

Zigakibart demonstrates clinical safety and efficacy in a Phase 1/2 trial of healthy volunteers and patients with IgA nephropathy

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Abstract

Q6 Introduction: Zigakibart is a humanized IgG4 monoclonal antibody that binds the cytokine A Proliferation-Inducing Ligand (APRIL, also known as TNFSF13). APRIL is a critical factor in immunoglobulin (Ig) A nephropathy (IgAN) pathogenesis.

Methods: Here, we report healthy volunteers (63 overall) and 100-week data from an ongoing Phase 1/2 clinical trial in 40 patients with IgAN (NCT03945318) treated with zigakibart.

Q7 Results: In healthy volunteers, zigakibart was well tolerated following intravenous administration of single doses ranging from 10–1350 mg or multiple doses ranging from 50–450 mg every two weeks. Zigakibart exposure increased in a dose-proportional manner, with corresponding durable reductions in levels of free APRIL, IgA and IgM, and to a lesser extent, IgG. In patients with IgAN, zigakibart 600 mg, administered subcutaneously every two weeks, was well tolerated with no treatment-emergent adverse events leading to study drug discontinuation or death. A 60% reduction in proteinuria and sustained estimated glomerular filtration rate stabilization were observed at week 100. There was a notable decrease in hematuria, as well as rapid and durable reductions in IgA, galactose-deficient IgA (Gd-IgA1), and IgM levels, with a modest reduction in IgG.

Conclusions: Overall, zigakibart demonstrated robust pharmacological activity, and clinical evidence shows an acceptable safety profile with clinically meaningful proteinuria reduction and sustained estimated glomerular filtration rate stabilization in patients with IgAN, providing a potentially disease-modifying approach for the treatment of IgAN. The effects of zigakibart on proteinuria and long-term

kidney function in adults with IgAN are being evaluated in the ongoing phase 3 BEYOND study (NCT05852938).

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KEYWORDS: anti-APRIL; glomerulonephritis; IgA nephropathy; phase 1/2; TNFSF13; zigakibart

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Lay Summary

IgA nephropathy (IgAN) is a long-term kidney disease in which the immune system attacks the kidneys, causing inflammation, kidney injury, and kidney failure. Currently, there are very few treatments that target the underlying causes of IgAN. Researchers have found that a protein called a proliferation-inducing ligand (APRIL) plays a role in producing harmful antibodies linked to IgAN. Zigakibart is a new treatment being developed to block APRIL. In healthy volunteers, people without IgAN or other diseases, who received single or multiple doses of zigakibart, the treatment showed promise as a potential therapy for IgAN. The early (phase 1/2) clinical trial described herein showed that zigakibart, given every 2 weeks to patients with IgAN, had a good safety profile, reduced urinary protein levels by 60% (a sign of improved kidney health), and stabilized kidney function. A larger (phase 3) clinical trial is underway to gather more data on the safety and efficacy of zigakibart in treating patients with IgAN.

IgA nephropathy (IgAN) is the leading cause of primary glomerulonephritis and contributes significantly to the global patient burden of chronic kidney disease and kidney failure.^{1–3} Historically, options for IgAN management focused primarily on supportive care, yet despite this approach, a significant proportion of patients remained at high risk of

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progressive chronic kidney disease advancing to kidney failure,^{3,4} highlighting the widespread need for novel treatments targeting the pathogenic mechanisms underlying IgAN. Recently, treatment options for IgAN have been expanded to include budesonide (delayed-release) and sparsentan, both of which received full approval in the United States.^{5–8} In addition, iptacopan, a first-in-class complement inhibitor, and atrasentan, a potent and selective endothelin A receptor antagonist, were granted accelerated approval in the United States.^{9,10} There are also several novel targeted therapies being investigated in late-stage clinical trials.

IgAN is a chronic autoimmune disease, and its pathogenesis is described by a “multihit” mechanism. The production of galactose-deficient IgA1 (Gd-IgA1) is associated with the development of autoantibodies against Gd-IgA1, which together form circulating immune complexes that deposit in the glomeruli, activating downstream pathways—including the complement and endothelin systems—resulting in inflammation, fibrosis, and subsequent kidney injury.¹¹

A proliferation-inducing ligand (APRIL, also known as TNFSF13) is a cytokine belonging to the tumor necrosis factor superfamily, involved in B-cell activation and differentiation into plasma cells as well as B-cell and plasma cell survival. Homotrimeric APRIL acts via binding to the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TNFRSF13B) and B-cell maturation antigen (TNFRSF17) receptors.^{12–14} APRIL is also thought to induce IgA class switching and increase the survival of IgA-producing plasma cells. In IgAN, this coincides with increased circulating Gd-IgA1 levels and glomerular immune complex accumulation.^{15–17} Human APRIL transgenic mice show an increase in serum IgA¹⁸ and IgA antibody responses.¹⁹ Polymorphisms in the *APRIL* gene confer increased susceptibility to, and severity of, IgAN.^{20–22} In addition, in patients with IgAN, high plasma levels of APRIL and Gd-IgA1 are associated with proteinuria and lower estimated glomerular filtration rate (eGFR).^{17,23} Anti-APRIL therapy is anticipated to decrease plasma cell survival, thereby reducing circulating IgA and Gd-IgA1 levels and immune complex formation and thus attenuating kidney injury.^{16,24}

Zigakibart is a humanized IgG4 monoclonal antibody that binds to and blocks APRIL binding to B-cell maturation antigen and transmembrane activator and calcium modulator and cyclophilin ligand interactor.^{14,25} It is currently under development for treatment of IgAN. By targeting APRIL, zigakibart interferes with B-cell differentiation and the survival of Gd-IgA1-producing plasma cells, thereby leading to decreased Gd-IgA1 levels and consequently reducing immune complex formation, thus exhibiting disease-modifying potential in IgAN. Here, we present the results of a phase 1/2 trial showing that zigakibart has an acceptable safety profile in both healthy volunteers (HVs; parts 1 and 2) and patients with IgAN (part 3) and is efficacious in reducing proteinuria and stabilizing eGFR in patients with IgAN (ClinicalTrials.gov identifier NCT03945318). Furthermore, we show that targeting APRIL

reduces circulating Igs, especially IgA and IgM, in HVs and inhibits hallmarks of IgAN in patients. The safety and efficacy of zigakibart is being further investigated in the ongoing pivotal clinical phase 3 BEYOND study in patients with IgAN (ClinicalTrials.gov identifier NCT05852938).¹³

METHODS

Study design

ADU-CL-19. ADU-CL-19 is an ongoing phase 1/2 trial (ClinicalTrials.gov identifier NCT03945318) evaluating the safety, tolerability, pharmacokinetics (PKs), and pharmacodynamics (PDs) of zigakibart.

Parts 1 and 2 in HVs. Part 1 (single ascending dose—healthy volunteer [SAD-HV]) was a double-blind, randomized, placebo-controlled SAD design conducted in HVs. A total of 36 HVs were enrolled in part 1. Five dose cohorts were evaluated; the dose levels were 10, 50, 150, 450, and 1350 mg. HVs in each cohort were randomly assigned in a 3:1 ratio to receive either zigakibart or placebo. Each HV received a single dose of the assigned study drug administered by i.v. infusion. Sentinel dosing was used within each cohort. The starting dose cohort (10 mg) had a reduced sample size ($n = 4$) and was included as an additional safety measure. In the starting dose cohort, 3 HVs received zigakibart (10 mg) and 1 HV received placebo, with the first 2 sentinel subjects randomized in a 1:1 ratio to receive zigakibart or placebo in a double-blind manner. In this cohort, the first sentinel HV was dosed; after a minimum of 48 hours, the second sentinel HV was dosed. After a minimum of another 48 hours, the remaining 2 HVs were dosed on the same day. In all subsequent SAD-HV cohorts, 6 HVs received zigakibart at the assigned dose level and 2 HVs received placebo. A sentinel pair of HVs was dosed first (1 HV received zigakibart and 1 HV received placebo) in a double-blind manner, followed by a minimum 48-hour waiting period before the remaining HVs in the cohort were dosed. Before initiating a higher dose cohort, the safety review team reviewed the available blinded safety, tolerability, and PK/PD data through day 8 to determine whether it was safe to escalate to the next anticipated dose.

Part 2 (multiple ascending dose—healthy volunteer [MAD-HV]) was a double-blind, randomized, placebo-controlled MAD design conducted in HVs. Up to 4 dose cohorts were planned for evaluation; the anticipated dose levels were 50, 150, 450, and 1350 mg. Based on the PD observed with the 450 mg every 2 weeks (Q2W) dose, it was deemed unnecessary to evaluate the 1350-mg dose. HVs in each cohort were randomly assigned in a 2:1 ratio to receive either zigakibart or placebo. A total of 27 HVs were enrolled, and 3 dose cohorts were evaluated at dose levels of 50, 150, and 450 mg. Each HV received zigakibart or placebo administered by i.v. infusion Q2W for a total of 3 doses (i.e., on day 1, day 15, and day 29). In each MAD-HV cohort, 6 HVs received zigakibart at the assigned dose level and 3 HVs received placebo. Before initiating a higher dose cohort, the safety review team reviewed the available blinded safety, tolerability, and PK/PD

Table 1 | Baseline characteristics of patients with IgAN in the phase 1/2 study

Characteristic	Cohort 1 (n = 10)	Cohort 2 (n = 30)	Overall (N = 40)
Age (yr)	38.5 (27, 59)	38.5 (21, 74)	38.5 (21, 74)
Sex: male	9 (90.0)	19 (63.3)	28 (70.0)
Race			
White	10 (100)	14 (46.7)	24 (60.0)
Asian	0	13 (43.3)	13 (32.5)
Black/African American	0	1 (3.3)	1 (2.5)
Missing	0	2 (6.7)	2 (5.0)
Time from biopsy to enrollment, ^a yr	2.1 (0.2, 7.7)	3.1 (0.1, 8.3)	2.6 (0.1, 8.3)
BMI, kg/m ²	30.5 (25.5, 35.7)	27.0 (18.1, 36.6)	28.0 (18.1, 36.6)
Blood pressure, mm Hg			
Systolic	127 (113, 133)	126 (106, 139)	126 (106, 139)
Diastolic	83 (69, 88)	81 (57, 89)	82 (57, 89)
eGFR, ml/min per 1.73 m ²	69.0 (30, 122)	64.0 (30, 131)	66.5 (30, 131)
eGFR category			
<60 ml/min per 1.73 m ²	3 (30.0)	12 (40.0)	15 (37.5)
≥60 ml/min per 1.73 m ²	7 (70.0)	18 (60.0)	25 (62.5)
24-h urinary protein excretion, g/d	1.2 (0.7, 6.5)	1.1 (0.3, 7.0)	1.1 (0.3, 7.0)
24-h urinary protein excretion category			
<1 g/d	2 (20.0)	14 (46.7)	16 (40.0)
1–<2 g/d	3 (30.0)	11 (36.7)	14 (35.0)
2–<3 g/d	1 (10.0)	3 (10.0)	4 (10.0)
≥3 g/d	2 (20.0)	2 (6.7)	4 (10.0)
24-h UPCr (mg/g)	591.8 (413.0, 4551.2)	769.5 (210.5, 3228.2)	722.3 (210.5, 4551.2)

BMI, body mass index; eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; Q2W, twice a week; UPCr, urinary protein-to-creatinine ratio.

^aTime from IgAN biopsy to enrollment = (treatment start date – IgAN biopsy date)/365.25. Missing day part of the IgAN biopsy date was imputed as the first day of the month.

Data are presented as median (minimum, maximum) or n (%).

Data cutoff date: November 1, 2024. Safety analysis set. Cohort 1: 450 mg i.v./600 mg s.c. Q2W. Cohort 2: 600 mg s.c. Q2W. Screening visit was used as baseline for eGFR and blood pressure.

data through day 36 to determine whether it was safe to escalate to the next anticipated dose.

The primary objective of parts 1 and 2 was to characterize the safety and tolerability of zigakibart in HVs. The secondary objectives were to characterize the PK of zigakibart administered by i.v. infusion after a single dose and multiple doses, assess the immunogenicity of zigakibart after a single dose and multiple doses, and characterize the PD effect of zigakibart on Igs after a single dose and multiple doses. Full inclusion and exclusion criteria for parts 1 and 2 are listed in [Supplementary Methods](#).

Part 3. Part 3 is an ongoing open-label study that enrolled patients 18 years or older with biopsy-proven IgAN, total urinary protein level ≥ 0.5 g/24 h, or urinary protein-to-creatinine ratio ≥ 0.5 g/g, and eGFR ≥ 30 ml/min per 1.73 m² and who were on a stable/optimized dose of renin-angiotensin system inhibitors for ≥3 months before screening (unless intolerant to renin-angiotensin system inhibitors). Full inclusion and exclusion criteria are listed in [Supplementary Methods](#). In part 3, patients received zigakibart 450 mg i.v. Q2W and transitioned to 600 mg s.c. Q2W²⁶ at ≥24 weeks in cohort 1 while cohort 2 was initiated on, and is receiving, 600 mg s.c. Q2W; for both cohorts, the treatment duration is up to 124 weeks. The primary objective is to characterize the safety and tolerability of zigakibart. The

secondary objectives include characterizing the PD effects of zigakibart on Igs and assessing changes in proteinuria and kidney function in patients with IgAN. A full list of the objectives and end points is provided in [Supplementary Methods](#).

The study is being conducted in compliance with the International Council on Harmonisation Good Clinical Practice guideline, consistent with the principles that have their origin in the Declaration of Helsinki. The study is being conducted only at centers where institutional review board/ethics committee approval has been obtained. Written informed consent was obtained from each patient before study enrollment. Study assessments and procedures for all 3 parts of the study are outlined in [Supplementary Methods](#).

Statistical analyses

Analyses for all 3 parts of the study were performed as described in [Supplementary Methods](#).

RESULTS

Zigakibart in HVs

HV characteristics and disposition. A total of 36 HVs were enrolled in part 1 and 27 HVs in part 2. Baseline characteristics and demographics are summarized in [Supplementary Table S1](#).

Table 2 | TEAEs reported in the phase 1/2 study

AE category (overall N = 40)		n (%)
TEAEs	Patients with any TEAE	34 (85.0)
	Patients with serious TEAEs	1 (2.5)
	Patients with any infection TEAE	31 (77.5)
	Infection TEAEs occurring in ≥ 2 patients	
	COVID-19	18 (45.0)
	Upper respiratory tract infection	13 (32.5)
	Influenza	6 (15.0)
	Bronchitis	5 (12.5)
	Nasopharyngitis	5 (12.5)
	Sinusitis	4 (10.0)
	Pharyngitis streptococcal	4 (10.0)
	Urinary tract infection	3 (7.5)
	Asymptomatic COVID-19	2 (5.0)
	Ear infection	2 (5.0)
	Viral gastroenteritis	2 (5.0)
	Rhinitis	2 (5.0)
	Viral upper respiratory tract infection	2 (5.0)
Treatment-related TEAEs	Patients with any treatment-related TEAE	10 (25.0)
	Treatment-related TEAEs occurring in ≥ 2 patients	
	Injection-site erythema	5 (12.5)
	Fatigue	3 (7.5)
	Injection-site pain	2 (5.0)

AE, adverse event; COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

Data cutoff date: November 1, 2024. Safety analysis set. A TEAE was defined as an adverse event occurring after the first dose of the study drug through to the end of the study visit.

Safety. There was no increase in treatment-emergent adverse events (TEAEs) in HVs who received zigakibart compared with placebo in either study part. There were no serious TEAEs, TEAEs leading to discontinuation, or AESIs. In part 1, the highest number of TEAEs was reported in the SAD placebo cohort. In part 2, the highest number of TEAEs was reported in the MAD-2 150-mg dose cohort. There were no reports of increased infections associated with zigakibart treatment compared with placebo in either part 1 or part 2, and serum concentrations of IgG remained within the normal reference ranges. There were no serious adverse events of infections reported in either part 1 or part 2. For more details on TEAEs, see [Supplementary Results](#).

Analysis of PK, PD, and biomarker data

Pharmacokinetics. The time course of individual serum concentrations of zigakibart after single i.v. infusions of 10, 50, 150, 450, and 1350 mg over 2 hours and multiple i.v. infusions of 50, 150, and 450 mg over 2 hours Q2W are shown in [Supplementary Figures S1 and S2](#), respectively. The distribution by dose of peak concentration and area under the curve from 1 to 8 days for single and multiple doses of zigakibart are shown in [Supplementary Figure S3](#). A summary of PK parameters of zigakibart after single i.v. infusions of 10,

50, 150, 450, and 1350 mg and multiple i.v. infusions of 50, 150, and 450 mg is provided in [Supplementary Table S2](#).

Serum concentrations, peak concentration, and exposure (area under the curve from 1 to 8 days) increased approximately dose proportionally from 10 to 1350 mg, with a slight trend toward greater than dose-proportional concentrations and exposures at higher doses. Peak serum zigakibart concentrations are typically reached within 2–4 hours postdose (relative to the start of infusion time). Based on the SAD cohorts (SAD-1 and SAD-2) with terminal phase data, the half-life of zigakibart ranged from ~ 9 to 34 days. Multiple-dose PKs in HVs were assessed in part 2 of ADU-CL-19, in which 3 doses of zigakibart (50, 150, and 450 mg) were evaluated after a Q2W dosing regimen for a total of 3 doses. As presented in [Supplementary Table S3](#), at the doses studied, slightly greater than dose-proportional increases in systemic exposure were noted. Minimal interindividual variability in PK parameters—peak concentration and area under the curve from 0 to ∞ —was observed, with values ranging from $\sim 6\%$ to 21%. In HVs, after repeat dosing, terminal half-lives ranged from ~ 2 to 4 weeks and were comparable to those noted upon single dose administration. Following a Q2W dosing regimen up to 3 repeat doses, modest accumulation was observed across dose cohorts, with accumulation ratios ranging from 2- to 3-fold.

Treatment-emergent antidrug antibodies were detected in 2 of 18 subjects receiving placebo (11.1%) and 4 of 45 (8.9%) receiving zigakibart. No neutralizing antidrug antibodies were detected. The potential effect on PK could not be determined, as zigakibart concentrations were already low when antidrug antibodies were detected.

PD and biomarker evaluations. Serum-free APRIL levels Mean serum free APRIL concentrations observed in subjects after i.v. infusion are shown in [Supplementary Figure S4](#) and described in [Supplementary Results](#).

Serum Ig levels Most subjects in the SAD-HV and MAD-HV cohorts had IgA, IgG, and IgM levels within the normal reference ranges over the course of the study. A dose-dependent reduction in IgA levels was observed in the SAD-HV cohorts over time. The mean percent change from baseline to day 85 in IgA levels in the placebo cohort was +1.70%. The mean percent changes from baseline to day 85 were -6.03% , -7.60% , -8.93% , -31.12% , and -53.51% in the 10-, 50-, 150-, 450-, and 1350-mg dose cohorts, respectively. A dose-dependent reduction in IgA levels was observed in the MAD-HV cohorts over time. The mean percent change from baseline to day 113 in IgA levels in the placebo cohort was +1.75%. The mean percent changes from baseline to day 113 were -5.97% , -23.91% , and -54.69% in the 50-, 150-, and 450-mg dose cohorts, respectively ([Supplementary Figure S5](#)).

The observed reduction in IgM levels was similar to the effect of zigakibart on IgA reduction. The mean percent change from baseline to day 85 in IgM levels in the placebo cohort was +7.85%. The mean percent changes from baseline to day 85 were -11.79% , -11.47% , -16.01% , -48.44% ,

Serum Igs (combined cohorts 1 and 2)

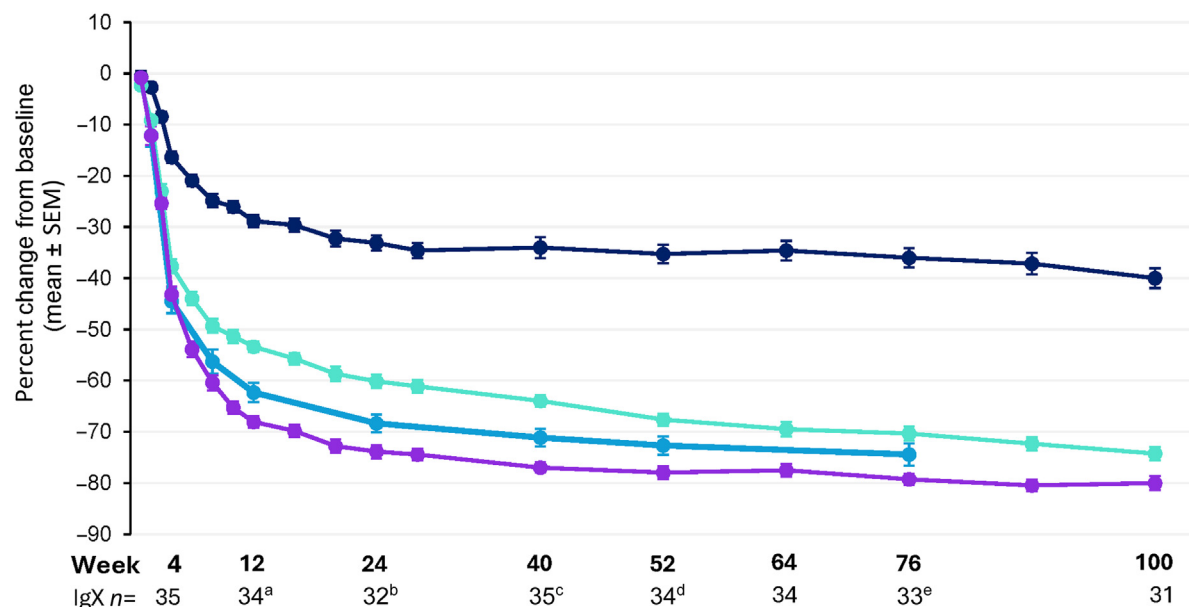


Figure 1 | Zigakibart selectively suppresses serum levels of IgA and galactose-deficient IgA1 (Gd-IgA1). Percent change from baseline in serum Ig levels in patients treated with zigakibart. Data cutoff date: November 1, 2024. ^a $n = 33$ for IgA and Gd-IgA1. ^b $n = 31$ for IgM. ^c $n = 33$ for Gd-IgA1. ^d $n = 33$ for IgM and Gd-IgA1. ^e $n = 18$ for Gd-IgA1. Data are presented as mean percent change from baseline $\pm$ SEM. The Ig biomarker analysis set was used for Ig analyses ($n = 35$). Ig values reflect predose measurements. Baseline was defined as the last nonmissing value collected before receiving the first dose of the study drug.

and -70.54% in the 10-, 50-, 150-, 450-, and 1350-mg dose cohorts, respectively. A dose-dependent reduction in IgM levels was observed in the MAD-HV cohorts over time. The mean percent change from baseline to day 113 in IgM levels in the placebo cohort was -2.63% . The mean percent changes from baseline to day 113 were -9.68% , -40.67% , and -71.19% in the 50-, 150-, and 450-mg dose cohorts, respectively (Supplementary Figure S5).

A less pronounced reduction was seen for IgG; the mean percent change from baseline in IgG levels in the SAD-HV placebo cohort at the end of the study (day 85) was $+3.63\%$, and the mean percent changes from baseline to day 85 were -8.69% , -4.12% , $+0.10\%$, -11.88% , and -25.70% in the 10-, 50-, 150-, 450-, and 1350-mg dose cohorts, respectively. The mean percent change from baseline in IgG levels in the MAD placebo cohort at the end of the study (day 113) was -1.16% , and the mean percent changes from baseline to day 113 were -3.57% , -15.67% , and -23.87% in the 50-, 150-, and 450-mg dose cohorts, respectively (Supplementary Figure S5).

Zigakibart reduces IgA, Gd-IgA, and proteinuria and stabilizes eGFR in patients with IgAN

Patient characteristics and disposition. Overall, 40 patients were enrolled (cohort 1: $n = 10$; cohort 2: $n = 30$). Patient demographic and clinical characteristics were similar across cohorts (Table 1). The overall median age was 38.5 years; 70% of patients were male; 60% were White (note that all patients in cohort 1 were White); and 33% were Asian. The median

(range) protein excretion rate at baseline was 1.1 (0.3–7.0) g/d; the median (range) eGFR value at baseline was 66.5 (30–131) ml/min per 1.73 m²; and 37.5% of patients had an eGFR of <60 ml/min per 1.73 m². At the time of the week 100 interim analysis, the median (range) treatment duration was 120 (2–127) weeks. Two and 7 patients in cohort 1 and cohort 2, respectively, discontinued study treatment, most frequently because of protocol violations (1 and 3 patients, respectively) (Supplementary Table S3).

Safety. Zigakibart was generally well tolerated, with no TEAEs leading to study drug discontinuation or death. TEAEs were observed in 34 patients (85%); 1 serious TEAE of amnesia occurred, which was not treatment related and did not result in study drug interruption. The most common TEAEs were infections of grade 1 or 2 in severity (78%) (Table 2); 2 patients experienced grade 3 infections, which were not treatment related. One patient experienced several infections deemed treatment related. All infection TEAEs resolved while on study treatment.

Clinical laboratory findings of IgG levels <3.0 g/l occurred in 2 patients; in both patients, day 1 levels were below the lower limit of normal, neither event required intervention, no infections occurred while IgG levels were <3.0 g/l, and both events occurred with concurrent administration of steroids. Seven patients (17.5%) experienced TEAEs classed as infusion-related or injection-site reactions. Four patients (10%) reported grade ≥ 3 TEAEs, all deemed unrelated to the study drug.

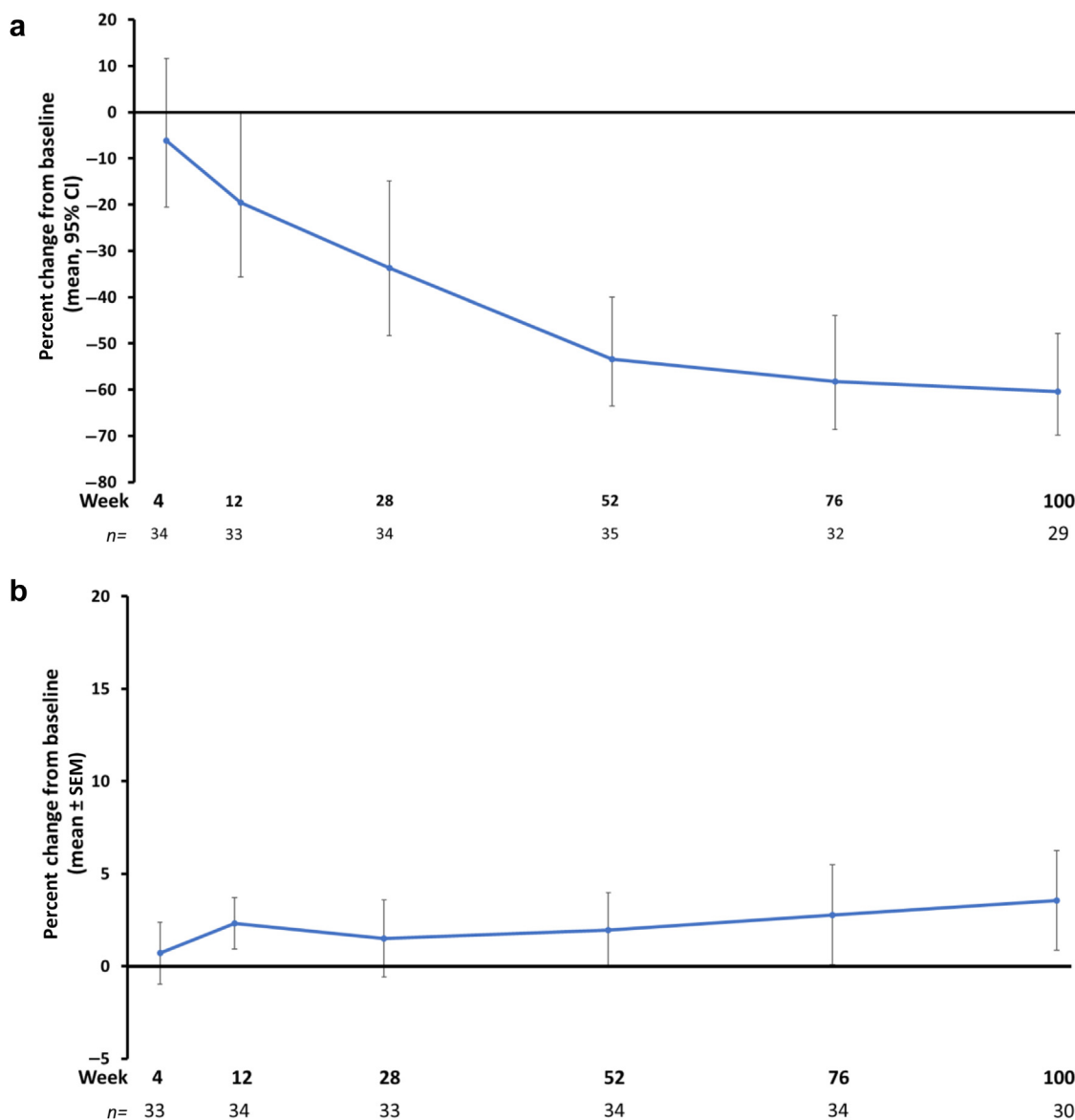


Figure 2 | Zigakibart improves kidney function. Percent change from baseline in (a) 24-hour urinary protein-to-creatinine ratio (UPCR) and (b) estimated glomerular filtration rate (eGFR) through week 100. Data cutoff date: November 1, 2024. Data are presented as geometric mean percent change from baseline $\pm$ 95% confidence interval (CI) for UPCR and mean percent change from baseline $\pm$ SEM for eGFR. The biomarker analysis set was used for the analyses ($n = 35$). Baseline was defined as the last nonmissing value collected before receiving the first dose of the study drug.

Pharmacodynamics. Treatment with zigakibart resulted in rapid and durable reductions in IgA (74.3%; week 100), Gd-IgA (74%; week 76), and IgM (80%; week 100) levels (Figure 1). Reduction in IgG levels was modest (36%) (Figure 1). Data were consistent between the cohorts (Supplementary Figure S6).

Efficacy. A rapid and durable reduction in proteinuria was observed in patients with IgAN across a wide range of baseline proteinuria levels. This response was observed as early as 12 weeks (19.6%); at week 100, 24-hour urinary protein-to-creatinine ratio was reduced by 60.4% from baseline in both cohorts combined (Figure 2a). The reductions were consistent between the cohorts (Supplementary Figure S6).

Sustained eGFR stabilization was observed with zigakibart treatment through 100 weeks in patients across a wide range of baseline eGFR levels, with an annual eGFR slope (95% confidence interval) of $+0.48$ (-0.74 to 1.70) ml/min per 1.73 m^2 , estimated from a random coefficient model (Figure 2b; Supplementary Figure S7).

Biomarkers. Circulating lymphocyte counts remained stable through week 100 (Figure 3a and b). Overall, 30–34 patients with baseline dipstick test results (85.7%) had hematuria. All 4 patients with negative hematuria at baseline remained negative throughout the treatment period, that is, through week 100 for all except 1 patient who discontinued the study after week 76 after withdrawal of

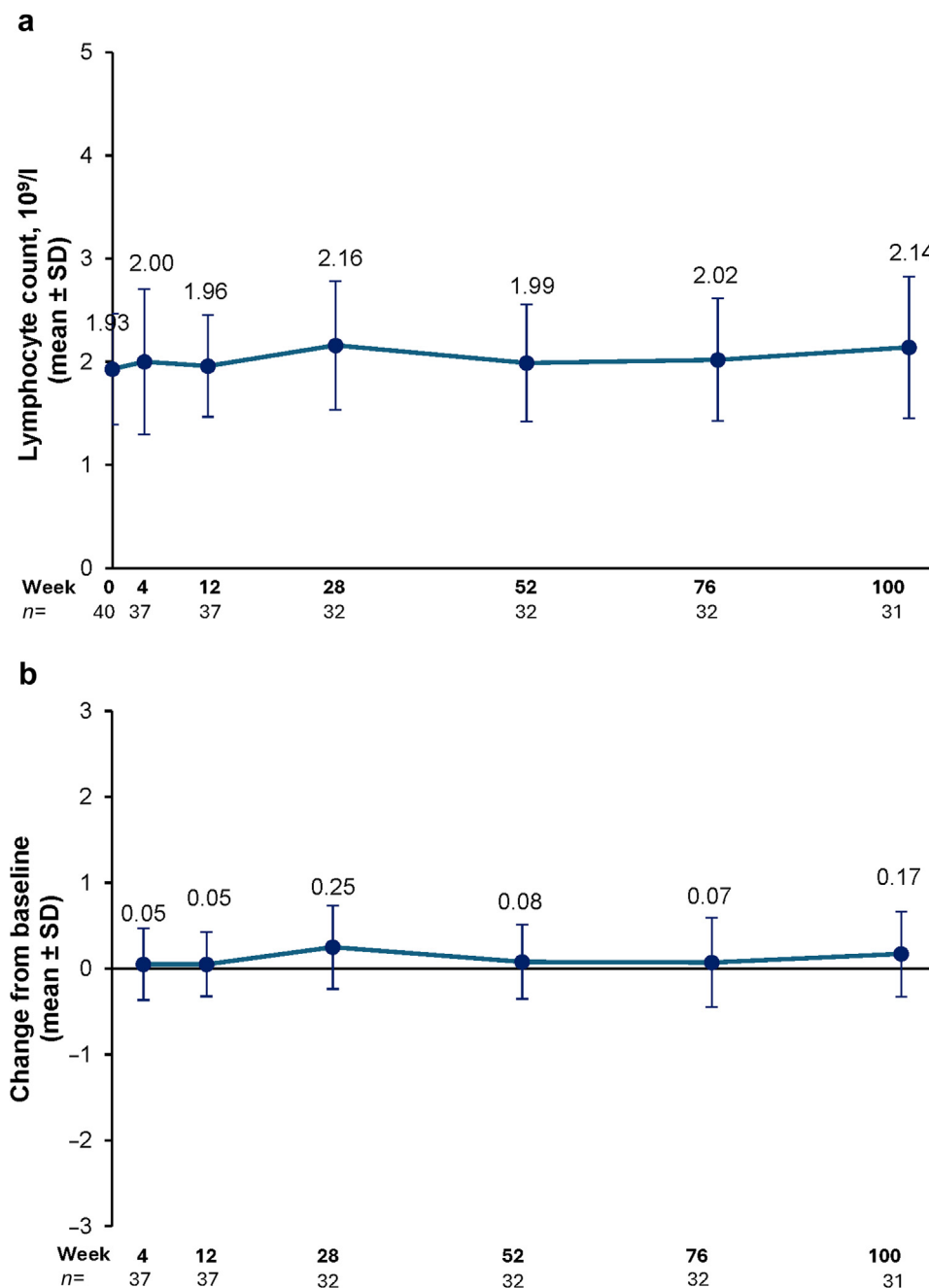


Figure 3 | Long-term treatment with zigakibart does not affect absolute lymphocyte counts in patients with IgA nephropathy. (a) Absolute lymphocyte count. **(b)** Mean change from baseline in lymphocyte count. Data cutoff date: November 1, 2024. The safety analysis set ($N = 40$) was used for lymphocyte analyses. *Baseline* was defined as the last nonmissing value collected before receiving the first dose of the study drug. All postbaseline assessments—scheduled and unscheduled—were considered.

consent. An increasing proportion of patients who had positive hematuria at baseline tested negative over time after treatment with zigakibart. By week 100, 82.4% of patients who had positive hematuria at baseline tested negative (Figure 4).

DISCUSSION

We report here for the first time the full clinical characterization of zigakibart to date, including data from HVs and

patients with IgAN. These data show that zigakibart has an acceptable safety profile and clinically meaningful efficacy in terms of proteinuria reduction and stabilization of eGFR in patients with IgAN.

APRIL is considered to play a critical role in the pathogenesis of IgAN. Elevated levels of APRIL correlate with increased Gd-IgA1 levels, proteinuria, decreased kidney function, and reduced kidney survival.¹⁶ Therefore, pharmacological therapies that block APRIL signaling and reduce Gd-

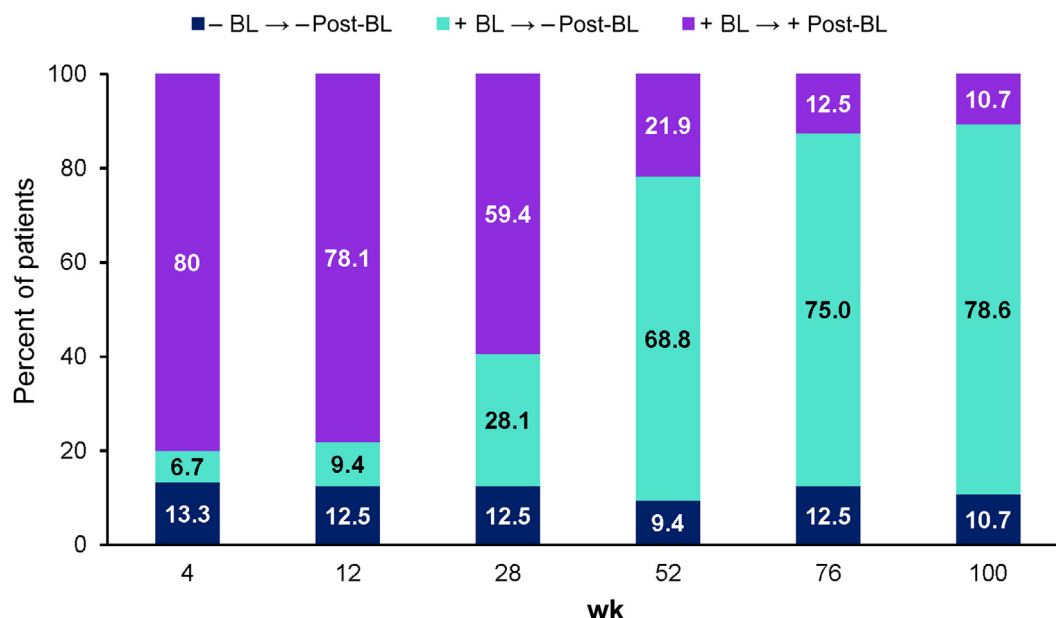


Figure 4 | Zigakibart reduces the occurrence of hematuria in patients with IgA nephropathy. Change in hematuria positivity in patients treated with zigakibart over time through week 100. Data cutoff date: November 1, 2024. Positive or negative hematuria was determined using dipstick analysis. The positive category included test values of trace, small, moderate, large, 1+, 2+/-2, 3+, and abnormal. Denominators for percentages are based on the number of subjects with nonmissing data at both time points (i.e., baseline [BL] and post-BL).

IgA1 levels could potentially modify the disease process in patients with IgAN.⁷

Zigakibart is a monoclonal antibody that selectively targets APRIL and specifically blocks its interaction with transmembrane activator and calcium modulator and cyclophilin ligand interactor and B-cell maturation antigen receptors. Zigakibart was well tolerated in HVs (parts 1 and 2) after i.v. administration of single doses ranging from 10 to 1350 mg (part 1) or multiple doses ranging from 50 to 450 mg Q2W (part 2). There were no reports of increased infections associated with zigakibart compared with placebo in either part 1 or part 2; serum concentrations of IgG remained within the normal reference range.

Serum levels of free APRIL were measured in HVs to evaluate target engagement after dosing with zigakibart. Zigakibart drove dose-dependent increases in target engagement, rapidly reaching >90% target engagement at peak exposure levels after i.v. administration of a single dose of ≥ 450 mg. Multiple doses demonstrated similar and more durable effects at approximately one-third of the single dose level. Reductions in free APRIL levels were followed by corresponding reductions in serum Ig levels. Infections were observed at similar rates across placebo-treated subjects and zigakibart-treated cohorts (up to 1350 mg).

The safety and efficacy of zigakibart are being evaluated in patients with biopsy-proven IgAN in this ongoing, multicenter, phase 1/2 open-label study. Zigakibart treatment rapidly reduced serum IgA, Gd-IgA1, and IgM levels, demonstrating a strong PD effect. Reduction in IgG levels was more modest, similar to other therapies targeting APRIL.²⁴ Zigakibart treatment led to clinically meaningful and

durable reductions in proteinuria (60.4% at 100 weeks) and sustained eGFR stabilization through 100 weeks in patients with IgAN who were receiving optimized supportive care. Reducing proteinuria by 40%–50% after 9 months of treatment predicts a $\sim 60\%$ lower risk of kidney failure or death in IgAN.^{26,27} The stabilization of eGFR is an important treatment goal in the context of IgAN prognosis. Analysis of the UK National Registry of Rare Kidney Diseases (RaDaR) demonstrated that even a decline of as small as 1 ml/min per 1.73 m² per year could result in $\sim 40\%$ of adult patients younger than 50 years at diagnosis experiencing kidney failure or death within their expected lifetime.³ Zigakibart was well tolerated, resulting in few severe or serious safety events, none of which led to study drug discontinuation. The conduct of the study coincided with a high prevalence of coronavirus disease 2019 (incidence rate in the study was 45%) in the participating countries, with a frequent overlap of patients presenting with upper respiratory tract infections suggesting that an upper respiratory tract infection was a frequent manifestation of coronavirus disease 2019 infection.

Although this was a single-arm study in patients with IgAN, reduction in proteinuria and change in eGFR are objective measures and reasonably likely surrogate end points for assessing the effect of a treatment on progression to kidney failure in IgAN.²⁶ The safety and efficacy of zigakibart are being investigated in a larger population of patients with IgAN in the global, randomized, placebo-controlled, phase 3 BEYOND study.¹³

In conclusion, these findings provide evidence that zigakibart strongly inhibits APRIL in HVs. Treatment with zigakibart in patients with IgAN was well tolerated and resulted in

robust and durable reductions in Gd-IgA1 levels and proteinuria, reduced frequency of hematuria, and sustained stabilization of eGFR, which were maintained over 100 weeks of treatment. Importantly, these results suggest that zigakibart intercepts IgAN pathogenesis early to disrupt the downstream disease process, suggesting a promising role for zigakibart as a potentially disease-modifying approach to IgAN treatment.

DISCLOSURE

JD is a former employee of Aduro and a coinventor of a BION-1301 patent. LK is a principal investigator of studies sponsored by Akebia Therapeutics, Alpine Immune Sciences, AstraZeneca, Boehringer Ingelheim, CARA Therapeutics, Chinook Therapeutics, CSL Behring, Galderma, Mineralys Therapeutics, Novartis, Omeros, Otsuka, γReata Pharmaceuticals, Sanifit, Travele Therapeutics, Walden Biosciences, Vera Therapeutics, and Visterra. SGK reports consulting or speaker fees/honoraria from Alexion, Chinook, Alpine, and Roche and research grants from Roche, Vertex Pharmaceuticals, CSL Vifor, Alexion, Novo Nordisk, and Otsuka. HvE is a former employee of Aduro and a coinventor of patents describing hAPRIL.01 and zigakibart. AVE is a former employee and a shareholder of Aduro Biotech and a co-inventor of patents related to zigakibart. HT reports research grant support as principal investigator for the zigakibart study and speaker fees from Bayer. WS and YS are employees of Novartis. JB reports consulting and speaker fees from Alnylam, Argenx, Astellas, BioCryst, Calliditas, Chinook, Dimerix, Galapagos, Novartis, Omeros, Travele Therapeutics, Vera Therapeutics, and Visterra; grant support from Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travele Therapeutics, and Visterra; research projects for Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travele Therapeutics, and Visterra; and clinical trials for Chinook (ADU-CL-19 and ALIGN), Novartis (APPLAUSE), Omeros (ARTEMIS-IGAN), Visterra (ENVISION), Calliditas (NeflgARD), and Vera Therapeutics (ORIGIN). All the other authors declared no competing interests.

DATA STATEMENT

The authors declare that all data supporting the preclinical findings of this study are available within the manuscript and its [Supplementary Material](#). Novartis is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. These requests are reviewed and approved by an independent review panel based on scientific merit. All data provided are anonymized to respect the privacy of patients who participated in the trial, in accordance with applicable laws and regulations. This trial data availability is according to the criteria and process described at www.clinicalstudydatarequest.com.

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AUTHOR CONTRIBUTIONS

JD, HvE, AVE, JB, and YS contributed to the study design. JD, LK, SGK, EYL, HT, BW, IA, and JB contributed to data acquisition. JD, HvE, AVE, and YS performed data analysis. JD, HvE, AVE, JB, YS, and WS performed data interpretation. All authors reviewed and edited the manuscript and approved the final version for publication. The corresponding author has full access to all study data and bears final responsibility for the decision to submit the manuscript for publication.

Supplementary material is available online at www.kidney-international.org.

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Q46