Results from the Phase 2 Study of Cemdisiran in Adult Patients with IgA Nephropathy

Jonathan Barratt[1], See Cheng Yeo[2], Anders Fernström[3], Sean J. Barbour[4], C. John Sperati[5], Russell Villanueva[6], Ming-Ju Wu[7], Dazhe Wang[8], Anna Borodovsky[8], Prajakta Badri[8], Elena Yureneva[8], Ishir Bhan[8], Daniel Cattran[9]

[1]Leicester General Hospital, Leicester, UK
[2]Tan Tock Seng Hospital, Renal Medicine Clinic, Singapore, Singapore
[3]Department of Nephrology and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden
[4]University of British Columbia, Division of Nephrology, British Columbia, Canada
[5]Johns Hopkins University, Baltimore, MD, US
[6]National Kidney and Transplant Institute, Quezon City, Philippines
[7]Taichung Veterans General Hospital, Taichung, Taiwan
[8]Alnylam Pharmaceuticals, Cambridge, MA, USA
[9]Toronto General Hospital, Toronto, Ontario, Canada

Presented at the American Society of Nephrology (ASN) in Orlando, Florida, 1–6 November 2022

Alnylam's IgA Nephropathy clinical program is being conducted in partnership with Regeneron Pharmaceuticals, Inc.

Disclosure for Jonathan Barratt, PhD, FRCP

Conflict	Disclosure
Research Support	Argenx, Calliditas, Chinook Therapeutics, Galapagos, GSK, Novartis, Travere Therapeutics, Vera Therapeutics
Medical/scientific advisor	Alnylam Pharmaceuticals, Argenx, Astellas, Biocryst, Calliditas, Chinook Therapeutics, Dimerix, Galapagos, GSK, Novartis, Omeros, Travere Therapeutics, UCB, Vera Therapeutics, Visterra

Introduction

IgA Nephropathy Disease Background

- Most common type of glomerulonephritis[1,2]
  - Incidence: ~2.5 out of 100,000 individuals are affected per year
  - Racial and ethnic variations

- Clinical features: hematuria, proteinuria, kidney injury, and hypertension[1]
  - High-grade proteinuria is a strong risk factor for CKD[3]

- IgA deposits in the glomerular mesangium, activating an immunologic response[1,4]

- Complement deregulation and activity are proposed to be dominant drivers of renal injury in IgAN[5]
  - Markers of complement activation may identify patients with IgAN likely to progress to significant renal impairment

- Treatment options currently limited; strategies aim to reduce proteinuria and control hypertension[1,4]
  - ~30% reduction in proteinuria considered clinically meaningful[6]
  - Immunosuppression may be considered, but efficacy is limited, and toxicity can be high
  - Patients can progress to kidney failure, with earlier treatment likely linking to better outcomes[3]

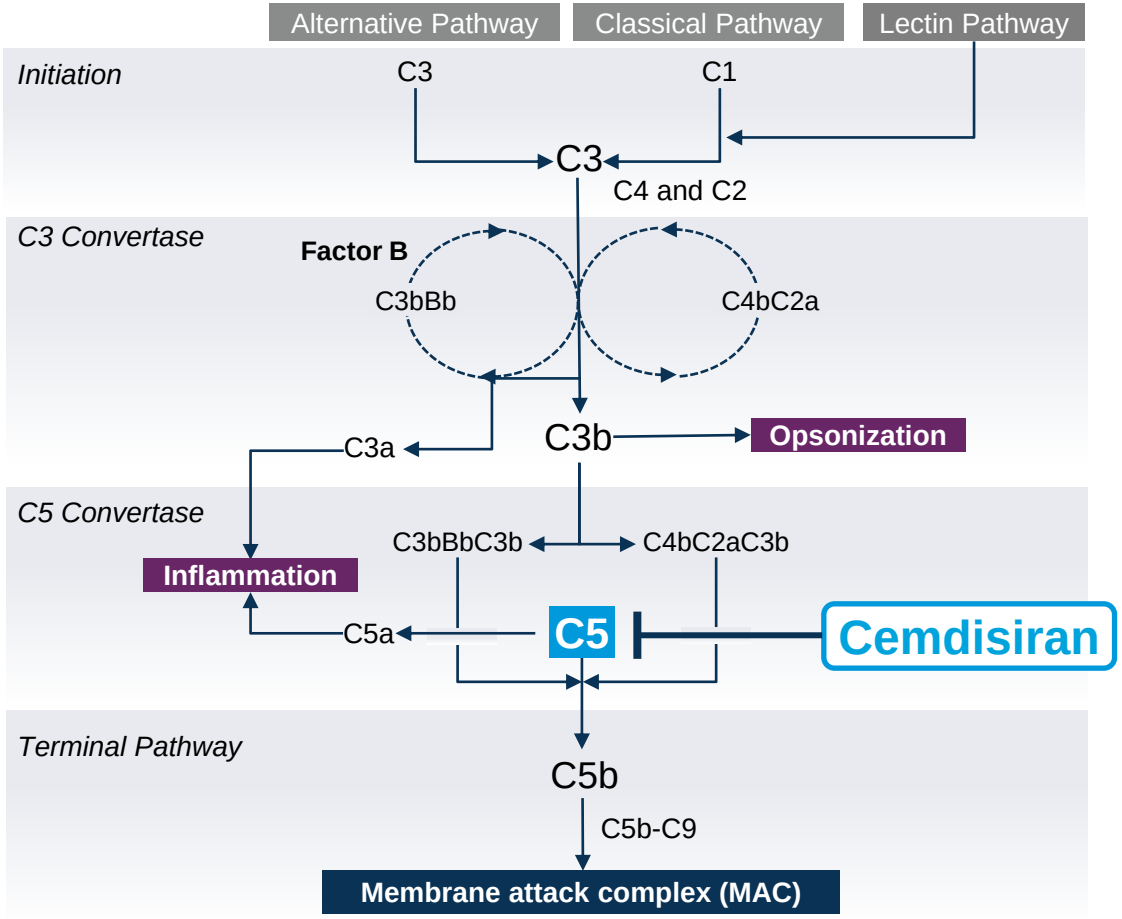
- There remains an unmet need for effective, disease-specific treatment options

CKD, chronic kidney disease; IgAN, immunoglobulin A nephropathy.

1. Rajasekaran A et al *Am J Med Sci* 2021;361:176–164; 2. McGrogan A et al *Nephrol Dial Transplant* 2011;414–430; 3. Berthoux F et al. *Semin Nephrol* 2008;28:4–9; 4. Floege J et al. *Kidney Int* 2019;95:268-280. 5. Tortajada A et al. *Mol Immunol* 2019;114:123-32; 6. Inker LA et al *Am J Kidney Dis* 2021;78:340–9.

Cemdisiran, an Investigational RNAi Therapeutic for Patients with IgAN

Mechanism of Action



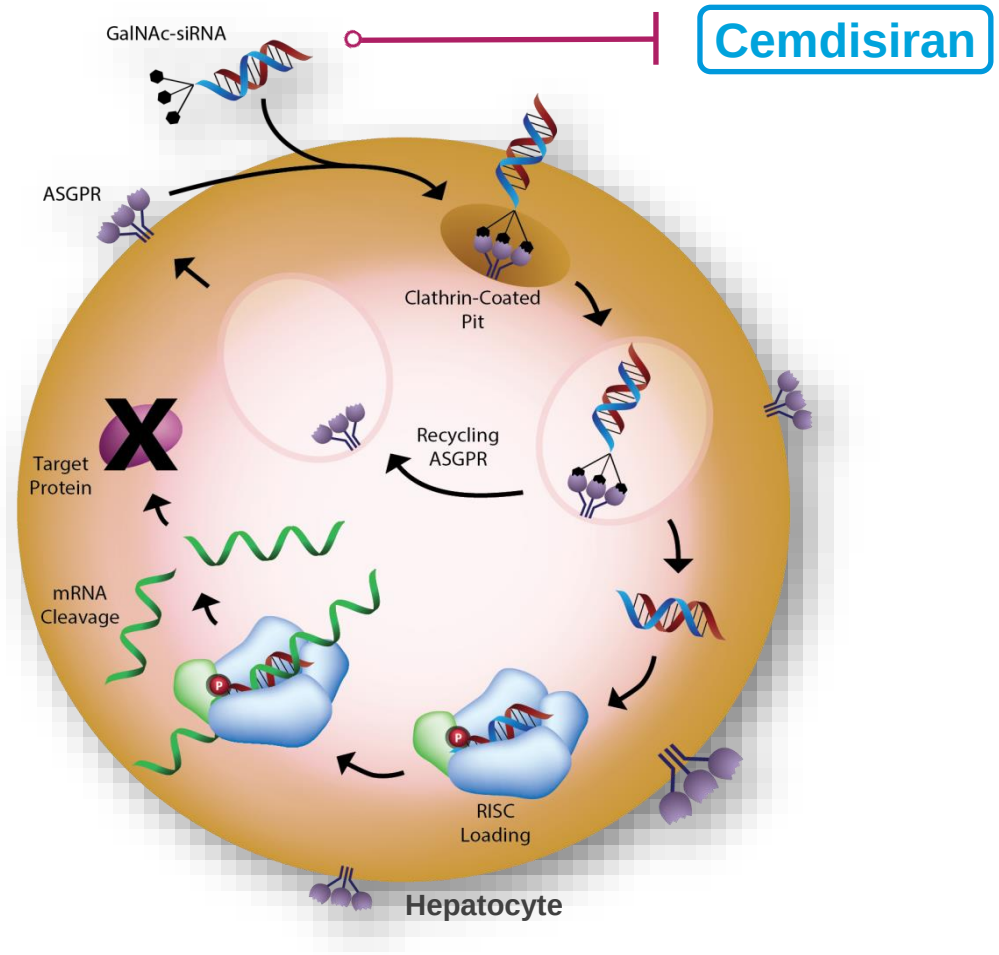
- Cemdisiran is a subcutaneously administered, investigational RNAi therapeutic that inhibits hepatic production of C5 and is in development for the treatment of complement-mediated diseases

C5, C5 component of the complement pathway; IgAN, immunoglobulin A nephropathy; RNAi, RNA interference.

Cemdisiran, an Investigational RNAi Therapeutic for Patients with IgAN

RNAi Technology

- Cemdisiran uses RNAi technology to inhibit hepatic production of C5 protein, reducing complement-mediated inflammation
- Liver-specific targeting is achieved through GalNAc–siRNA conjugates that bind ASGPR, expressed on the surface of hepatocytes[1]
- siRNA is incorporated into the RISC complex and leads to cleavage of C5 mRNA

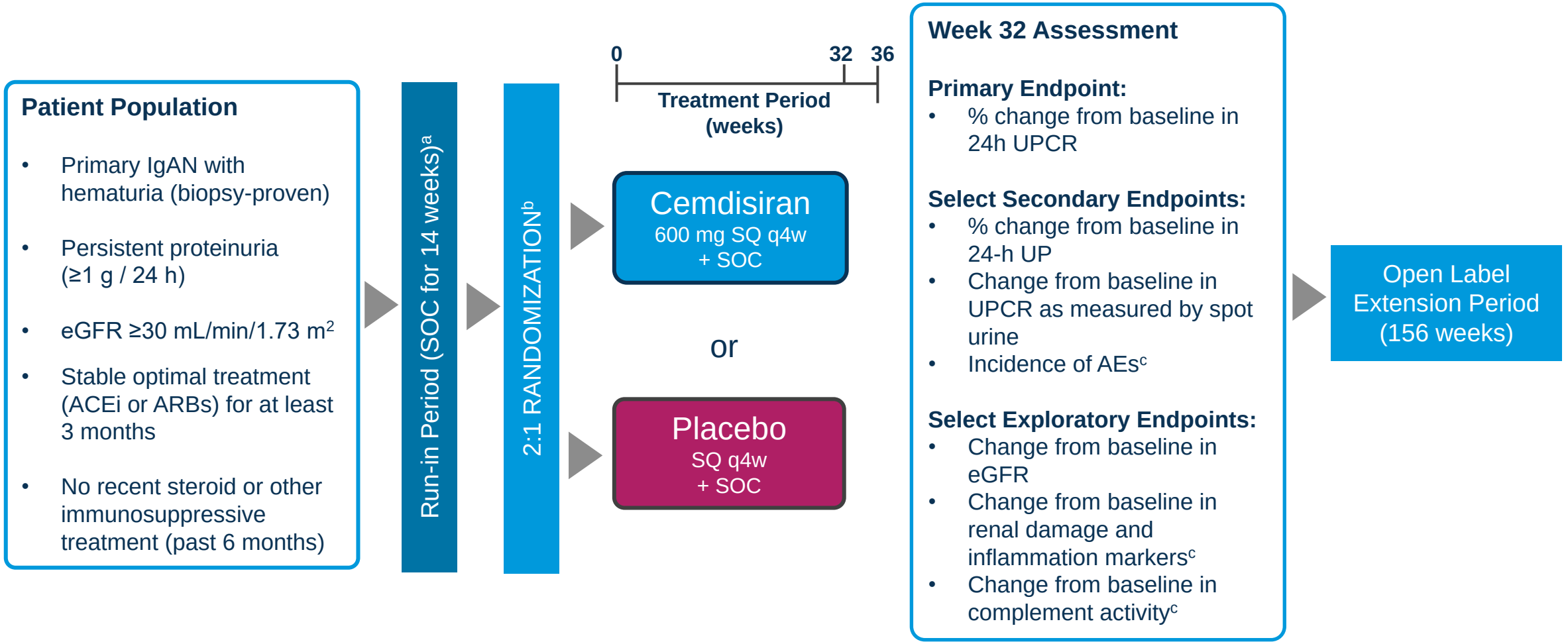


ASGPR, asialoglycoprotein receptor; C5, C5 component of the complement pathway; GalNAc–siRNA, N-acetylgalactosamine–small interfering ribonucleic acid; IgAN, immunoglobulin A nephropathy; mRNA, messenger ribonucleic acid; RISC, ribonucleic acid-induced silencing complex; RNAi, RNA interference; siRNA, small interfering ribonucleic acid; SOC, standard of care.

1. Nair et al. *J Am Chem Soc* 2014;136:16958–61.

Cemdisiran Phase 2 IgA Nephropathy Study Design

Randomized, Double-blind Study (NCT03841448)



[a]During the run-in period, patients' blood pressure, kidney function, hematuria, proteinuria, and treatment with SOC will be documented by the Investigator. SOC was considered to be ACEi or ARB. Patients with proteinuria ≥1 g/24 h within 2 weeks of the end of the run-in period, and who meet blood pressure and eGFR criteria, will be eligible to roll into the treatment period. [b]Stratified by baseline urine proteinuria levels (≥1 g/24 h and <2 g/24 h versus ≥2 g/24 h). [c]Monitored during the course of the study.

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; q4w, every 4 weeks; SOC, standard of care; SQ, subcutaneously; UP, urine protein; UPCR, urine protein to creatinine ratio.

Demographic and Baseline Disease Characteristics

	Placebo (N=9)	Cemdisiran (N=22)
Age, mean (range) (years)	37.6 (23–56)	40.5 (18–59)
Male, n (%)	3 (33.3)	13 (59.1)
Race, n (%) Asian White Other/Missing	 4 (44.4) 4 (44.4) 1 (11.1)	 12 (54.5) 8 (36.4) 2 (9.1)
Time since diagnosis, median (IQR) (years)	2.5 (4.6)	1.8 (1.9)
Systolic blood pressure, mean (SD) (mmHg)	116.1 (7.2)	125.0 (11.7)
Diastolic blood pressure, mean (SD) (mmHg)	68.0 (12.9)	79.8 (7.9)
24-hour UP, mean (SD) (g/24 hour)	2.9 (1.3)	2.5 (1.5)
24-hour UPCR, mean (SD) (g/g)	2.0 (0.8)	1.6 (1.0)
eGFR, median (Q1, Q3) (mL/min/1.73 m^2)	47 (39, 76)	68 (54, 94)
Prior treatment with an ACEi, n (%)	1 (11.1)	7 (22.0)
Prior treatment with an ARB, n (%)[a]	8 (88.9)	14 (63.6)

- Baseline demographic and disease characteristics were largely similar between the two treatment groups

[a]One patient in the cemdisiran group had prior combination of hydrochlorothiazide and telmisartan.

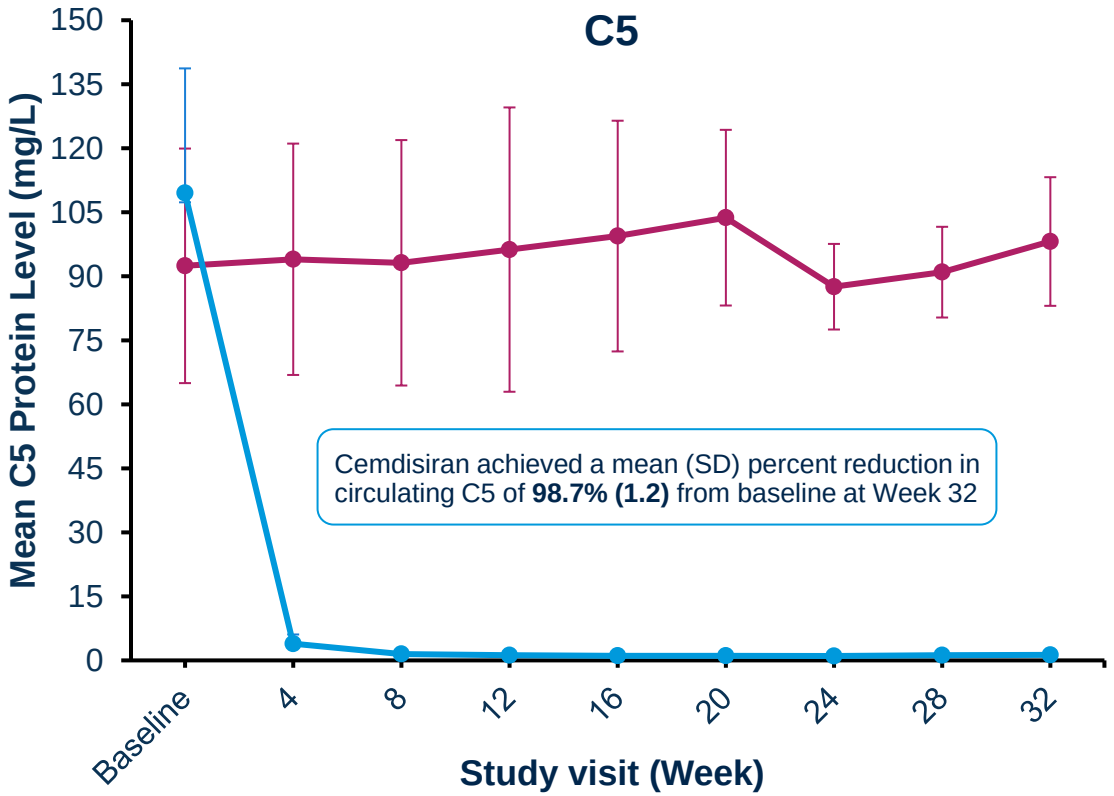
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range; Q, quartile; SD, standard deviation; UP, urine protein; UPCR, urine protein to creatinine ratio.

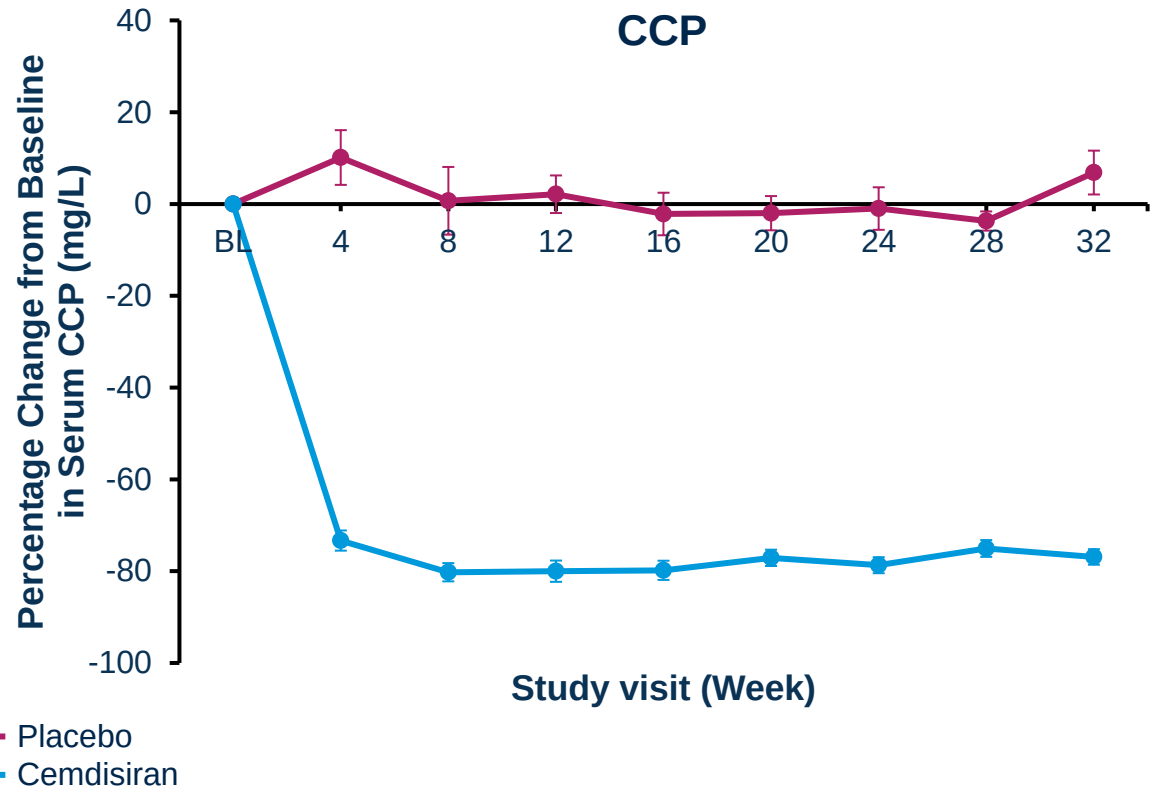
Demographic and Baseline Disease Characteristics

Oxford MEST-C score, n (%)	Placebo (N=9)	Cemdisiran (N=22)[a]
Mesangial Hypercellularity Lesions (M)		
0	2 (22.2)	7 (31.8)
1	7 (77.8)	13 (59.1)
Endocapillary Cellularity Lesions (E)		
0	6 (66.7)	15 (68.2)
1	3 (33.3)	5 (22.7)
Segmental Sclerosis Lesions (S)		
0	2 (22.2)	2 (9.1)
1	7 (77.8)	19 (86.4)
Interstitial Fibrosis/Tubular Atrophy Lesions (T)		
0	3 (33.3)	10 (45.5)
1	6 (66.7)	9 (40.9)
2	0	1 (4.5)
Cellular/Fibrocellular Crescents (C)		
0	6 (66.7)	15 (68.2)
1	3 (33.3)	3 (13.6)
2	0	2 (9.1)

[a]Missing cemdisiran values: M=2, E=2, S=1, T=2, C=2.

Cemdisiran Treatment Resulted in a Rapid and Sustained Decrease in C5 Protein Level and Complement Activity Compared with Placebo (Exploratory Endpoints)





No. of Patients:

Placebo	9	9	9	9	9	9	8	7	8
Cemdisiran	22	21	20	20	21	21	20	19	20

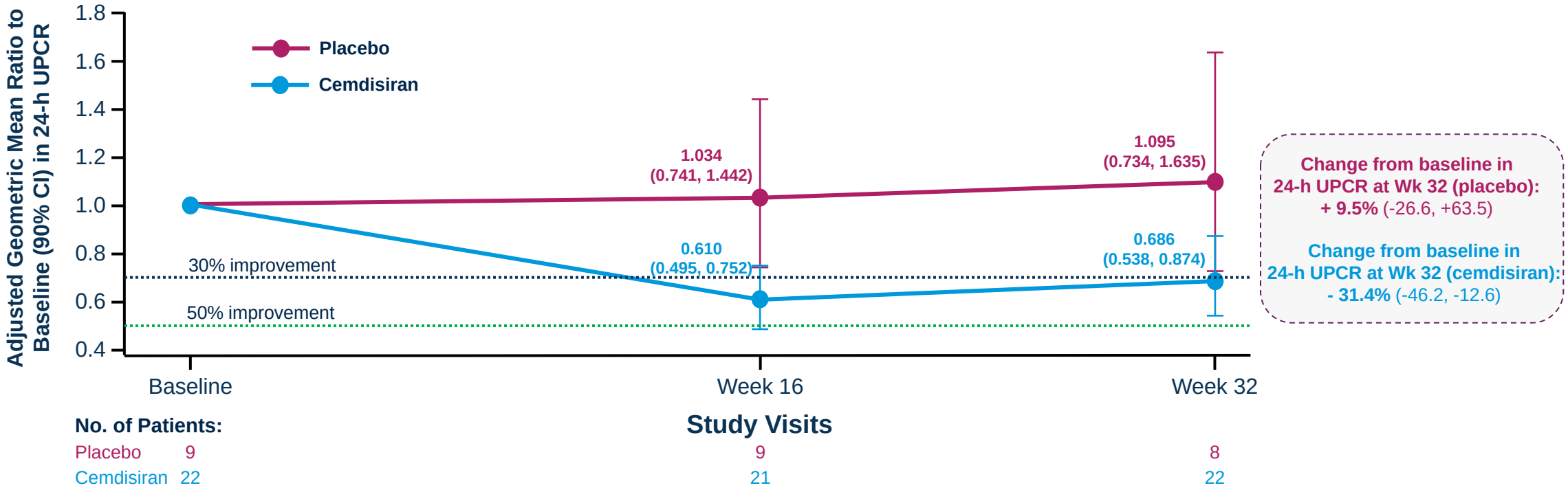
Placebo	9	9	9	9	9	9	8	7	8
Cemdisiran	22	21	20	21	21	22	20	19	20

Error bars are SD. Where error bars for cemdisiran are not visible it is due to small range.

BL, baseline; C5, C5 component of the complement pathway; CCP, complement classical pathway; SD, standard deviation.

Cemdisiran Treatment Led to a Clinically Meaningful Proteinuria Reduction Compared with Placebo at Week 32 (Primary Endpoint)

- Change from baseline in 24-hour UPCR compared with placebo at Week 32 was **-37.4%** (90% CI: -61.0, 0.5)[a]



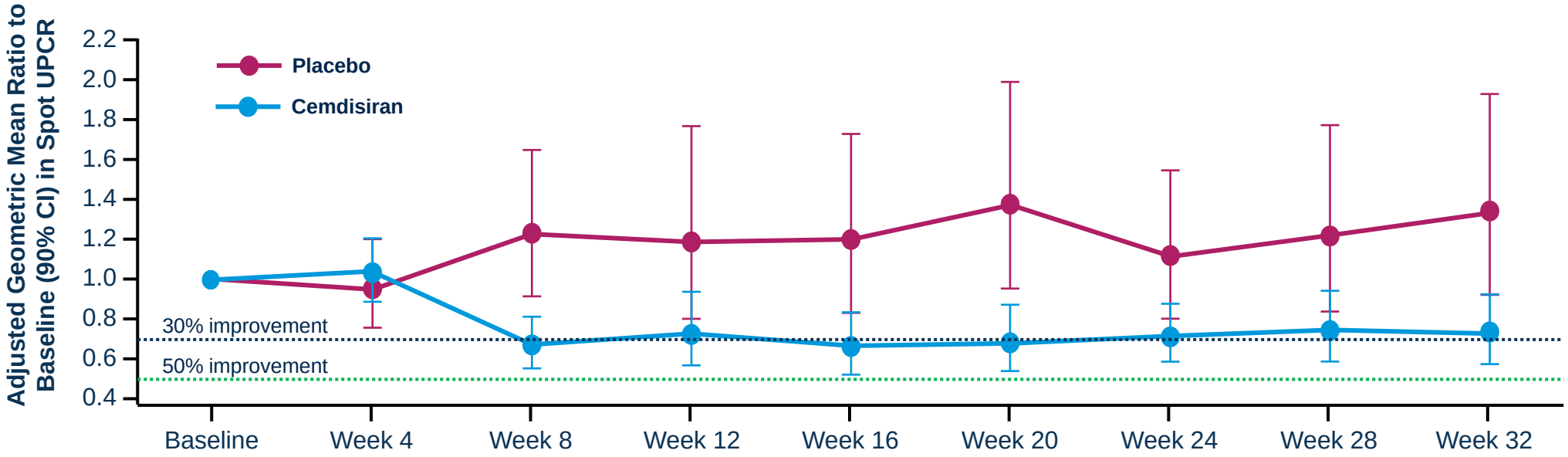
No. of Patients:	Baseline	Week 16	Week 32
Placebo	9	9	8
Cemdisiran	22	21	22

[a]Placebo-adjusted geometric mean percent change and 90% CI. A mixed-effect model repeated-measures approach was adopted, where the outcome variable was analyzed in log-scale and the model included fixed effects of treatment, scheduled visits, interaction term of treatment and scheduled visits, baseline 24-hour UPCR in log-scale, and patient as a random effect; the model-based least squares mean difference was then transformed back to the original UPCR scale. Negative numbers reflect a decrease in proteinuria. This Phase 2 study was descriptive only and did not include statistical hypothesis testing. At baseline, the mean (SD) 24-hour UPCR (g/g) values were 1.6 (1.0) in the cemdisiran group and 2.0 (0.8) in the placebo group.

CI, confidence interval; h, hour; SD, standard deviation; UPCR, urine protein to creatinine ratio; Wk, week.

Cemdisiran Treatment Led to a Clinically Meaningful Reduction in Spot UPCR Compared with Placebo at Week 32 (Secondary Endpoint)

- Change from baseline in spot UPCR compared with placebo at Week 32 was **-45.8%** (90% CI: -60.1, -26.3)[a]
- Monthly spot UPCR assessment of proteinuria shows similar evidence of efficacy to 24-hour UPCR, with onset of effect by Week 8 that remained stable over time



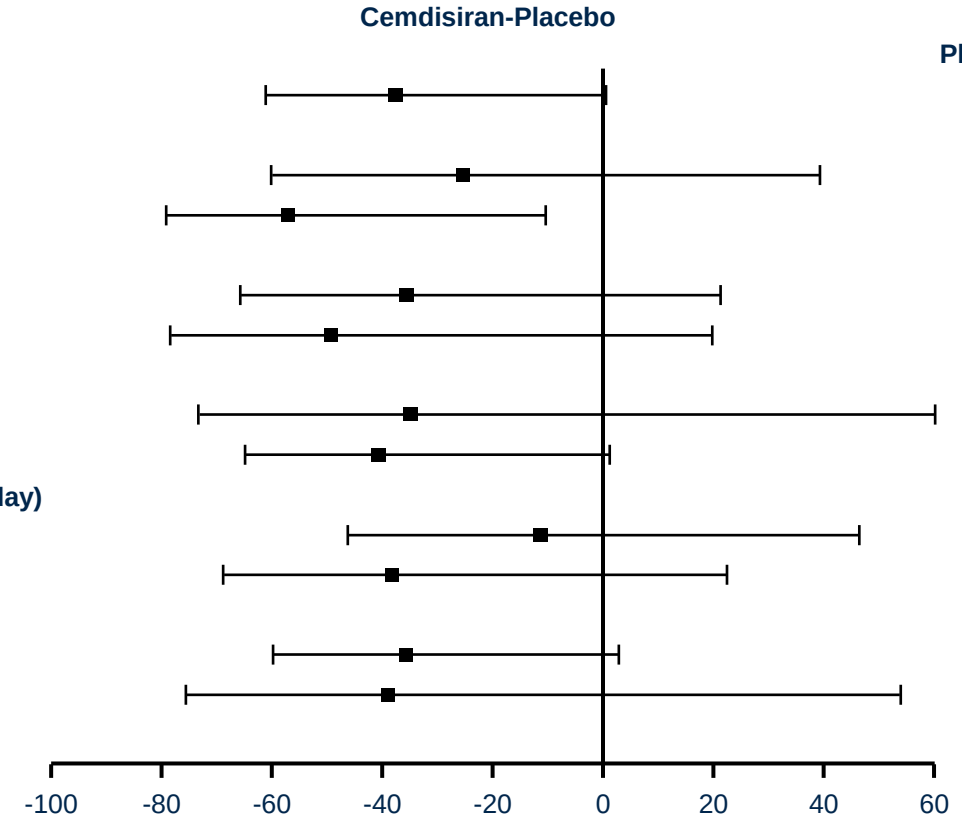
No. of Patients:

Placebo	9	9	9	8	9	9	8	7	8
Cemdisiran	22	21	20	20	21	22	20	19	20

[a]Placebo-adjusted geometric mean percent change and 90% CI. Negative numbers reflect a decrease in proteinuria. This Phase 2 study was descriptive only and did not include statistical hypothesis testing. At baseline, the mean (SD) baseline spot UPCR (g/g) values were 1.8 (1.2) in the cemdisiran group and 1.9 (1.2) in the placebo group.

CI, confidence interval; UPCR, urine protein to creatinine ratio.

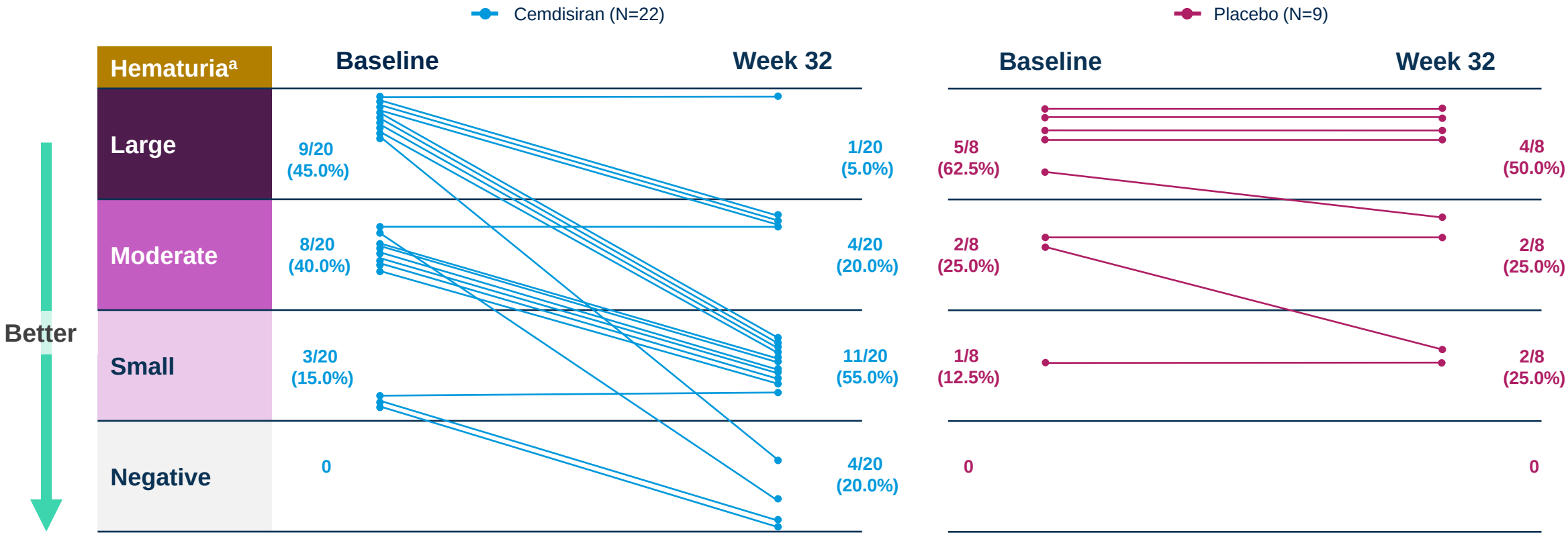
Improvements with Cemdisiran Treatment in 24-hour UPCR Compared with Placebo at Week 32 were Consistent in Pre-Defined Subgroups



Subgroup	Placebo-Adjusted GM % Change	90% CI
Overall (N=31)	-37.367	(-60.951, 0.460)
Age at time of consent		
<Median (N=15)	-25.357	(-59.935, 39.064)
≥Median (N=16)	-56.762	(-79.180, -10.206)
Gender		
Male (N=16)	-35.398	(-65.671, 21.383)
Female (N=15)	-49.056	(-78.310, 19.654)
Race		
Asian (N=16)	-34.560	(-73.221, 59.915)
Non-Asian (N=15)	-40.271	(-64.674, 0.990)
Baseline 24-hour urine protein (g/day)		
<2 (N=11)	-11.188	(-46.042, 46.179)
≥2 (N=20)	-38.000	(-68.531, 22.153)
Baseline eGFR (ml/min/1.73m^2)		
<60 (N=15)	-35.649	(-59.650, 2.630)
≥60 (N=16)	-38.668	(-75.532, 53.734)

CI, confidence interval; eGFR, estimated glomerular filtration rate; GM, geometric mean; UPCR, urine protein to creatinine ratio.

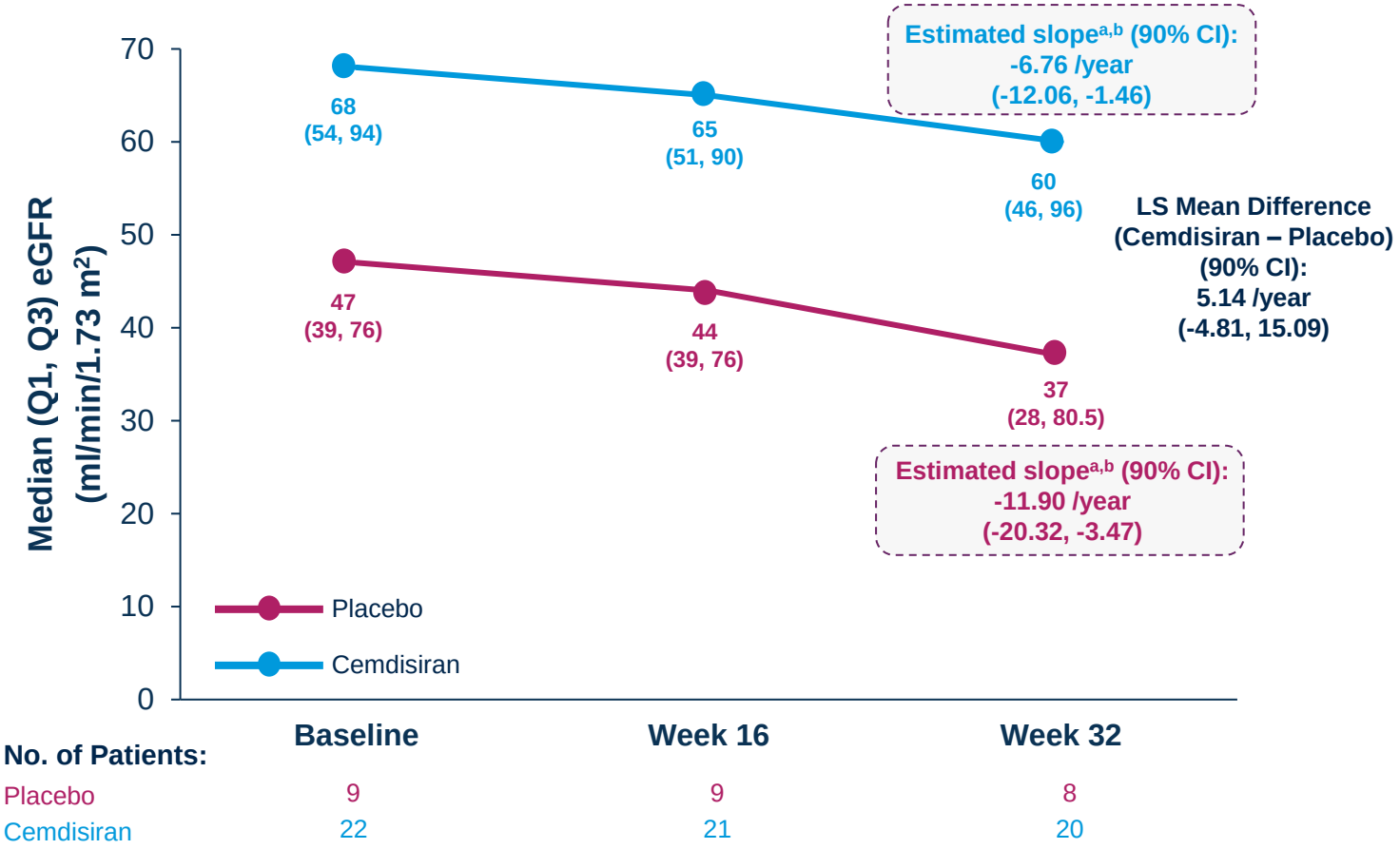
A Higher Proportion of Patients Receiving Cemdisiran Had Improvement in Hematuria at Week 32 Compared with Placebo (Secondary Endpoint)



- At Week 32, 77.2% of cemdisiran-treated patients showed improvement in hematuria grade from baseline compared with 22.2% of placebo-treated patients (dipstick analysis)
- No patient in either group worsened hematuria grade

[a]Hematuria measured by urine dipstick in mITT population, using light reflectance spectroscopy method. Hematuria category indicates reference range from dipstick color change. Percentage of patients in each category at Baseline and Week 32 is calculated using the total number of evaluable patients in the treatment group as the denominator.

Preliminary Data Suggest eGFR Trend May be Consistent with Effects on Proteinuria Over 32 Weeks of Treatment (Exploratory Endpoint)



eGFR	Placebo	Cemdisiran
Baseline	n=9	n=22
Actual: median (Q1, Q3), ml/min/1.73 m²	47 (39, 76)	68 (54, 94)
Week 16	n=9	n=21
Change from Baseline: median (Q1, Q3), ml/min/1.73 m²	-4 (-8, 0)	0 (-5, 5)
Week 32	n=8	n=20
Change from Baseline: median (Q1, Q3), ml/min/1.73 m²	-6 (-10, -3)	0 (-7, 4)

[a]The random coefficient model for eGFR includes baseline eGFR, treatment, time from baseline assessment in years (baseline time denoted as 0), and the interaction of treatment and time as fixed effects and intercept, time as random effects. Restricted maximum likelihood method is used. Asymptotic standard errors are used to model the within-patient errors and degrees of freedom are computed using Kenward and Rogers method. [b]Estimated slope is LS mean estimate per year based on Week 36 data.

CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least squares; Q, quartile.

Cemdisiran Phase 2 IgAN Safety Summary (Double-Blind Period)

- One death occurred in the cemdisiran arm due to cardiorespiratory collapse; not considered related to study drug
  - Considered both a serious and a severe AE, which occurred due to post-operative complications following bypass surgery
- No other AEs led to treatment or study discontinuation
- Two treatment interruptions occurred in the cemdisiran arm (9.1%); both were considered related to study drug
  - One patient (4.5%) had urticaria and one patient (4.5%) had an atopic dermatitis flare-up
- No severe infections or deaths or hospitalizations due to sepsis were reported, and no *Neisseria* spp, encapsulated bacteria or *Aspergillus* spp. infections were observed
- AEs ≥10% in the cemdisiran arm included injection-site reactions (ISRs, 40.9%) and peripheral edema (13.6%)
  - Most ISRs were mild and transient; peripheral edema was reported as mild and not related to cemdisiran
- No safety signals related to cemdisiran on liver function tests[a], hematology, or renal function

Cemdisiran Phase 2 IgAN Safety Summary[b]

At least one treatment-emergent AE, n (%)	Placebo (N=9)	Cemdisiran (N=22)
AEs	8 (88.9)	19 (86.4)
Serious AEs	0	1 (4.5)
Severe AEs	0	1 (4.5)
AEs leading to treatment interruption	1 (11.1)	2 (9.1)[c]
Death[d]	0	1 (4.5)

[a]Transient elevations in ALT and AST were observed with cemdisiran treatment, however, there were no safety concerns. [b]Treatment-emergent AEs includes events occurring or worsening on or after the first dose of study drug and through 28 days after the last dose or any study drug-related AEs. AEs with missing causality are considered related. AEs with missing severity are considered severe. [c]Both treatment interruptions in the cemdisiran arm were transient. [d]All fatal AEs are summarized regardless of treatment-emergent classification.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IgAN, immunoglobulin A nephropathy; spp, species.

Summary

- As previously presented[1], monthly subcutaneous doses of cemdisiran led to a clinically meaningful reduction from baseline in 24-hour UPCR observed at Week 32 relative to placebo
  - 37.4% reduction in 24-hour UPCR observed at Week 32 relative to placebo
  - Improvements were consistent across the pre-defined subgroups

- Circulating C5 levels were robustly lowered with cemdisiran treatment compared with placebo, with the timing of this pharmacodynamic effect consistent with the Week 8 onset of effect observed in the spot urine data

- Cemdisiran resulted in a rapid and sustained decrease in complement activity (CCP) compared with placebo

- Early analyses of the eGFR trend suggest slower decline in eGFR in cemdisiran-treated participants as compared with placebo

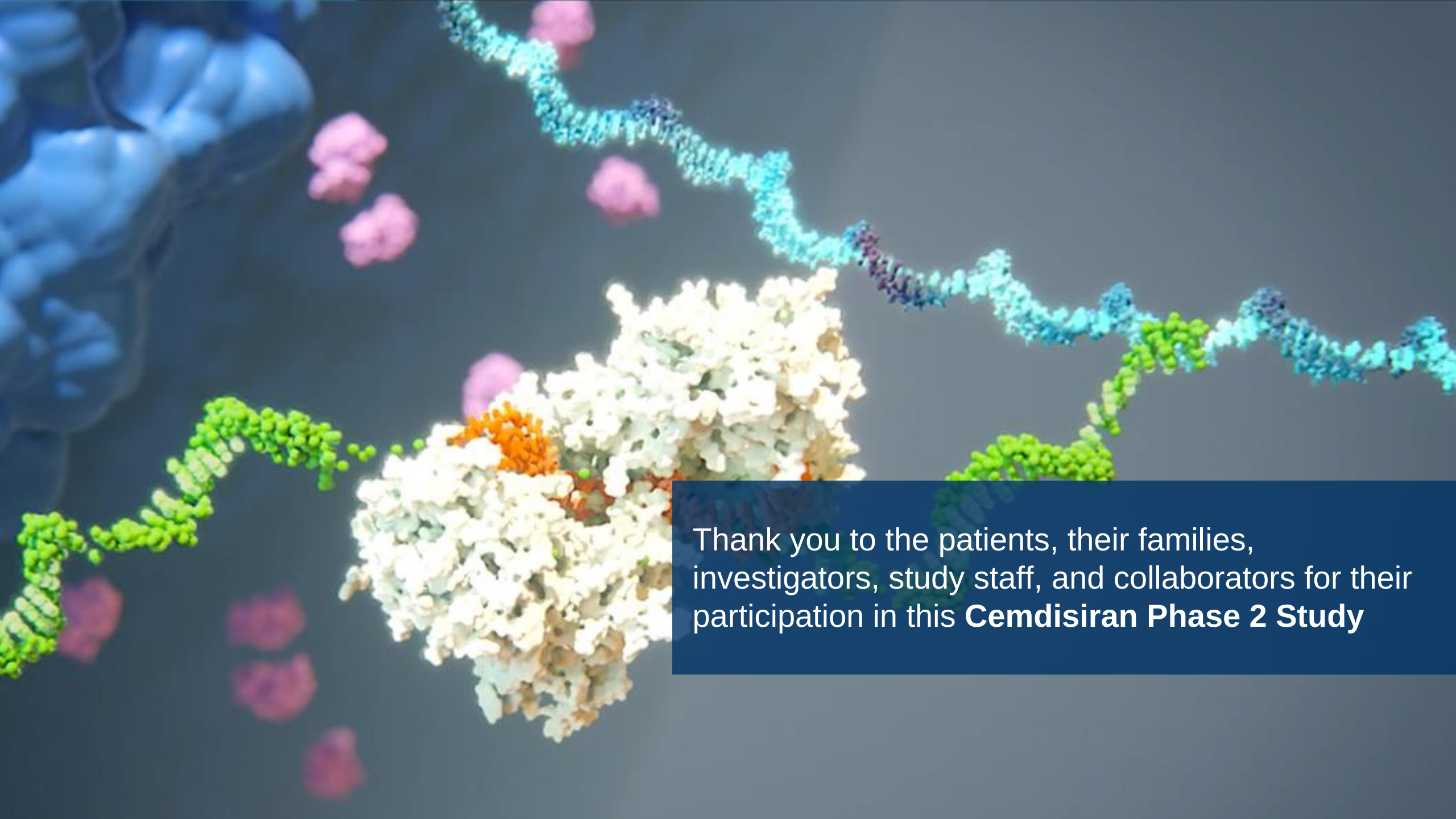
- While not a validated surrogate endpoint in IgAN[2], hematuria also showed a trend towards improvement with cemdisiran compared with placebo

- Cemdisiran was generally well tolerated in patients with IgAN; the most common AE was injection site reactions which were generally mild and transient

- These data support further evaluation of cemdisiran as a potential therapy in IgAN

AE, adverse events; C5, C5 component of the complement pathway; CAP, complement alternative pathway; CCP, complement classical pathway; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; UPCR, urine protein to creatinine ratio.

1. Barrett et al, 2022. Presented as a Poster at *18th European Meeting on Complement in Human Disease (EMCHD);* 2. FDA. Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure: https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure. Accessed September 2022.



Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in this **Cemdisiran Phase 2 Study**