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RESEARCH ARTICLE

Results of a phase 1/2 study of cemdisiran in healthy subjects and patients with paroxysmal nocturnal hemoglobinuria

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Abstract

Complement dysregulation underpins the physiopathology of paroxysmal nocturnal hemoglobinuria (PNH). Cemdisiran, an RNA interference investigational treatment, silences complement component 5 (C5) expression in the liver. Previously reported results showed sustained reduction in C5 levels following cemdisiran monotherapy, with >90% reduction in patients with PNH.

This phase 1/2 study evaluated single (Part A, $n = 32$; 50–900 mg) or multiple (Part B, $n = 24$; 100–600 mg) ascending doses of cemdisiran or placebo (double-blind, randomized 3:1) in healthy adults, or cemdisiran in patients with PNH who were naive to, or receiving, eculizumab (Part C, $n = 6$; 200 or 400 mg weekly; open-label). The primary objective was to assess the safety and tolerability of cemdisiran. Other assessments included change in complement activity, lactate dehydrogenase levels, and inhibition of hemolysis following cemdisiran treatment.

Cemdisiran was generally well tolerated in this study. Overall, 75%, 89%, and 100% of subjects in Parts A, B, and C, respectively, experienced ≥1 non-serious adverse event (AE). Most events were Grade 1 or 2 in severity and the most common AEs included nasopharyngitis and headache. Cemdisiran elicited robust, sustained reductions in the complement activity in healthy adults and patients with PNH. In Part C, exploratory analyses showed that cemdisiran monotherapy was insufficient to prevent hemolysis in patients with PNH as measured by serum lactate dehydrogenase levels. Cemdisiran and eculizumab combination therapy reduced the dose of eculizumab required to provide adequate control of intravascular hemolysis.

These results demonstrate a potential benefit of cemdisiran coadministration in patients who are inadequate responders to eculizumab alone.

KEYWORDS
cemdisiran, complement C5, paroxysmal nocturnal hemoglobinuria

1 | INTRODUCTION

The complement system is a key component of the innate immune system [1, 2]. Dysregulation of the complement cascade underlies several rare, life-threatening diseases such as paroxysmal nocturnal hemoglobinuria (PNH). PNH is caused by a somatic mutation in the phosphatidylinositol glycan class A gene in hematopoietic stem cells. This leads to a deficiency in glycosylphosphatidylinositol (GPI)-anchored complement-regulatory glycoproteins CD55 and CD59. The absence of these proteins in PNH red blood cells (RBCs) results in unrestrained complement component 3 (C3) and 5 (C5) activation, and therefore in the assembly of the membrane attack complex (MAC), leading to intravascular hemolysis [3, 4]. As a consequence of hemolysis, patients with PNH present with anemia, smooth muscle dystonia, fatigue, and hemoglobinuria. Thrombosis is the main cause of mortality if patients are left untreated [3].

Therapies targeting C5 and C3 (i.e., eculizumab, ravulizumab, and pegcetacoplan) have been shown to be effective for the treatment of PNH [5–7]. However, eculizumab and ravulizumab require intravenous administration, which can be burdensome to patients. In addition, despite treatment with eculizumab, some patients with PNH may experience breakthrough intravascular hemolysis at the end of a treatment cycle [8, 9]. Studies in patients with PNH suggest that the recommended eculizumab dosing regimen may be inadequate to maintain complete complement blockade in some patients, who may require a higher dose to reduce ongoing intravascular hemolysis [3, 10]. Response to eculizumab can also vary due to C5 gene polymorphisms (e.g., Arg885His) [11]. Thus, there remains a need for alternative treatment options for PNH and other complement-mediated diseases.

Cemdisiran (ALN-CC5) is an investigational, subcutaneously administered small interfering RNA (RNAi) conjugated to *N*-acetylgalactosamine (GalNAc) that inhibits C5 synthesis in hepatocytes, the major source of C5 biosynthesis [12]. RNAi is an endogenous mechanism for the control of gene expression whereby target messenger RNA is cleaved by small interfering RNAs bound to the RNA-induced silencing complex [13–15]. Cemdisiran, the first investigational RNAi therapeutic to target the complement system, is in development for the treatment of complement-mediated disorders [16]. We have previously reported the pharmacokinetics (PK) and pharmacodynamics (PD) of cemdisiran from the phase 1/2 study in healthy volunteers and patients with PNH. After subcutaneous administration of a single dose, cemdisiran levels peaked within 0.5–1 h and declined rapidly by approximately 8 h [17] Cemdisiran treatment resulted in robust, sustained, and dose-dependent reductions in serum C5 levels in healthy adults and patients with PNH, reduced lactate dehydrogenase (LDH) levels in patients with PNH, and demonstrated an acceptable safety profile with the majority of adverse events (AEs) being mild to moderate in severity [17]. Here, we report comprehensive safety data, as well as the effects of cemdisiran on complement activity and hemolysis, from the phase 1/2 study.

2 | MATERIALS AND METHODS

2.1 | Study oversight

This multicenter, phase 1/2, randomized, double-blind, placebo-controlled, single-ascending dose (SAD) and multiple-ascending dose (MAD) study in healthy adults and adult patients with PNH (ALN-CC5-001; NCT02352493; EudraCT no. 2014-002462-69) was initiated in January 2015 and conducted at three centers in the United Kingdom and one center in Spain. The study was performed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki [18, 19]. The protocol was approved at each study center by an institutional review board and/or independent ethics committee. A Safety Review Committee (SRC) regularly reviewed data to monitor appropriateness of dosing/dose escalations. All participants provided the written informed consent.

2.2 | Study objectives and design

The primary objective was to evaluate safety and tolerability of SAD or MAD of cemdisiran in healthy adults and multiple doses in patients with PNH. Secondary objectives were to characterize cemdisiran PK and PD effects on C5 levels (previously reported [17]) and complement activity. Exploratory objectives included assessment of PD effects of cemdisiran on inhibition of complement pathway activity in healthy adults and in patients with PNH, and on LDH levels (previously reported [17]) in patients with PNH. The clinical activity of cemdisiran was assessed as monotherapy in patients with PNH with the original goal of transitioning patients on eculizumab to cemdisiran monotherapy.

Full details of the study design and participants have been previously published [17]. An overview of the study design is shown in Figure S1, and additional details are provided in the Supporting Information. In Part A, healthy subjects were randomized 3:1 to receive a single dose of cemdisiran (ranging from 50–900 mg) or placebo in a double-blind manner. Part B was a randomized (3:1), placebo-controlled, double-blind, MAD phase in healthy adults. In Part B, participants received one of the following regimens: 100, 200, or 400 mg cemdisiran weekly (qw) for 5 doses; 200 mg qw for 5 doses followed by every other week (q2w) for 4 doses; 200 mg qw for 5 doses followed by monthly (qm) for 2 doses; or 600 mg q2w for 7 doses as determined by the SRC assessment of safety, tolerability, and available PD data from Part A. Part C was an open-label, multiple-dose phase in patients with PNH. Patients were either eculizumab-naive or receiving stable maintenance dosing. Patients on stable dosing of eculizumab continued to receive eculizumab concomitantly with cemdisiran. It was planned that in Part C patients would receive cemdisiran 200 or 400 mg qw for up to 17 weeks; dosing was stopped as described in Section 3.

2.3 | Participants

Subjects eligible for Parts A and B were 18–45 years of age, with 12-lead electrocardiogram (ECG), body mass index (BMI), and blood pressure within the normal range. Subjects eligible for Part C had a documented PNH diagnosis, and elevated LDH (≥1.5 × upper limit of normal [ULN]) if eculizumab-naive, or history of elevated LDH if receiving a stable eculizumab dose.

2.4 | Assessments

Safety variables consisted of AEs, including relationship to study drug (defined as AEs considered to be related or possibly related to study medication by the investigator), and serious AEs (SAEs; graded using Common Terminology Criteria for Adverse Events [CTCAE] version 4.0). Vital signs, physical examination, 12-lead ECG, and clinical laboratory parameters were also assessed.

PD analyses included serum complement activity based on complement alternative pathway (CAP) and complement classical pathway (CCP) enzyme-linked immunosorbent assays (ELISAs). Samples were collected at screening, Day −1, and Day 0 for the baseline assessment of CAP and CCP. Serum C5 was measured by liquid chromatography/tandem mass spectrometry as described previously [17]. Exploratory analyses included complement hemolytic activity as assessed by a sensitized sheep RBC lysis assay, and serum LDH levels (Part C only). Study participants were monitored for AEs through Day 70 (post-dose follow-up period) in Part A, and through Day 140 post-dose in Parts B and C.

2.5 | Data analysis

Sample size was not determined based on power calculations. The safety analysis population comprised all participants who received ≥1 dose of study drug; PD analyses populations comprised all participants who received ≥1 dose of study drug and had ≥1 evaluable post-dose assessment. Data were summarized using descriptive statistics.

3 | RESULTS

3.1 | Participant demographics and disposition

3.1.1 | Parts A and B in healthy adults

Demographics for Parts A, B, and C have been previously reported [17]. A total of 56 healthy adults received cemdisiran (n = 42) or placebo (n = 14). In Part A, 20 healthy adults across 5 cohorts (n = 3/cohort) received single-dose cemdisiran (n = 15; range 50–900 mg) or placebo (n = 5). An additional subgroup of 12 healthy Japanese adults received single doses of 50 mg (n = 3), 200 mg (n = 3), and 600 mg (n = 3) of cemdisiran or placebo (n = 3). Mean age in cemdisiran-treated subjects in Part A was 27 years (Table S1). In Part B, 24 healthy adults across six cohorts (n = 3/cohort) received multiple doses of cemdisiran (n = 18; range 100–600 mg) or placebo (n = 6). Mean age in cemdisiran-treated subjects in Part B was 28 years (Table S2).

3.1.2 | Part C in patients with PNH

Part C enrolled 6 patients with PNH: 3 eculizumab-naive and 3 on a stable maintenance regimen of eculizumab (Table 1). Mean age (range) was 44 (25–58) years and mean (SD) body weight was 71.6 (7.8) kg. Each eculizumab-naive patient had elevated LDH at baseline (412–1644 IU/L; LDH reference range, 135–214 IU/L). As previously reported, cemdisiran treatment was halted after evaluation of monotherapy efficacy in 3 patients as LDH levels remained >1.5 × ULN in eculizumab-naive patients, despite marked reductions in C5 levels and complement activity [17]. Following data review, cemdisiran was discontinued in all patients with PNH for the remainder of the study. It was then assessed whether reduced maintenance eculizumab doses could prevent intravascular hemolysis in combination with the ongoing effects of cemdisiran. Eculizumab-naive patients began a reduced maintenance eculizumab regimen of 600 mg q4w with no loading dose. Patients on eculizumab treatment prior to study entry transitioned to a reduced maintenance eculizumab regimen of 900 mg q4w (Table 1).

3.2 | Safety

3.2.1 | Parts A and B in healthy adults

AEs were reported in 6 (75.0%) placebo-treated subjects and 18 (75.0%) cemdisiran-treated subjects in Part A (Table 2), and 6 (100%) placebo-treated and 16 (88.9%) cemdisiran-treated subjects in Part B (Table 3). All AEs were Grade 1 or 2 severity. The most frequent AEs in the cemdisiran groups in Parts A and B were nasopharyngitis (41.7% and 44.4%, respectively) and headache (25.0% and 16.7%, respectively). No SAEs or discontinuations due to AEs were reported. AEs considered possibly related to study treatment were reported in 4 subjects in Part A (placebo: 1; cemdisiran: 3) and 9 subjects in Part B (placebo: 1; cemdisiran: 8). The most common related AEs were administration-site conditions and infections. Additional AEs related to treatment were sleep disorders (somnolence and insomnia), nausea, aphthous stomatitis, headache, and contusion. Injection-site reactions (ISRs) were reported in 3 patients in Part A and 4 patients in Part B; none met the CTCAE criteria for ISR. Most patients had no clinically meaningful changes in clinical laboratory parameters, 12-lead ECG, vital signs, or physical examinations in Parts A or B. The proportion of healthy volunteers with AEs was similar in placebo and cemdisiran groups in Parts A and B.

TABLE 1 Cemdisiran and eculizumab dosing schedule in patients with PNH in Part C.

	Cemdisiran treatment phase (up to 17 weeks)			Monitoring phase	
Patient	Eculizumab-naive or eculizumab dose	Cemdisiran dose	Total number of cemdisiran doses administered	Eculizumab dose	Date of transition to or start of lower dose of eculizumab
1	Naive	400 mg qw × 8	8	600 mg q4w[d] × 8 900 mg q2w × 2	Day 56
2	Naive	200 mg qw × 13 400 mg qw × 4	17	600 mg q4w[d] × 6	Day 140
3	Naive	200 mg qw × 13 400 mg qw × 4	17	600 mg q4w[d] × 6	Day 140
4	900 mg q2w[a]	400 mg qw × 4	4	900 mg q4w[d] × 9	Day 91
5	900 mg q2w[a]	400 mg qw × 3	3	900 mg q4w[d] × 6	Day 84
6	1200 mg q2w[b] → 900 mg q2w[c]	200 mg qw × 12	12	900 mg q2w × 5 900 mg q4w[d] × 5	Day 140

[a]Labeled dose for maintenance for PNH.
[b]Greater than labeled dose for maintenance for PNH (inadequate responder).
[c]Eculizumab 900 mg q2w dose started at Study Week 8 (Day 57).
[d]Reduced dose and/or frequency of dosing compared with labeled dose for maintenance for PNH. qw, once weekly; q2w, every other week; q4w, every 4 weeks; PNH, paroxysmal nocturnal hemoglobinuria.

TABLE 2 Overview of AEs in healthy adults receiving a single dose of cemdisiran or placebo (3:1) in Part A.

		Cemdisiran dose cohort								
n (%)	Placebo *n* = 8	50 mg *n* = 3	50 mg Japanese *n* = 3	200 mg *n* = 3	200 mg Japanese *n* = 3	400 mg *n* = 3	600 mg *n* = 3	600 mg Japanese *n* = 3	900 mg *n* = 3	All cemdisiran treated *n* = 24
Any AE	6 (75.0)	0	3 (100)	2 (66.7)	2 (66.7)	3 (100)	3 (100)	2 (66.7)	3 (100)	18 (75.0)
SAE	0	0	0	0	0	0	0	0	0	0
Discontinued due to AE	0	0	0	0	0	0	0	0	0	0
AE possibly related to study drug	1 (12.5)	0	1 (33.3)	1 (33.3)	0	0	1 (33.3)	0	0	3 (12.5)
AEs in ≥2 subjects										
Nasopharyngitis	3 (37.5)	0	2 (66.7)	1 (33.3)	1 (33.3)	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)	10 (41.7)
Headache	1 (12.5)	0	1 (33.3)	1 (33.3)	0	0	2 (66.7)	0	2 (66.7)	6 (25.0)
Influenza-like illness	0	0	1 (33.3)	0	1 (33.3)	0	1 (33.3)	0	1 (33.3)	4 (16.7)
Nausea	2 (25.0)	0	0	0	1 (33.3)	0	2 (66.7)	0	0	3 (12.5)
Injection site pain	0	0	0	0	0	0	2 (66.7)	0	0	2 (8.3)
Vulvovaginal candidiasis	0	0	1 (33.3)	0	0	1 (33.3)	0	0	0	2 (8.3)
Arthralgia	0	0	0	0	0	1 (33.3)	1 (33.3)	0	0	2 (8.3)
Toothache	3 (37.5)	0	0	0	0	0	0	0	0	0

Abbreviations: AE, adverse event; SAE, serious adverse event.

3.2.2 | Part C in patients with PNH

In Part C, ≥1 AE was reported in all 6 patients (Table 4). AEs were Grade 1 or 2 severity in all but 1 patient. There were no SAEs or discontinuations due to AEs. AEs reported by ≥2 patients were fatigue, headache, and oropharyngeal pain. No patients in the eculizumab-naive group experienced study drug-related AEs. One patient in the eculizumab-treated group experienced related AEs of administration-site conditions and one experienced a related AE of increased transaminases. Further details of safety are reported in Badri et al. [17].

TABLE 3 Overview of AEs in healthy adults receiving multiple doses of cemdisiran or placebo (3:1) in Part B.

		Cemdisiran dose cohort						
n (%)	Placebo *n* = 6	100 mg qw *n* = 3	200 mg qw *n* = 3	400 mg qw *n* = 3	600 mg q2w *n* = 3	200 mg qw/q2w *n* = 3	200 mg qw/qm *n* = 3	All cemdisiran treated *n* = 18
Any AE	6 (100)	2 (66.7)	3 (100)	3 (100)	3 (100)	2 (66.7)	3 (100)	16 (88.9)
SAE	0	0	0	0	0	0	0	0
Discontinued due to AE	0	0	0	0	0	0	0	0
AE possibly related to study drug	1 (16.7)	1 (33.3)	2 (66.7)	2 (66.7)	1 (33.3)	2 (66.7)	0	8 (44.4)
AEs in ≥2 subjects								
Nasopharyngitis	4 (66.7)	0	2 (66.7)	1 (33.3)	3 (100)	0	2 (66.7)	8 (44.4)
Diarrhea	0	0	1 (33.3)	2 (66.7)	0	0	0	3 (16.7)
Headache	2 (33.3)	1 (33.3)	2 (66.7)	0	0	0	0	3 (16.7)
Cough	0	1 (33.3)	1 (33.3)	1 (33.3)	0	0	0	3 (16.7)

Abbreviations: AE, adverse event; qm, every month; qw, every week; q2w, every other week; SAE, serious adverse event.

TABLE 4 Overview of AEs in patients with PNH receiving multiple doses of cemdisiran or eculizumab in Part C.

	Cemdisiran dose cohort		
n (%)	Eculizumab-treated *n* = 3	Eculizumab-naive *n* = 3	All cemdisiran treated *n* = 6
Any AE	3 (100)	3 (100)	6 (100)
SAE	0	0	0
Discontinued due to AE	0	0	0
AE possibly related to eculizumab[a]	1 (33.3)	0	1 (16.7)
AE related to cemdisiran[a,b]	2 (66.6)	0	2 (33.3)
AEs in ≥2 subjects			
Fatigue	2 (66.7)	1 (33.3)	3 (50.0)
Headache	1 (33.3)	1 (33.3)	2 (33.3)
Oropharyngeal pain	1 (33.3)	1 (33.3)	2 (33.3)

[a]Study drug-related AEs are deemed to be either "definitely related" or "possibly related" to the study drug by the investigator.
[b]One AE possibly related and one AE definitely related.
Abbreviations: AE, adverse event; PNH, paroxysmal nocturnal hemoglobinuria; SAE, serious adverse event.

3.3 | Pharmacodynamics

3.3.1 | Healthy adults on single (Part A) or multiple dose (Part B) cemdisiran

Previously reported results have shown that cemdisiran reduced C5 by ≥90% in healthy volunteers [17], including one individual with an Arg885His polymorphism in the C5 gene. In line with this, single and multiple cemdisiran doses also reduced CCP and CAP activity. In Part A, single 600 mg doses achieved inhibition of CCP activity of 87.3% ± 1.4% (up to 89% maximum inhibition) and CAP activity inhibition of 72.5% ± 7.5% (up to 81% maximum inhibition) (Figure 1A,B). In Part A, CCP and CAP activity reductions with single doses ≥200 mg ranged from 63.6% ± 2.5% to 87.3% ± 1.4% and 47.6% ± 3.2% to 72.5% ± 7.5%, respectively. In Part B, CCP (Figure 1C) and CAP (Figure 1D) activity reductions ranged from 75.9% ± 7.3% to 89.1% ± 1.9% and 68.4% ± 1.0% to 78.0% ± 5.7%, respectively, for all cohorts treated with ≥200 mg.

Dose-dependent reductions in sheep red blood cell (sRBC) lysis were observed in all cohorts compared with placebo (Figure 2). Single 600 and 900 mg doses resulted in up to 80.8% and 69.9% inhibition of complement hemolytic activity (sRBC lysis), respectively (Figure 2A). Multiple 600 mg q2w doses (highest dosage) achieved 86.8% inhibition of complement hemolytic activity (Figure 2B).

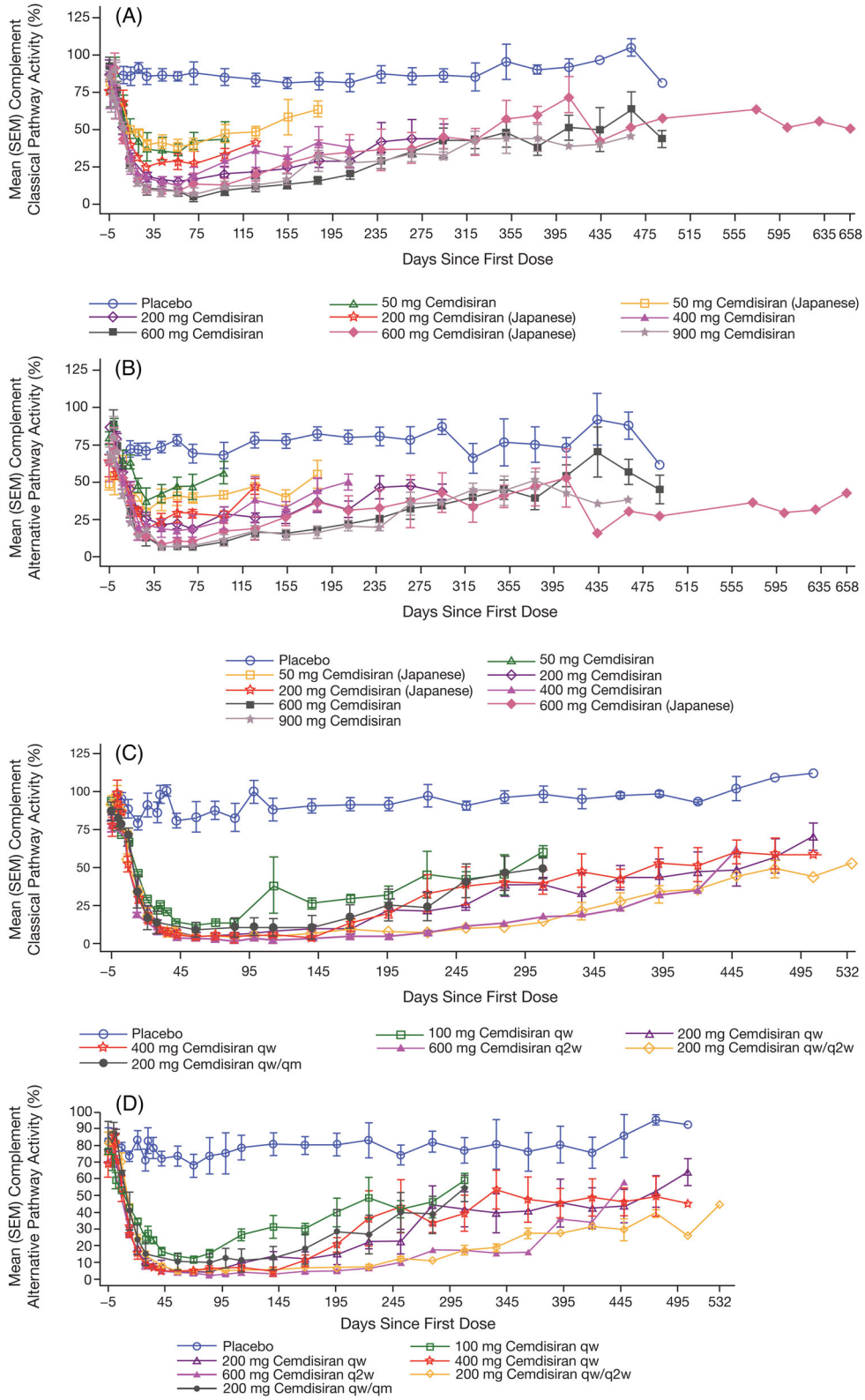

FIGURE 1 Mean ± SEM CCP and CAP relative to baseline following a single dose, Part A (a,b), or multiple doses, Part B (c,d), of cemdisiran or placebo in healthy adults. After complement activity had returned to near normal range, monitoring was discontinued. In Part A, only one patient was being monitored in the Japanese 600 mg cohort after Day 400. For Part B (c,d), the final cemdisiran dose was administered on Day 28 for the 100, 200, and 400 mg qw cohorts, and on Day 84 for the 200 mg qw/q2w, 600 mg q2w, and 200 mg qw/qm cohorts, with the exception of one patient in the 600 mg q2w group whose last cemdisiran dose was administered on Day 70. CAP, complement alternative pathway; CCP, complement classical pathway; qm, every month; qw, every week; q2w, every other week; SEM, standard error of the mean.

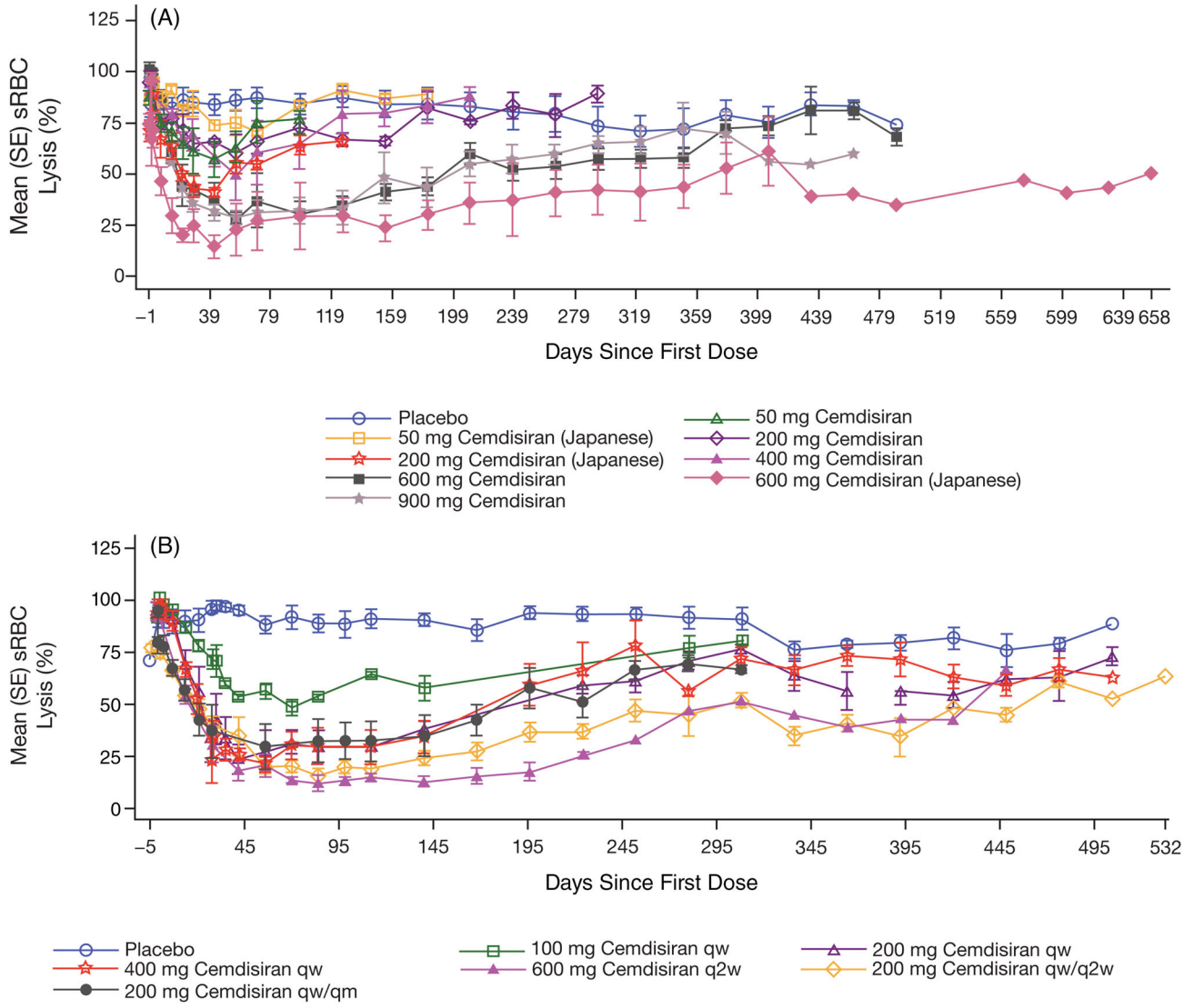

FIGURE 2 Mean (SE) sRBC lysis following a single dose, Part A (a) or multiple doses, Part B (b) of cemdisiran or placebo in healthy adults. For Part B (b), the final cemdisiran dose was administered on Day 28 for the 100, 200, and 400 mg qw cohorts, and on Day 84 for the 200 mg qw/q2w, 600 mg q2w, and 200 mg qw/qm cohorts, with the exception of one patient in the 600 mg q2w group whose last cemdisiran dose was administered on Day 70. sRBC, sheep red blood cell.

3.3.2 | Part C: eculizumab-naive patients with PNH on cemdisiran

Maximum decreases in CCP activity ranged from 91.0%–96.7% with cemdisiran treatment (Figure 3A–C), maximum decreases in CAP activity ranged from 89.3%–100%, and maximum inhibition of hemolysis ranged from 66.7%–81.5% (Figure 4A). The effects of cemdisiran on LDH levels in these patients with PNH have been previously described [17]. In Patient 1, LDH levels remained essentially unchanged and >1.5 × ULN throughout treatment (Figure 3A). In Patients 2 and 3, LDH decreased from baseline by up to 49.7% (Day 86) and 36.6% (Day 77), respectively (Figure 3B,C), but remained >1.5 × ULN through Day 112. Initiation of low-dose eculizumab following discontinuation of cemdisiran dosing led to additional lowering of LDH (Figure 3A–C).

3.3.3 | Part C: patients with PNH on maintenance eculizumab and cemdisiran

CCP and CAP activity were suppressed at baseline due to eculizumab treatment and remained suppressed with cemdisiran treatment (Figures 3D–F, 4B). In Patients 4 and 5, LDH levels were within the normal range at baseline and remained within the normal range during cemdisiran treatment except for one elevation (425 IU/L) in Patient 5 on Day 28 that was not related to an AE and had resolved by Day 56 (Table 1; Figure 3D,E).

Patient 6 had persistent chronic intravascular hemolysis at baseline, as evidenced by markedly elevated serum LDH and high CCP (Figure 3F) and CAP activity at the study entry (Figure 4B). During cemdisiran treatment, LDH levels decreased from 3.8 × ULN at baseline

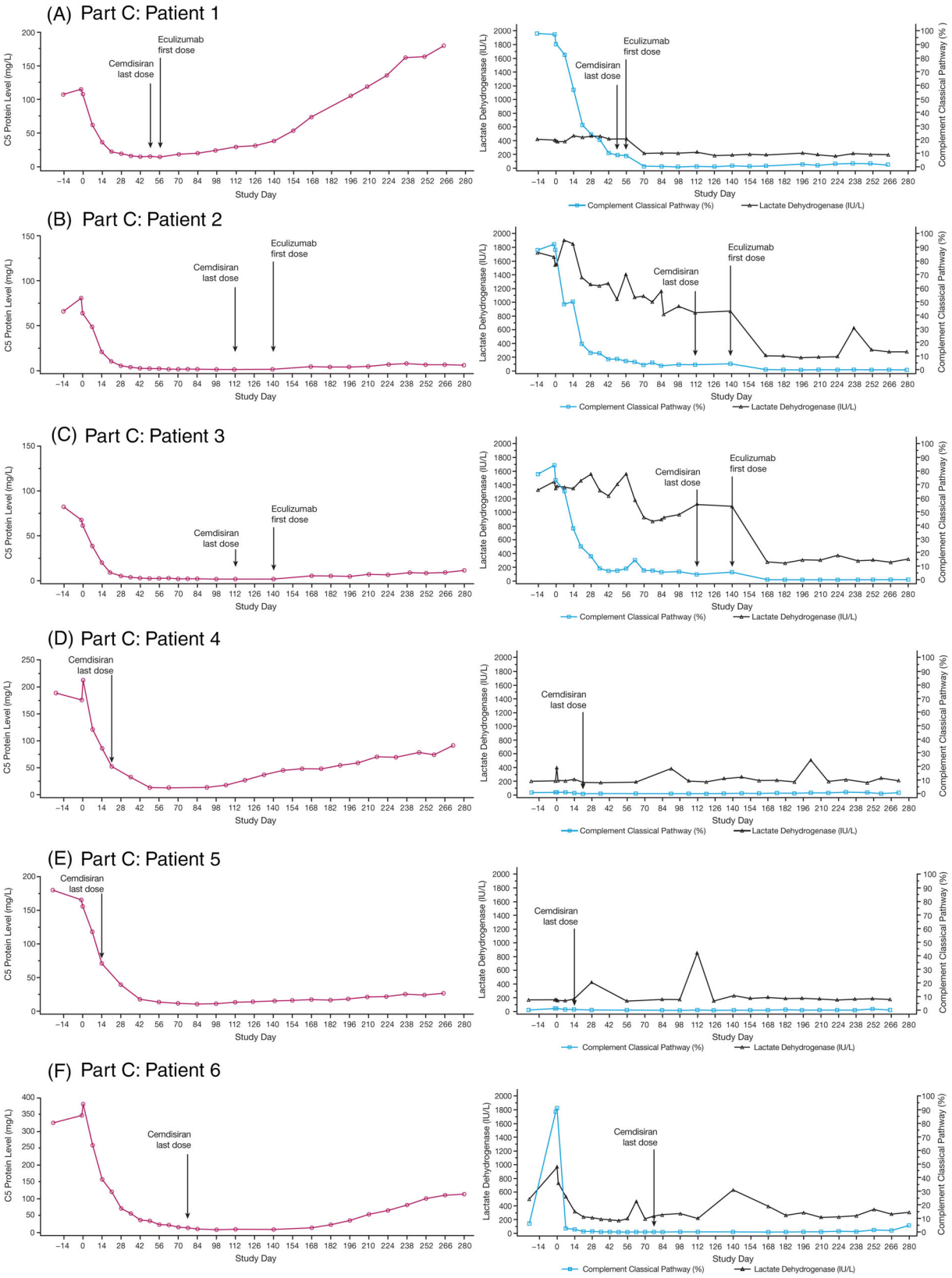

FIGURE 3 Serum C5 levels, CCP activity, and LDH values in individual patients with PNH naive to eculizumab (a–c) or eculizumab-treated (d–f) during treatment with multiple doses of cemdisiran. Eculizumab monthly dosing started after Day 56 for Patient 1 and after Day 140 for Patients 2 and 3 (a–c, respectively). Eculizumab monthly dosing started after Days 91, 84, and 140 for Patients 4–6, respectively (d–f, respectively). Left panels adapted from Badri et al. [17]. Normal values for LDH range from 135 to 214 IU/L. C5, component 5; CCP, complement classical pathway; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria.

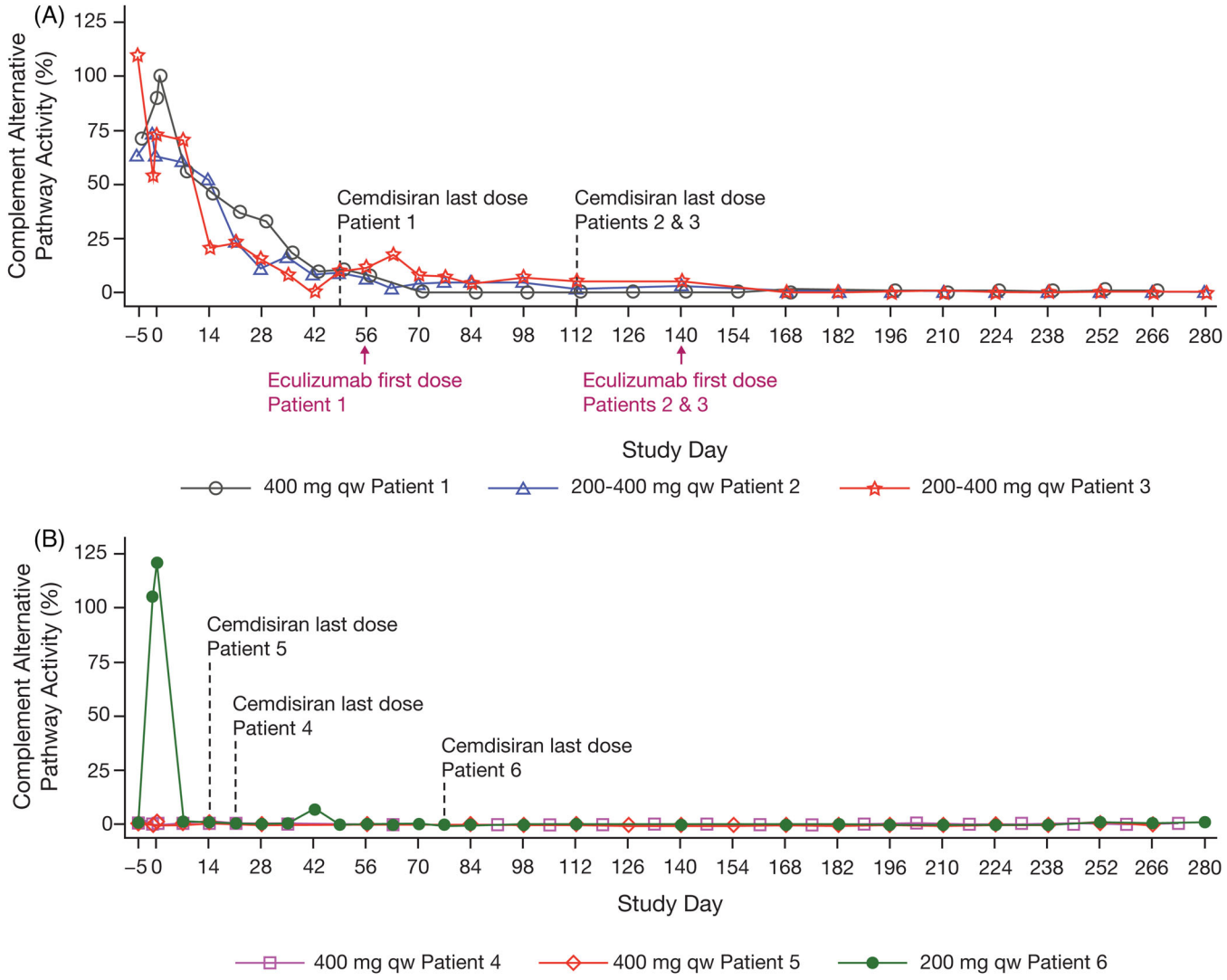

FIGURE 4 Serum CAP activity in eculizumab-naive (A) and -treated (B) patients with PNH during treatment with multiple doses of cemdisiran, Part C. CAP, complement alternative pathway; PNH, paroxysmal nocturnal hemoglobinuria.

to the normal range by Day 35, and C5, CCP, and CAP also declined (Figures 3F and 4B). Following discontinuation of further cemdisiran dosing, LDH remained near the ULN despite eculizumab dose reduction to 900 mg q2w (Day 70) and 900 mg q4w (Day 140), except for one breakthrough hemolysis episode associated with viral gastroenteritis (Day 63).

3.3.4 | Part C: patients with PNH on reduced eculizumab maintenance dosing after cemdisiran discontinuation

Following cessation of further cemdisiran dosing, patients were monitored for safety and ongoing PD effects through Day 280. Due to the prolonged PD effects of cemdisiran, patients were treated with reduced doses and/or frequencies of eculizumab during the monitoring phase to prevent residual intravascular hemolysis. In eculizumab-naive Patients 2 and 3, who received 600 mg eculizumab q4w starting on Day 140, CCP (Figure 3B,C) and CAP (Figure 4A) activity reductions were maintained through Day 280. In addition, intravascular hemolysis was inhibited to a greater extent (100% on Day 168) than with cemdisiran monotherapy (Figure 5), and LDH decreased by >80% (Figure 3B,C). In eculizumab-naive Patient 1, reduced eculizumab maintenance dosing from Day 56 was associated with increased serum C5 to baseline levels on Day 196 (Figure 3A) [17]. However, CCP (Figure 3A) and CAP (Figure 4A) activity remained low (approximately 100% inhibition) through Day 280. Inhibition of hemolysis was maintained (Figure 5). LDH levels reached the normal range at the start of the maintenance treatment and stayed at or below the ULN for the monitoring phase, suggesting that sufficient complement activity inhibition was maintained (Figure 3A).

In patients previously on eculizumab who received 900 mg eculizumab maintenance q4w following discontinuation of cemdisiran, inhibition of complement activity (Figures 3D–F and 4B) and

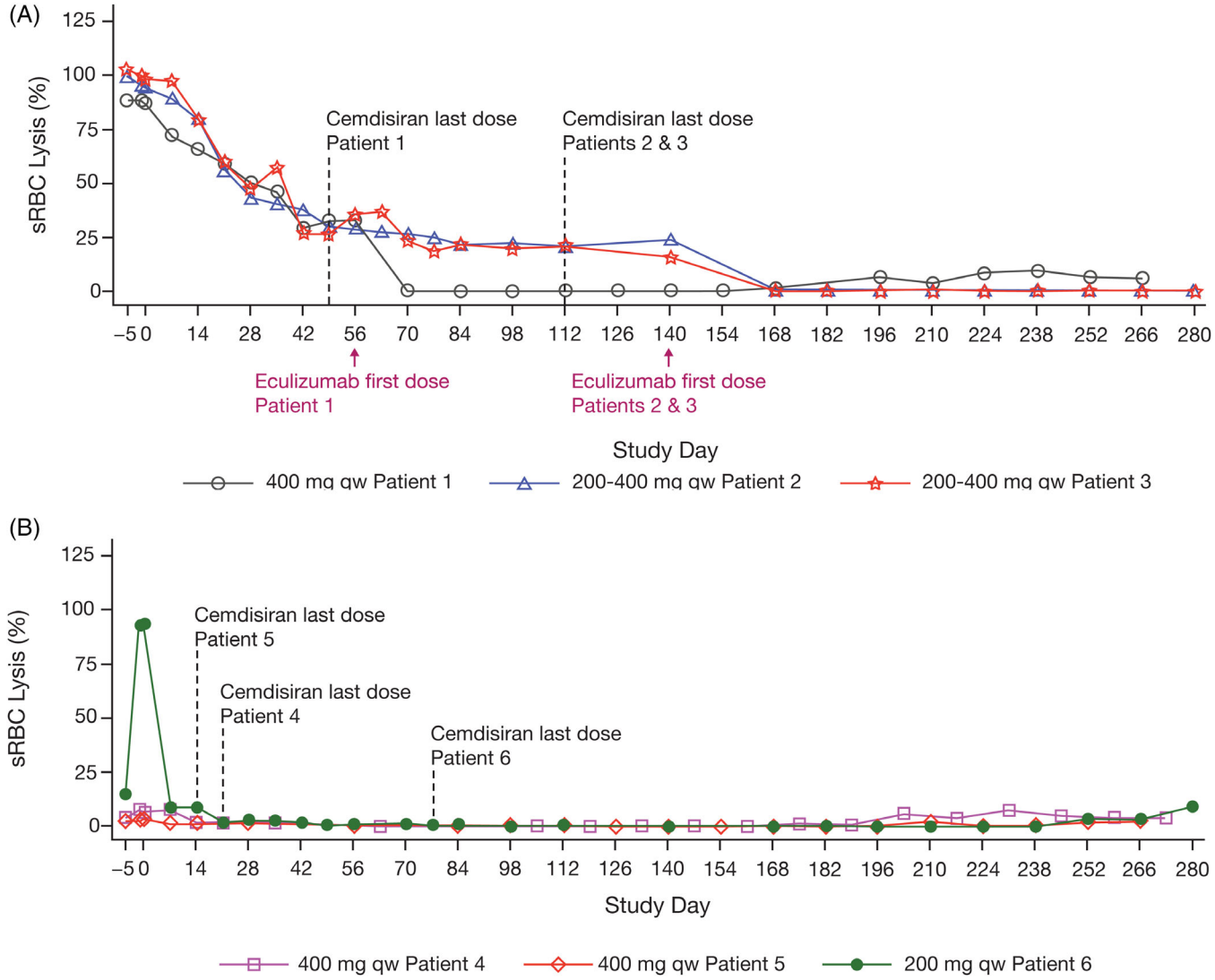

FIGURE 5 sRBC lysis in eculizumab-naive (A) and -treated (B) patients with PNH during treatment with multiple doses of cemdisiran, Part C. PNH, paroxysmal nocturnal hemoglobinuria; sRBC, sheep red blood cell.

hemolysis (Figure 5) was maintained through Day 280 in all patients. LDH levels remained within or near the ULN for Patients 4, 5, and 6, with the exception of 2–3 transient elevations for each patient which did not correspond to changes in the complement activity levels (CCP) (Figure 3D–F).

4 | DISCUSSION

Cemdisiran was well tolerated across these small cohorts of healthy adults and patients with PNH. Most AEs were mild or moderate in severity, there were no SAEs or discontinuations, and the incidence of ISRs was low. Treatment-related AEs consisted mainly of administration-site conditions.

Overall, cemdisiran resulted in robust, sustained, and dose-dependent reduction in C5 levels and inhibition of complement activity in healthy adults and patients with PNH. Serum C5 reduction of >97% in healthy adults at the 600 mg dose has been previously presented [17]. Here, we show that this was associated with a reduction of up to 89% in the complement pathway activity. The complement activity inhibition with cemdisiran treatment was highly durable; a single 600 mg dose resulted in >80% reduction in CCP between Days 21 and 182 which corresponded with previously reported mean C5 reductions of ≥90% from Days 21 through 238 [17]. Multiple dosing regimens ≥200 mg resulted in comparable PD due to the prolonged C5 suppression with a single dose. The clinical course of PNH has been found to differ between Caucasian and Japanese patients [20]. Cemdisiran showed similar safety and efficacy in Japanese and non-Japanese cohorts. One Japanese healthy volunteer who received 600 mg cemdisiran was heterozygous for the Arg885His polymorphism in the C5 gene, which is associated with poor response to eculizumab. In this individual, C5 levels were reduced similarly to other healthy adults who received 600 mg cemdisiran, consistent with the C5 polymorphism falling outside of the

cemdisiran target site and not impacting the ability of cemdisiran to silence C5.

In the eculizumab-naive patients with PNH, cemdisiran monotherapy resulted in up to 96.7% reduction in complement activity (measured by CCP). Although decreases were also observed in LDH, a direct marker of intravascular hemolysis, levels remained above 1.5 × ULN. As the degree of reduction in serum C5 and complement activity inhibition after cemdisiran treatment was insufficient to fully control hemolysis in the 3 eculizumab-naive patients, further treatment with cemdisiran was discontinued. The planned transition of eculizumab-treated patients to cemdisiran monotherapy was also not implemented, and concomitant cemdisiran was discontinued.

As previously described, cemdisiran demonstrated a prolonged inhibition of C5 synthesis in healthy subjects. With this reduction of C5 levels, lower concentrations of an anti-C5 antibody may be needed to achieve inhibition. Indeed, both eculizumab-naive and -treated patients subsequently received eculizumab at a lower (up to 67% less) and more extended than labeled dose at the discretion of the investigator [17]. Badri et al. previously described how C5 levels remained suppressed and LDH levels in both groups were maintained within the normal range at reduced eculizumab doses and with the ongoing pharmacological effect of cemdisiran until the end of the monitoring period on Day 280 [17]. The current exploratory analyses demonstrated that LDH level normalization and complement activity inhibition were maintained at reduced doses of eculizumab for up to 6 and 5 months in eculizumab-naive and -treated patients, respectively, after cemdisiran dosing ended. This suggests that cemdisiran may be most beneficial in PNH when co-administered with a C5 targeting antibody. This hypothesis is currently being tested in a phase 2 trial of cemdisiran and anti-C5 antibody pozelimab combination therapy in adults with PNH (NCT04811716).

Of note, in one patient (Patient 6) who was considered an inadequate responder to eculizumab alone (despite a high dose) and had elevated LDH levels at baseline, the addition of cemdisiran normalized LDH levels. Baseline total C5 levels (including both free and eculizumab-bound C5 levels) were higher in all patients who had previously been treated with eculizumab than eculizumab-naive patients. This may be expected, as studies have shown total C5 levels can increase over time with eculizumab treatment [6, 21, 22]. However, baseline C5 levels were highest in Patient 6, which may reflect the inadequate response to eculizumab and could indicate reduction of C5 levels would be beneficial in patients who are inadequate responders to eculizumab. This patient experienced a severe AE of elevated liver transaminases that was considered possibly related to treatment, described in Badri et al. [17]. Cemdisiran was restarted under an investigator-requested, compassionate-use program, and the patient has remained on cemdisiran treatment (600 mg quarterly) for ~5 years without recurrence of this phenomenon.

This study highlighted the importance of blocking complement activity in PNH, as near complete C5 inhibition was required to reduce LDH below the ULN. Other complement-mediated diseases (e.g., myasthenia gravis [MG], IgA nephropathy [IgAN]) may require a lower degree of C5 suppression compared with PNH because of differences in target cell types, as nucleated cells are more resistant to MAC attack than anucleated RBCs [2, 23]. Cemdisiran monotherapy may be beneficial for these conditions. Indeed, C5-directed silencing provided benefit in a preclinical model of MG, where complete C5 suppression and complement activity inhibition were not required for effect [16].

Robust and sustained inhibition of the complement activity and hemolysis with subcutaneous cemdisiran supports monthly or less frequent dosing, which may be advantageous over intravenous or more frequent dosing. Monthly dosing of cemdisiran is being investigated in an ongoing clinical study in patients with IgAN (NCT03841448).

The small sample size for each dose level tested limits the ability to draw definitive conclusions. The nonrandomized study design with no control arm for the PNH cohort is also a limitation.

5 | CONCLUSIONS

In summary, cemdisiran was well tolerated. AEs were mild to moderate in severity and the most common AEs were nasopharyngitis and headache. Cemdisiran achieved robust and highly durable suppression of complement activity; however, cemdisiran monotherapy was not able to fully control intravascular hemolysis in patients with PNH. Exploratory findings suggest that coadministration of cemdisiran and eculizumab might reduce the dosing of eculizumab or improve the response of those patients with PNH whose response to eculizumab alone is inadequate.

AUTHOR CONTRIBUTIONS

Anna Gaya recruited patients, collected data, analyzed and interpreted the data, contributed to the manuscript, and approved the final version. Talha Munir recruited patients, collected data, analyzed and interpreted the data, contributed to the manuscript, and approved the final version. Alvaro Urbano-Ispizua developed the protocol, analyzed and interpreted the data, contributed to the manuscript, and approved the final version. Morag Griffin recruited patients, collected data, analyzed and interpreted the data, contributed to the manuscript, and approved the final version. Jorg Taubel recruited healthy adults, collected data, analyzed and interpreted the data, contributed to the manuscript, and approved the final version. Jim Bush recruited healthy adults, collected data, analyzed and interpreted the data, contributed to the manuscript, and approved the final version. Ishir Bhan contributed to the manuscript and data interpretation, and approved the final version. Anna Borodovsky developed the protocol, analyzed and interpreted the data, contributed to the manuscript, and approved the final version. Yue Wang analyzed and interpreted the data, contributed to the manuscript, and approved the final version. Prajakta Badri analyzed and interpreted the data, contributed to the manuscript, and approved the final version. Pushkal Garg developed the protocol, analyzed and interpreted the data, contributed to the manuscript, and approved the final version.

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CONFLICT OF INTEREST

Anna Gaya reported receiving honoraria from Alexion Pharmaceuticals, Inc., Novartis, and Sobi.

Talha Munir reported being an advisor and/or consultant for AstraZeneca, Janssen, MorphoSys, Roche, Sobi, and Sunesis; and receiving honoraria and/or travel support from AbbVie, Alexion, AstraZeneca, Gilead, Janssen, Novartis/GSK, Pharmacyclics, Roche, and Sobi.

Alvaro Urbano-Ispizua has nothing to disclose.

Morag Griffin reported receiving honoraria from Alexion Pharmaceuticals, Inc., and Sobi; participating in a Medscape educational program supported by a grant from Apellis; consultancy for Regeneron and BioCryst; and participating in advisory boards for Alexion Pharmaceuticals, Inc., and BioCryst.

Jorg Taubel reported being an employee of Richmond Pharmacology and was Principal Investigator for the ALN-HBV study in HV.

Jim Bush reported being an employee and stock owner of Labcorp.

Ishir Bhan reported being employed by and owning stock and stock options in Alnylam Pharmaceuticals.

Anna Borodovsky reported being employed by and owning stock and stock options in Alnylam Pharmaceuticals.

Yue Wang reported being employed by and owning stock and stock options in Alnylam Pharmaceuticals.

Prajakta Badri reported being employed by and owning stock and stock options in Alnylam Pharmaceuticals.

Pushkal Garg reported being employed by and owning stock and stock options in Alnylam Pharmaceuticals.

DATA AVAILABILITY STATEMENT

De-identified individual participant data that support these results will be made available in a secure-access environment 12 months after study completion and when the product and indication have been approved for no less than 12 months in the US and the EU. Access will be provided contingent upon the approval of a research proposal and the execution of a data sharing agreement. Requests for access to data can be submitted via the website www.vivli.org.

ETHICS STATEMENT

The study was performed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The protocol was approved at each study center by an institutional review board and/or independent ethics committee. A Safety Review Committee regularly reviewed data to monitor appropriateness of dosing/dose escalations. All participants provided written informed consent.

PATIENT CONSENT STATEMENT

All participants provided written informed consent.

CLINICAL TRIAL REGISTRATION

NCT02352493; EudraCT no. 2014-002462-69

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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