.

Figure 4. Rapid reduction in proteinuria was sustained for 18 months after the end of dosing, with a 55.2% mean reduction from baseline at week 96



Q2W, every 2 weeks; QW, every week; UPCR, urine protein to creatinine ratio; W, week.
Data are presented as model-based geometric mean with 95% CI. From a mixed-effects model for repeated measures analysis, with visit as a factor, and adjusted baseline value and baseline-by-visit interaction.

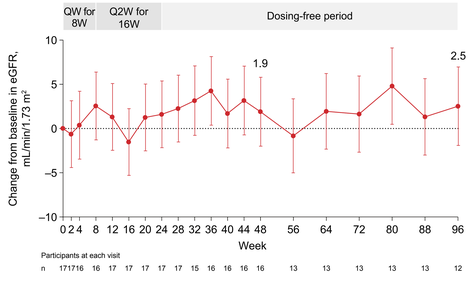
Figure 5. Resolution of hematuria in participants with hematuria at baseline*



Resolution of hematuria was defined as negative or trace hematuria among participants with positive hematuria at baseline and nonmissing hematuria data for the corresponding visit.
*1/17 participants did not have hematuria data at baseline.

- At week 96, hematuria resolved in 60% of participants who had hematuria at baseline (**Figure 5**).

Figure 6. Kidney function remained stable 18 months after the end of dosing, through week 96



eGFR, estimated glomerular filtration rate; Q2W, every 2 weeks; QW, every week; W, week.
Data presented as model-based mean and 95% CI. From a mixed-effects model for repeated measures analysis over all post-baseline visits, with change from baseline in eGFR as the outcome and visit as the factor.

Conclusions

Mezagitamab as an add-on to standard-of-care therapy for participants with primary IgAN was generally well tolerated, with favorable safety.

There were no serious adverse events or grade ≥3 infections through week 96.

Reductions in serum Gd-IgA1 and proteinuria were sustained at week 96, approximately 18 months after the last dose, suggesting prolonged efficacy beyond the treatment period.

Hematuria resolved in 60% of participants by week 96.

Kidney function remained stable up to week 96.

These findings indicate a potential disease-modifying effect of mezagitamab in IgAN that is sustained off therapy, supporting its continued evaluation in a phase 3 study (NCT06963827).

Disclosures

Jonathan Barratt has received consulting and speaker fees from Alnylam, argenx, Astellas Pharma, BioCryst, Calliditas Therapeutics, Chinook Therapeutics, Dimerix, Galapagos, Novartis, Omeros, Takeda, Travere Therapeutics, Vera Therapeutics, and Visterra; grant support from argenx, Calliditas Therapeutics, Chinook Therapeutics, Galapagos, GSK, Novartis, Omeros, Travere Therapeutics, and Visterra; support for clinical trials from Calliditas Therapeutics, Chinook Therapeutics, Novartis, Omeros, Vera Therapeutics, and Visterra; and support for research projects from argenx, Calliditas Therapeutics, Chinook Therapeutics, Galapagos, GSK, Isterra, Novartis, Omeros, and Travere Therapeutics. Yusuke Suzuki has received research funding from Aurinia Pharmaceuticals, Japan Kidney Association, mebix, Novartis, Pfizer, Rona Bioscience, Tokiwa, and Travere Therapeutics; consulting fees from Alexion, Alpine Immune Sciences, argenx, BioCryst, Chinook Therapeutics, George Clinical, Novartis, Otsuka, and Renalys Pharma; and payment or honoraria from AstraZeneca, Boehringer Ingelheim, Chinook Therapeutics, Daiichi Sankyo, Kyowa Kirin, Mitsubishi Tanabe Pharma Corporation, Novartis, and Otsuka. Van Anh Nguyen, Iwona Dobler, Cheryl Li, Parth Patwari, and MK Farmer are employees of Takeda Development Center Americas, Inc., and stockholders of Takeda Pharmaceutical Company Limited.

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