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

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Summary

- **Monthly subcutaneous doses of cemdisiran led to a clinically meaningful reduction 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**
  - **31.8% of patients treated with cemdisiran (vs 12.5% of placebo-treated patients) achieved ≥50% reduction in 24-hour UPCR at Week 32**
- **Spot urine data are consistent with 24-hour urine data and remain stable over time, with initial treatment effect emerging at Week 8**
- **Cemdisiran was generally well tolerated in patients with IgAN**
- **These data support further evaluation of cemdisiran as a potential therapy in IgAN**

Introduction

Disease Background

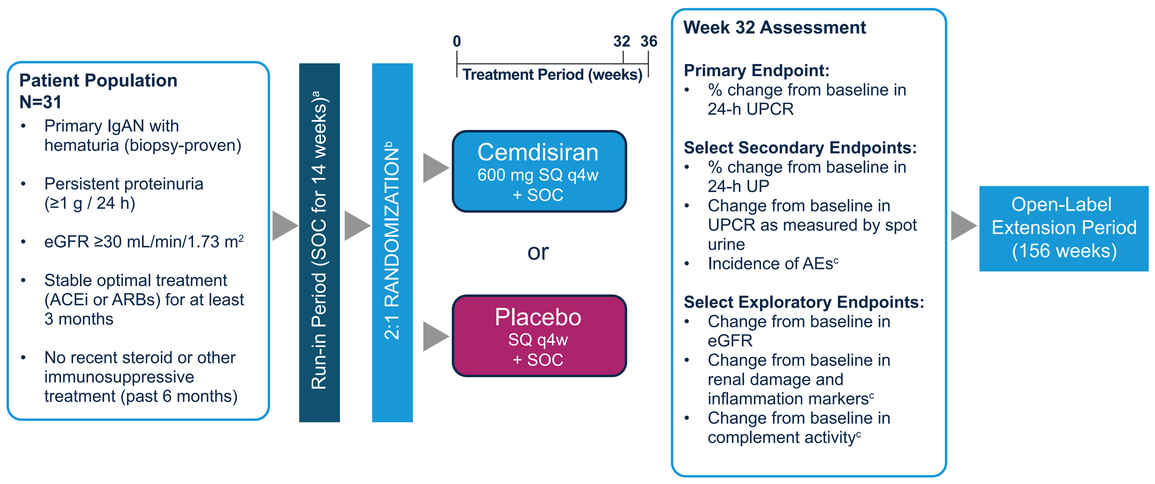
- IgAN is the most common type of glomerulonephritis
  - ~2.5 out of 100,000 individuals are affected each year, with some racial and ethnic variations[1,2]
- Clinical features can include hematuria, proteinuria, kidney injury, and hypertension[1]
  - High-grade proteinuria, particularly persistent proteinuria, is a strong risk factor for CKD progression[3]
- Disease results from IgA deposits in the glomerular mesangium, which activate an immunologic response that includes complement activation and promotion of inflammatory mediators[1,4]
- Treatment options are currently limited for patients with IgAN; management strategies aim to reduce proteinuria and control hypertension[1,4]
  - Intensive immunosuppression may be considered for severe disease but treatment efficacy is limited and toxicity can be high
  - Patients can progress to kidney failure with earlier treatment likely linking to better outcomes[5]
- There remains an unmet need for effective, disease-specific treatment options with fewer side effects

Cemdisiran

- 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
  - Demonstrated rapid and robust C5 suppression and an acceptable safety profile in healthy subjects[6]
- Cemdisiran was investigated in a phase 2, randomized, double-blind, placebo-controlled study (NCT03841448) in adult patients with IgAN who excrete >1 g of urine protein per day despite SOC

Methods

Cemdisiran Phase 2 IgA Nephropathy Study Design



[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.

Results

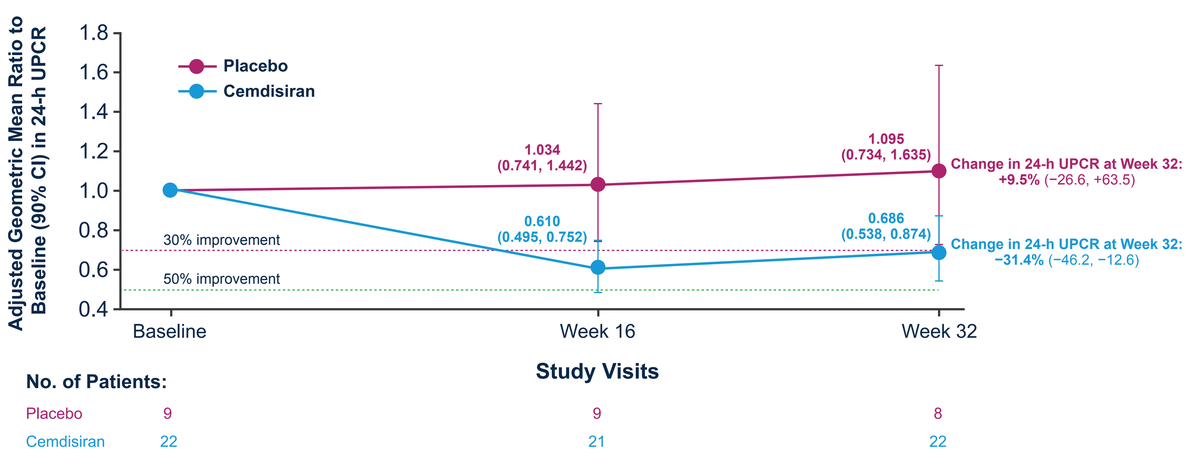
Demographic and Baseline Disease Characteristics

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

	Placebo (N=9)	Cemdisiran (N=22)
Age, mean (SD) (years)	37.6 (10.4)	40.5 (10.1)
Male, n (%)	3 (33.3)	13 (59.1)
Race, n (%)		
Asian	4 (44.4)	12 (54.5)
White	4 (44.4)	8 (36.4)
Other/Missing	1 (11.1)	2 (9.1)
BMI, mean (SD) (kg/m²)	26.8 (4.9)	30.4 (5.3)
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 h)	2.9 (1.3)	2.5 (1.5)
24-hour UPCR, mean (SD) (g/g)	2.0 (0.8)	1.6 (1.0)
eGFR, mean (SD) (mL/min/1.73 m²)	61 (33)	72 (27)
No ACEi or ARB received	1 (11.1)	1 (4.5)

Cemdisiran Treatment Led to a Clinically Meaningful Proteinuria Reduction Compared with Placebo at Week 32

- Primary endpoint of change from baseline in 24-hour UPCR compared with placebo at Week 32 was **–37.4%** (90% CI: –61.0, 0.5)[a]
- Secondary endpoint of change from baseline in 24-hour urine total protein compared with placebo at Week 32 was **–36.2%** (90% CI: –61.6, 6.0)[a] (data not shown)



No. of Patients:

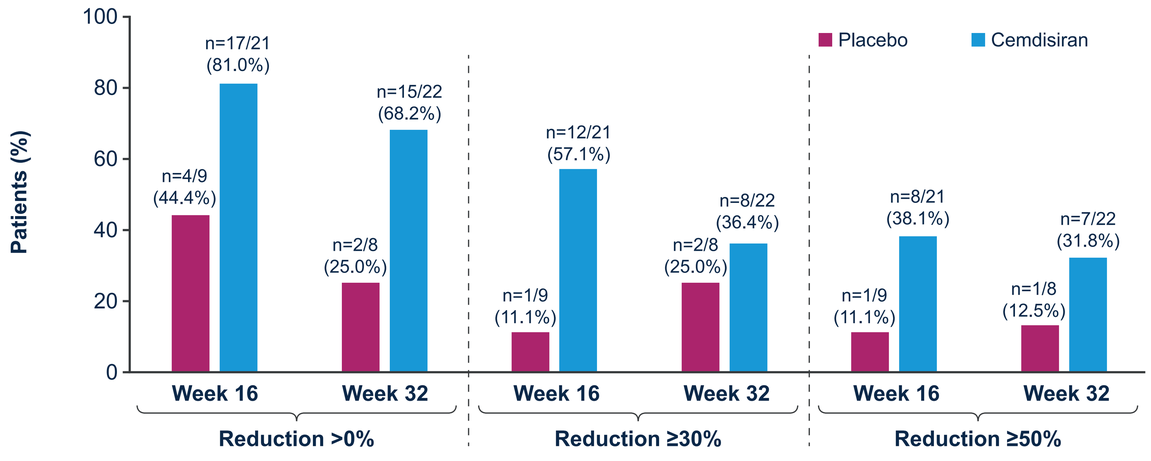
Placebo	9	9	8
Cemdisiran	22	21	22

[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. UPCR by spot urine at Week 32 was analyzed in a similar manner as appropriate. 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 1.8 (1.2) in the cemdisiran group and 2.0 (0.8) in the placebo group.

Higher Proportion of Patients Demonstrated Meaningful Reductions in 24-hour UPCR with Cemdisiran Compared with Placebo at Week 32

- **31.8%** of patients treated with cemdisiran achieved ≥50% reduction in 24-hour UPCR at Week 32, compared with 12.5% of placebo-treated patients[a]

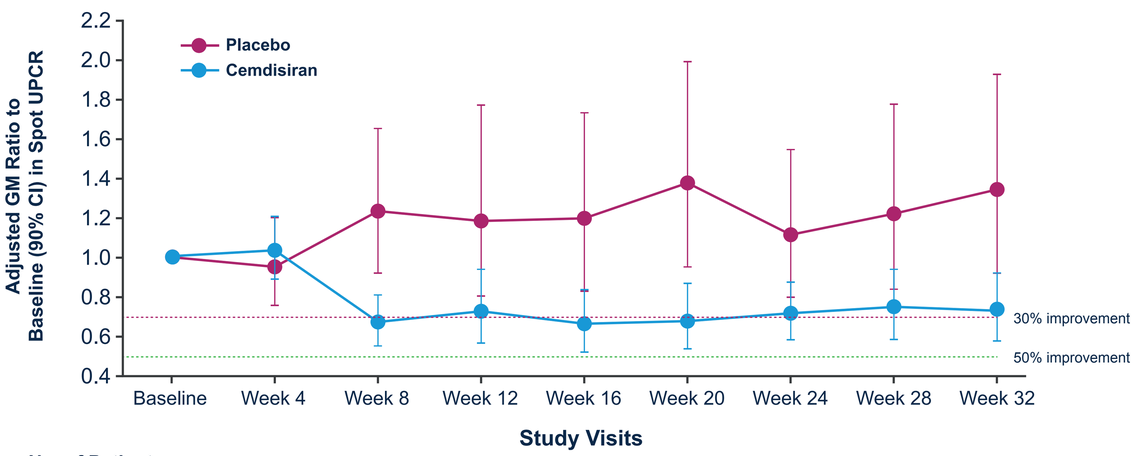
Proportion of Patients Achieving 24-hour UPCR Thresholds



[a]This Phase 2 study was descriptive only and did not include statistical hypothesis testing.

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

- Secondary endpoint of 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]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 (2.1) in the cemdisiran group and 1.9 (1.2) in the placebo group.

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

- No AEs led to treatment or study discontinuation
- One death occurred in the cemdisiran treatment arm due to cardiorespiratory collapse and was not considered related to study drug
  - Considered both a serious and a severe AE (see table), which occurred due to post-operative complications following bypass surgery
- 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
- AEs ≥10% in the cemdisiran arm included injection-site reactions (ISRs, 40.9%) and peripheral edema (13.6%)
  - The majority of ISRs were mild and transient; peripheral edema was reported as mild and not related to cemdisiran
- No safety signals regarding liver function tests[a], hematology, or renal function related to cemdisiran

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]
AEs leading to treatment discontinuation	0	0
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.

Thank you to the patients, their families, investigators, study staff, and collaborators for their continued participation in the cemdisiran Phase 2 IgAN study

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Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; C5, C5 component of the complement pathway; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ER, exposure-adjusted event rate per 100 PY; ESRD, end-stage renal disease; IgAN, immunoglobulin A nephropathy; MAC, membrane attack complex; OLE, open-label extension; PY, patient-years; q4w, every 4 weeks; SD, standard deviation; SOC, standard of care; SQ, subcutaneously; TEAE, treatment-emergent AE; UP, urine protein; UPCR, urine protein to creatinine ratio.

References: **1.** Rajasekaran A et al. *Am J Med Sci* 2021;361:176–164; **2.** McGrogan A et al. *Nephrol Dial Transplant* 2011; 26:414–430; **3.** Berthoux F et al. *Semin Nephrol* 2008;28:4–9; **4.** Floege J et al. *Kidney Int* 2019;95:268–280; **5.** Berthoux FC et al. *Semin Nephrol* 2008 28:4–9; **6.** Badri P et al. *Clin Pharmacokinet* 2021;60:365–378.