A Phase 1/2 Trial of Zigakibart in IgA Nephropathy (IgAN)

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Disclosures

Dr. Barratt

- Consulting and speaker fees from Alnylam, Argenx, Astellas, BioCryst, Calliditas, Chinook, Dimerix, Galapagos, Novartis, Omeros, Travere Therapeutics, Vera Therapeutics, Visterra
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- Research projects: Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere Therapeutics, Visterra
- Clinical trials: ADU-CL-19 & ALIGN (Chinook), APPLAUSE (Novartis), ARTEMIS-IGAN (Omeros), ENVISION (Visterra), NefIgARD (Calliditas), ORIGIN (Vera Therapeutics)

IgA nephropathy is the most common primary glomerulonephritis[1,2]

- The global incidence of IgAN is **2.5/100,000/year**[2]
- Approximately 30% of patients with **proteinuria 1–2 g/d** progress to **kidney failure** within as little as 10 years[3]
- Emerging evidence suggests that even patients with **low levels of persistent proteinuria (<1 g/d)** are at risk of **kidney failure**[4]
- IgAN has a **heterogeneous clinical presentation** requiring an individualized treatment approach
- **eGFR stabilization** is an important treatment goal in the context of IgAN prognosis; even a decline of as little as 1 mL/min/1.73 m^2 per year could result in ~40% of adult patients younger than 50 years at diagnosis reaching kidney failure/death within their expected lifetime[4]

APRIL, A proliferation-inducing ligand; eGFR, estimated glomerular filtration rate; Gd-IgA1, galactose-deficient IgA1; IgA, Immunoglobulin A; IgAN, Immunoglobulin A nephropathy.

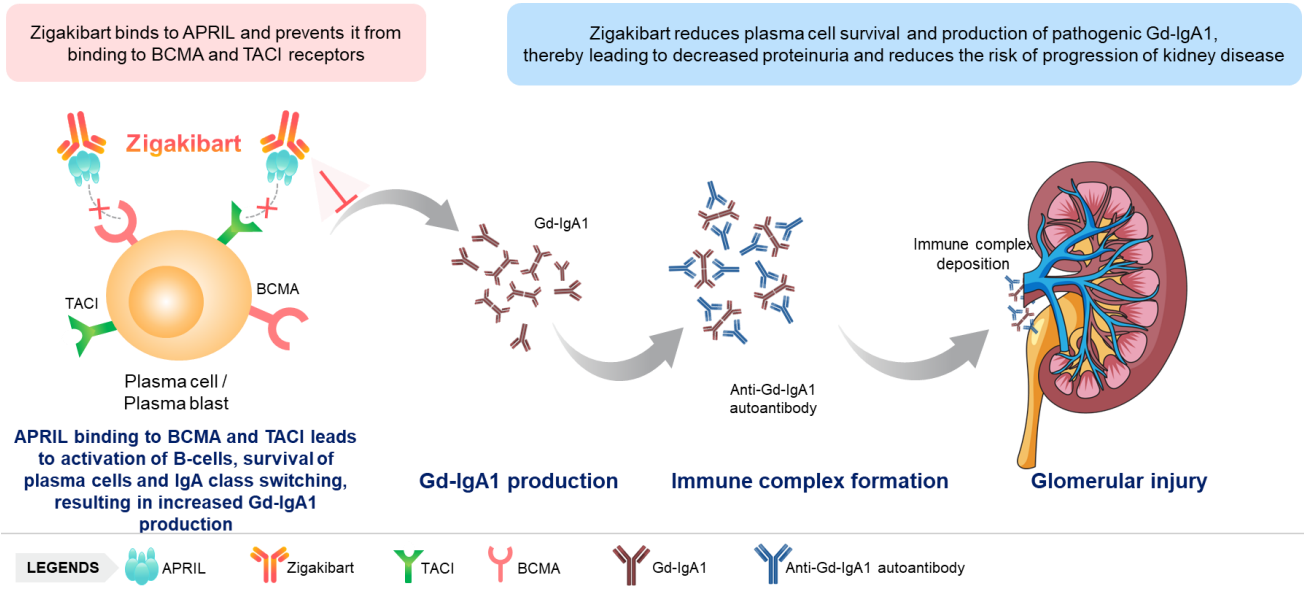
1. McGrogan A, et al. *Nephrol Dial Transplant*. 2011;26(2):414–430; 2. Lim RS, et al. *J Clin Med.* 2024;13(4):947; 3. Reich HN, et al. *J Am Soc Nephrol*. 2007;18:3177–83; 4. Pitcher D, et al. *Clin J Am Soc Nephrol*. 2023;18:727–38.

Zigakibart is a humanized monoclonal antibody that binds and blocks APRIL

Zigakibart

- **Zigakibart** is a humanized monoclonal antibody targeting APRIL
- **APRIL** is a TNF superfamily cytokine that drives IgA class switching and survival of IgA-secreting plasma cells in IgAN, leading to elevated Gd-IgA1 production and immune complex deposition in the mesangium[1–3]
- Promotion of IgA class switching by APRIL, survival of IgA-secreting plasma cells, and excess production of Gd-IgA1 is considered the initial “hit” in the multi-hit pathogenesis of IgAN[4,5]
- By decreasing Gd-IgA1 and preventing pathogenic immune complex formation, blocking APRIL with zigakibart is potentially disease-modifying[1,6]
- Here we present the results from Part 3 of the **Phase 1/2 trial of zigakibart** in patients with IgAN

Schematic representation of the mechanism of action of zigakibart in IgAN



APRIL, A-PRoliferation-Inducing Ligand; BCMA, B-cell maturation antigen; Gd-IgA1, galactose-deficient IgA1; IgAN, IgA nephropathy; TACI, transmembrane activator and CAML interactor; TNF, tumour necrosis factor.

1. Suzuki H, et al. *Semin Immunopathol*. 2021;43:669-678; 2. Zhai Y, et al. *Medicine*. 2016;95:e3099; 3. McCarthy DD, et al. *J Clin Invest*. 2011;121:3991-4002; 4. Boyd JK, et al. *Kidney Int*. 2012;81:833–43; 5. Yeo SC and Barratt J. *Clin Kidney J*. 2023;16(Suppl 2):ii9–ii18; 6. Suzuki H. *Clin Exp Nephrol*. 2019;23:26-31.

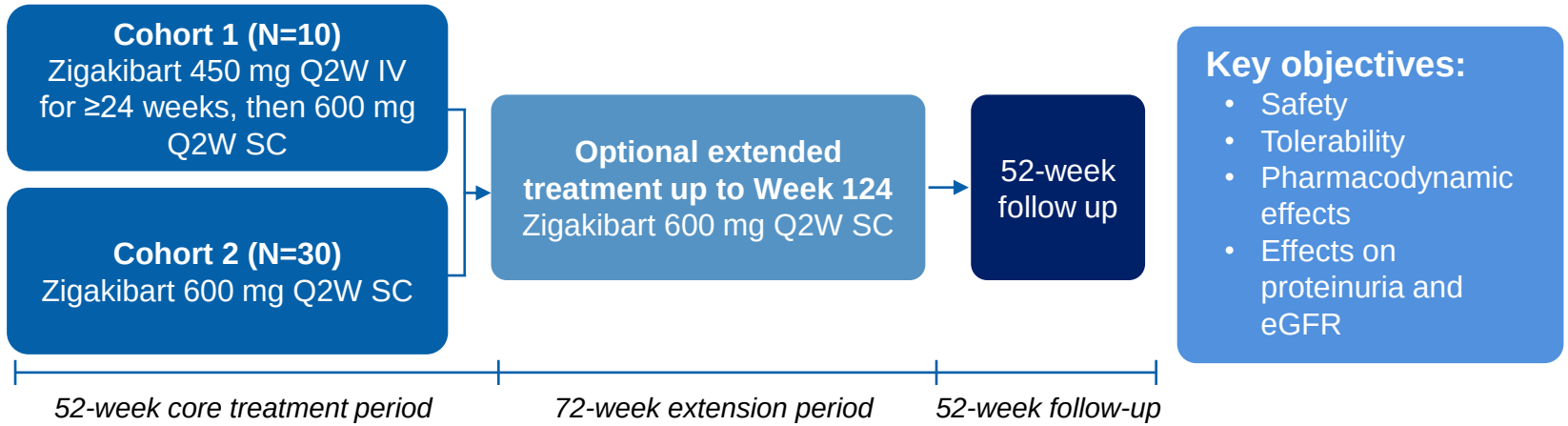
ADU-CL-19 is an ongoing Phase 1/2 trial of zigakibart (NCT03945318)

- Parts 1 and 2 (completed) assessed single- and multiple-ascending doses of zigakibart, respectively, in healthy volunteers (not reported here)
- Part 3 study design is shown below (**Figure**)
  - Treatment: Patients received zigakibart 450 mg Q2W IV, transitioning to 600 mg Q2W SC at ≥24 weeks (Cohort 1) or 600 mg Q2W SC (Cohort 2). Both cohorts will be treated for up to 124 weeks

Key eligibility criteria (Part 3)

- Patients ≥18 years with biopsy-proven IgAN
- Total urine protein ≥0.5 g/24 h or UPCR ≥0.5 g/g
- eGFR ≥30 mL/min/1.73 m^2, and
- On stable/optimized dose of RASi for ≥3 months prior to screening (or RASi intolerant)

Study design (Part 3)



eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; IV, intravenous; Q2W, every 2 weeks; RASi, renin-angiotensin system inhibitor; SC, subcutaneous; UPCR, urine protein–creatinine ratio.
Barratt J et al. Poster presented at: the American Society of Nephrology (ASN) Kidney Week 2024; October 23–27, 2024; San Diego, CA, USA (#FR-PO856).

Baseline demographic and disease characteristics were similar between cohorts

- Overall, 40 patients were enrolled (n=10 [Cohort 1], n=30 [Cohort 2]; **Table**)
  - Median age was 38.5 years, 70% were male, 60% were White, and 33% were Asian
- Demographic and clinical characteristics were similar between the two cohorts, except that all patients in Cohort 1 were White
- The median (min, max) duration of treatment was 102.0 (2.0, 155.0) weeks. This encompassed the 52-week core treatment period and optional extension treatment

Characteristics	Cohort 1 (N=10)	Cohort 2 (N=30)	Overall (N=40)
Age, years (min, max)	38.5 (27.0, 59.0)	38.5 (21.0, 74.0)	38.5 (21.0, 74.0)
Sex, male, n (%)	9 (90.0)	19 (63.3)	28 (70.0)
Race, n (%)			
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, years, median (min, max)	2.1 (0.2, 7.7)	3.1 (0.1, 8.3)	2.6 (0.1, 8.3)
eGFR, mL/min/1.73 m^2, median (min, max)	69.0 (30.0, 122.0)	64.0 (30.0, 131.0)	66.5 (30.0, 131.0)
24-h urine protein excretion, g/d, median (min, max)	1.2 (0.7, 6.5)	1.1 (0.3, 7.0)	1.1 (0.3, 7.0)
24-h UPCR, g/g, median (min, max)	0.6 (0.4, 4.6)	0.8 (0.2, 3.2)	0.7 (0.2, 4.6)

Data cutoff date: June 21, 2024. Safety analysis set. Time 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. Screening visit was used as baseline for eGFR.

eGFR, estimated glomerular filtration rate; UPCR, urine protein–creatinine ratio.

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Zigakibart was well-tolerated

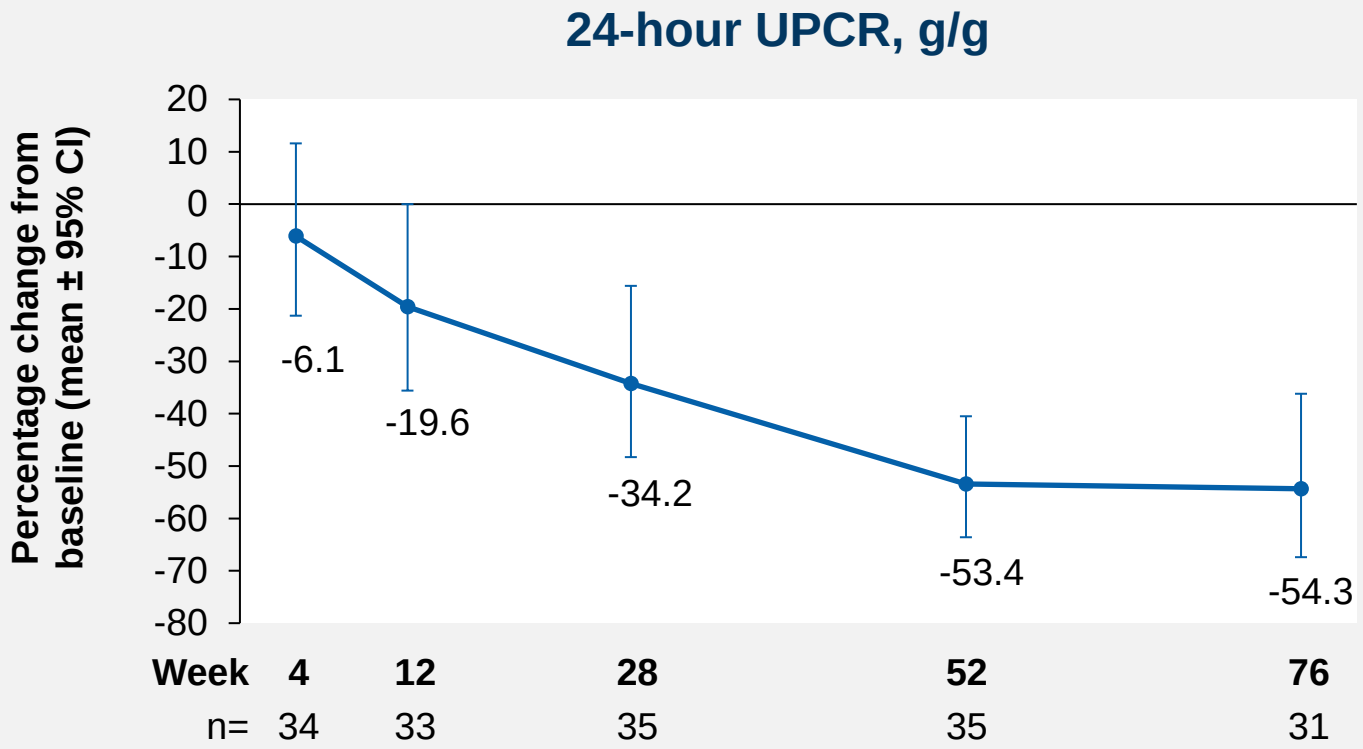
- No TEAEs leading to study drug discontinuation or deaths
- TEAEs were observed in 34 (85%) patients, most commonly infections (78%) of Grade 1 or 2 in severity
  - Two patients experienced three Grade 3 infections that were not treatment-related
  - One patient experienced seven infections deemed treatment-related
- One serious TEAE of amnesia occurred that was not study drug-related and did not result in interruption of the study drug
- IgG <3.0 g/L (clinical laboratory finding) occurred in two patients; both patients entered study on Day 1 with IgG levels below the LLN and the events occurred with concurrent administration of steroids after 28* and 88 weeks of zigakibart treatment. No infections occurred while IgG was <3.0 g/L

AE category (Overall N=40)		n (%)
TEAEs	**Patients with any TEAE**	34 (85.0)
	Patients with serious TEAE	1 (2.5)
	Patients with any infection and infestation TEAE	31 (77.5)
	Infection TEAE occurring in n ≥2 patients	
	COVID-19	18 (45.0)
	Upper respiratory tract infection	13 (32.5)
	Influenza	6 (15.0)
	Bronchitis	5 (12.5)
	Nasopharyngitis	4 (10.0)
	Sinusitis	4 (10.0)
	Pharyngitis streptococcal	3 (7.5)
	Urinary tract infection	3 (7.5)
	Asymptomatic COVID-19	2 (5.0)
	Ear infection	2 (5.0)
	Gastroenteritis viral	2 (5.0)
	Rhinitis	2 (5.0)
	Viral upper respiratory tract infection	2 (5.0)
Treatment-related TEAEs	**Patients with any treatment-related TEAE**	11 (27.5)
	Treatment-related TEAEs occurring in n ≥2 patients	
	Injection-site erythema	5 (12.5)
	Fatigue	3 (7.5)
	Injection-site pain	2 (5.0)

Data cutoff: June 21, 2024. A TEAE is defined as an adverse event occurring after the first dose of study drug through to the end of study visit. Safety analysis set (N=40).

*The patient received zigakibart for 28 weeks but was discontinued from the study at that point due to a protocol violation. Subsequently, the patient was treated with steroids and, at the 12-week follow-up (while on steroids), was found to have an IgG <3.0 g/L. LLN, lower limit of normal; IgG, Immunoglobulin G; TEAE, treatment-emergent adverse event. Barratt J et al. Poster presented at: the American Society of Nephrology (ASN) Kidney Week 2024; October 23–27, 2024; San Diego, CA, USA (#FR-PO856).

A rapid and sustained reduction in proteinuria was observed in patients with IgAN across a wide range of baseline proteinuria levels (range: 0.2–4.6 g/g)



At Week 76, 24-hour UPCR was reduced by 54% from baseline

Data cutoff: June 21, 2024. Biomarker analysis set (N=35). Data presented are geometric mean percentage change from baseline ± 95% CI for UPCR. Baseline is defined as the last non-missing value collected before receiving the first dose of the study drug. All post-baseline assessments were considered, scheduled, and unscheduled.

IgAN, immunoglobulin A nephropathy; SEM, standard error of the mean; UPCR, urine protein–creatinine ratio.

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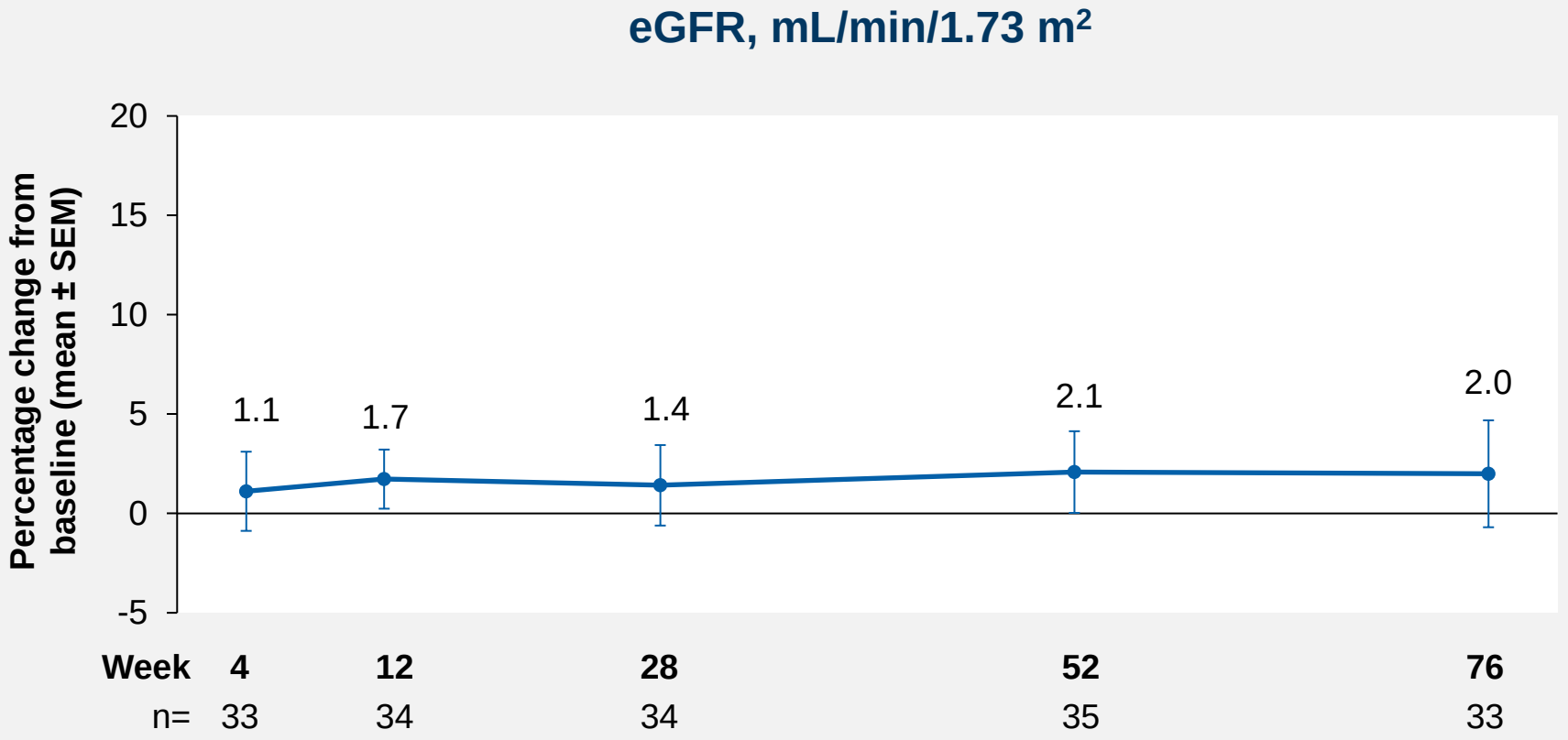
eGFR remained stable with zigakibart treatment over time in patients across a range of baseline eGFR levels (range: 30–131 mL/min/1.73 m^2)



Data cutoff: June 21, 2024. Biomarker analysis set (N=35). Data presented are mean percentage change from baseline ± SEM for eGFR. Baseline is defined as the last non-missing value collected before receiving the first dose of the study drug. All post-baseline assessments were considered, scheduled, and unscheduled.

eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; SEM, standard error of the mean.

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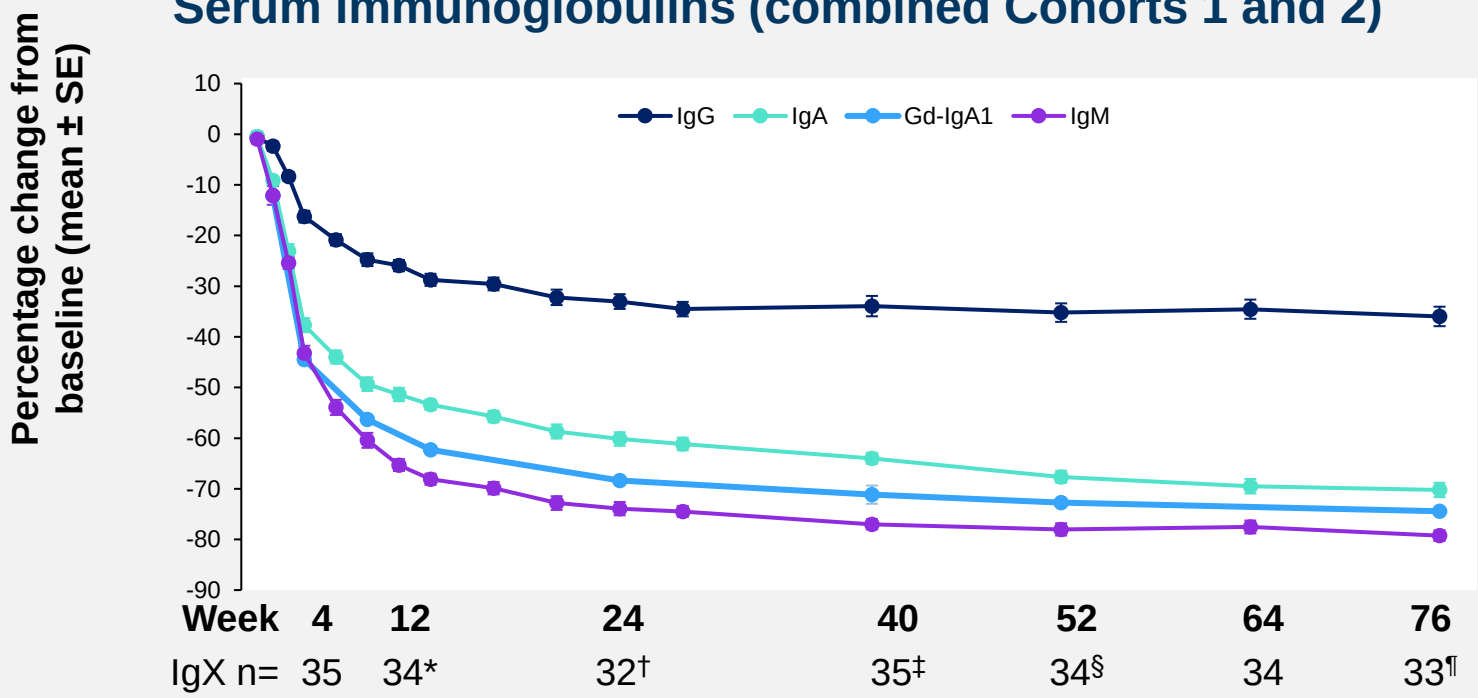
Treatment with zigakibart resulted in rapid and sustained reductions in IgA, Gd-IgA1, and IgM levels

- Treatment with zigakibart resulted in rapid and sustained reductions in IgA, Gd-IgA1, and IgM levels, which were reduced by 70%, 74%, and 79% from baseline, respectively, through Week 76. Reduction in IgG was mild to modest (36%)

Serum immunoglobulins (combined Cohorts 1 and 2)



Data cutoff: June 21, 2024. *n=33 for IgA and Gd-IgA1; †n=31 for IgM; ‡n=33 for Gd-IgA1; §n=33 for IgM; ¶n=18 for Gd-IgA1. Immunoglobulin biomarker analysis set used for immunoglobulin analyses (N=35). Ig reflect pre-dose measurements. Baseline is defined as the last non-missing value collected before receiving the first dose of the study drug. All post-baseline assessments were considered, scheduled, and unscheduled.

Gd-IgA1, galactose-deficient IgA1; IgA, immunoglobulin A; IgM, immunoglobulin M; IgG, immunoglobulin G; SE, standard error of the mean.

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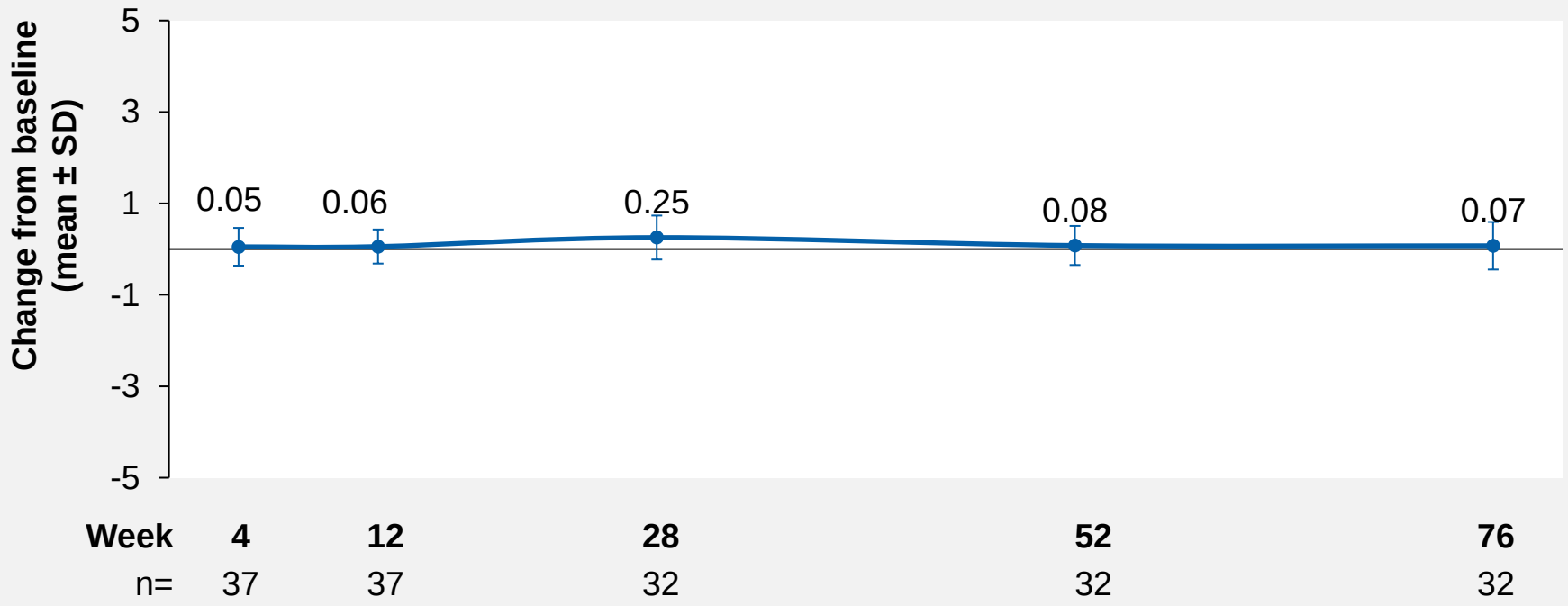
Circulating total lymphocyte counts remained stable through to Week 76

Mean change from baseline in total lymphocyte count, 10^9/L (combined Cohorts 1 and 2)



Data cutoff: June 21, 2024. Baseline is defined as the last non-missing value collected before receiving the first dose of the study drug. All post-baseline assessments were considered, scheduled, and unscheduled. Safety analysis set (N=40) used for lymphocyte count.

SD, standard deviation.

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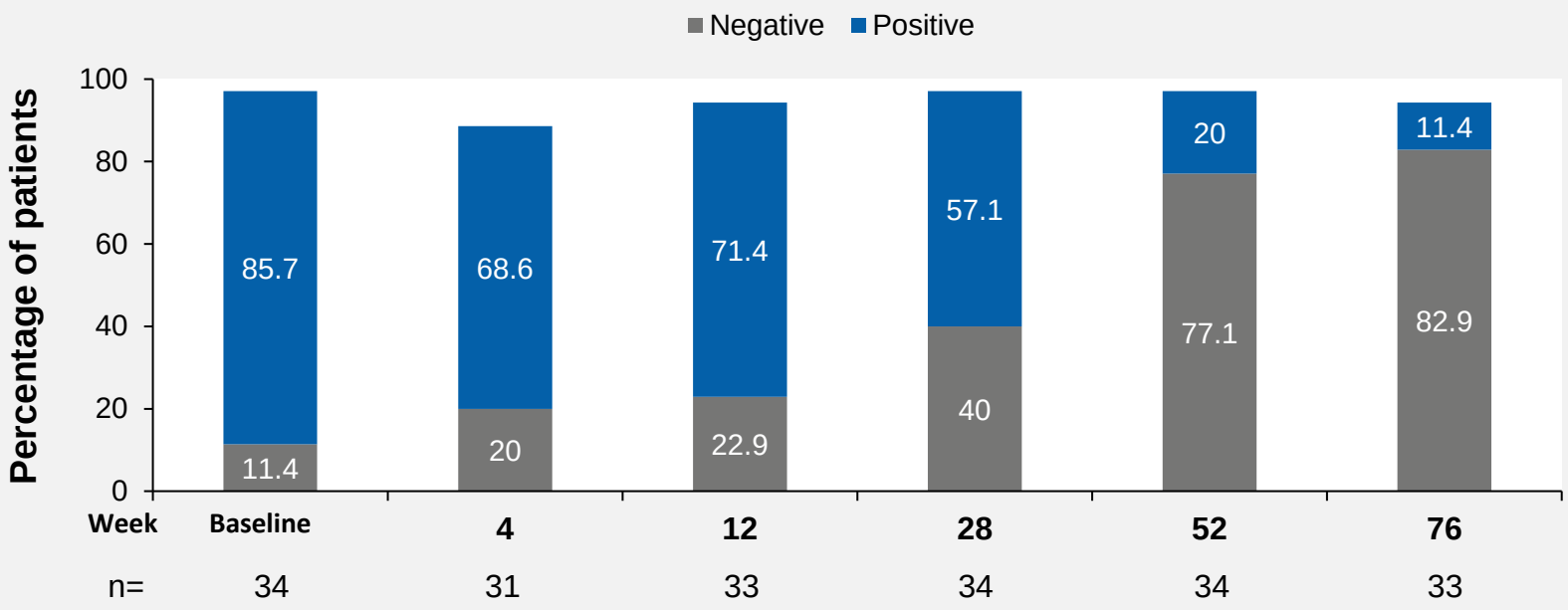
By Week 76, 83% of the patients had negative hematuria

- Overall, 30 of 35 (85.7%) patients had hematuria at baseline
- By Week 76, only 4 (11.4%), patients had positive hematuria assessed by dipstick test

Hematuria (combined Cohorts 1 and 2)



§Positive or negative hematuria determined by dipstick analysis and percentages calculated based on the biomarker analysis set (N=35). Data cutoff: June 21, 2024. Baseline is defined as the last non-missing value collected before receiving the first dose of the study drug. All post-baseline assessments were considered, scheduled, and unscheduled.

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Conclusions

- **Zigakibart**, an anti-APRIL monoclonal antibody, was **well-tolerated** with no AEs leading to study drug discontinuation or deaths
- Treatment with zigakibart led to:
  - **Rapid reduction in serum IgA, Gd-IgA1, and IgM** levels, demonstrating a **strong PD effect**
  - **Sustained, clinically meaningful reductions in proteinuria and eGFR stabilization** in patients with IgAN through 76 weeks of treatment
- The on-going global **Phase 3 BEYOND study** (NCT05852938) is also evaluating the efficacy and safety of zigakibart in adult patients with IgAN

APRIL, A proliferation-inducing ligand; AE, adverse events; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; PD, pharmacodynamic.
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