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ORIGINAL RESEARCH ARTICLE

Pharmacokinetic and Pharmacodynamic Properties of Cemdisiran, an RNAi Therapeutic Targeting Complement Component 5, in Healthy Subjects and Patients with Paroxysmal Nocturnal Hemoglobinuria

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Abstract

Background Cemdisiran, an *N*-acetylgalactosamine (GalNAc) conjugated RNA interference (RNAi) therapeutic, is currently under development for the treatment of complement-mediated diseases by suppressing liver production of complement 5 (C5) protein. This study was designed to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of cemdisiran in healthy subjects and in patients with paroxysmal nocturnal hemoglobinuria (PNH) in order to support dose selection for late-stage clinical trials.

Methods Healthy volunteers (HVs; $n = 32$, including 12 Japanese subjects) were randomized (3:1) to receive single doses of subcutaneous cemdisiran (50–900 mg) or placebo, or repeat doses of subcutaneous cemdisiran (100–600 mg) or placebo weekly, biweekly, weekly/biweekly, or weekly/monthly for 5, 8, or 13 weeks ($n = 24$). Cemdisiran 200 or 400 mg was administered weekly in an open-label manner, for varying durations, as monotherapy in three eculizumab-naïve PNH patients or in combination with eculizumab in three PNH patients who were receiving stable label doses of eculizumab (900 or 1200 mg biweekly) before the start of the study. After the last dose of cemdisiran, patients were followed for safety and ongoing pharmacologic effects with the eculizumab regimen (600 or 900 mg every month).

Results In HVs, cemdisiran was rapidly converted to a major active metabolite, AS(N-2)3′-cemdisiran, both declining below the lower limit of quantification (LLOQ) in plasma within 48 h, and showing minimal renal excretion. AS(N-2)3′-cemdisiran exhibited more than dose-proportional PK. The C5 protein reductions were dose-dependent, with > 90% reduction of C5 protein beginning on days 21–28 and maintained for 10–13 months following single and biweekly doses of 600 mg. The dose–response relationship, described by an inhibitory sigmoid maximum effect (E_{max}) model, estimated half-maximal effective dose (ED_{50}) of 14.0 mg and maximum C5 reduction of 99% at 600 mg. The PK and PD were similar between Japanese and non-Japanese subjects, and PNH patients and HVs. One of 48 subjects tested transiently positive for antidrug antibody with low titer, with no impact on PK or PD. In PNH patients, C5 suppression by cemdisiran enabled effective inhibition of residual C5 levels with lower dose and/or dosing frequency of eculizumab, which was maintained for 6–10 months after the last dose of cemdisiran.

Conclusions Consistent with the PK/PD properties of liver targeting GalNac conjugates, cemdisiran and AS(N-2)3′-cemdisiran plasma concentrations declined rapidly while showing rapid and robust C5 suppression maintained up to 13 months following single and multiple doses, which indicates long residence times of cemdisiran within hepatocytes. The long PD duration of action in liver, low immunogenicity and acceptable safety profiles enables low, infrequent SC dosing and support further evaluation of cemdisiran in complement-mediated diseases as monotherapy or in combination with a C5 inhibitor antibody.

Clinical Trial Registration No NCT02352493.

Extended author information available on the last page of the article

Key Points

Cemdisiran, a liver-targeted RNA interference (RNAi) therapeutic that suppresses liver production of complement 5 (C5) protein, is currently under development for the treatment of complement-mediated diseases.

Single- and multiple-dose PK, PD, and safety profile of cemdisiran in healthy subjects and patients with PNH was characterized in order to support dose selection of cemdisiran for late-stage clinical trials.

Plasma concentrations of cemdisiran and its major active metabolite AS(N-2)3′-cemdisiran were below the lower limit of quantification within 48 h after subcutaneous administration due to efficient liver uptake, with minimal renal excretion. The rapid, robust, and sustained C5 suppression maintained up to 13 months following single and multiple doses of cemdisiran with low immunogenicity enabled a low dose and infrequent subcutaneous dosing schedule.

This study supports further evaluation of cemdisiran as monotherapy or in combination with a complement inhibitor antibody in complement-mediated diseases.

1 Introduction

Complement-mediated diseases, including paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), immunoglobulin (Ig)A nephropathy (IgAN), and generalized myasthenia gravis (gMG), are life-threatening rare diseases if left untreated [1]. Terminal complement component 5 (C5), predominantly synthetized by hepatocytes, plays an important role in the disease pathology of these conditions. Reducing levels of circulating C5 protein would lead to the inhibition of terminal complement pathway activity, preventing the formation of the membrane attack complex (MAC) and release of the C5a anaphlatoxin [2], which in turn is expected to modify clinical symptoms in complement-mediated diseases.

Small-interfering ribonucleic acids (siRNA) are a new class of medicines that harness the natural RNA interference (RNAi) mechanism for the control of gene expression that utilizes siRNAs loaded onto the cytoplasmic RNA-induced silencing complex (RISC) to specifically target and cleave a complementary messenger RNA (mRNA), thus reducing the synthesis of the disease-causing protein [3–7]. Cemdisiran is a chemically modified double-stranded investigational siRNA in which the sense strand contains 21 nucleotides and the antisense (AS) strand contains 25 nucleotides. The 3′-end of the sense strand is conjugated to a tri-antennary *N*-acetylgalactosamine (GalNAc) for targeted delivery to the liver via binding to asialoglycoprotein receptors (ASGPR) on hepatocytes [8–11]. Once in the cytosol of the hepatocyte, cemdisiran specifically targets and cleaves C5 mRNA utilizing the endogenous RNAi pathway, resulting in decreased hepatic synthesis and lower circulating levels of C5 protein. Thus, it is hypothesized that cemdisiran will ameliorate the signs and symptoms of complement-mediated diseases, offering a novel approach for the treatment of these diseases.

Currently, the C5-directed monoclonal antibodies Soliris™ (eculizumab) [12] and ULTOMIRIS™ (ravulizumab-cwvz) [13] are approved medications for several complement-mediated diseases. For sustained inhibition of C5 protein, the labeled regimens are intravenous infusion of eculizumab (600 or 900 mg once every week for first 4 weeks, followed by 900 or 1200 mg once every 2 weeks), or ravulizumab (2400–3000 mg every 2 weeks, followed by 3000–3600 mg once every 8 weeks). Cemdisiran is being evaluated as a potential long-acting treatment with robust and durable C5 mRNA silencing. The infrequent subcutaneous administration of cemdisiran may reduce burden of care. In addition, some PNH patients have a rare missense mutation on C5 (c.2654G → A, which results in an amino acid substitution p.Arg885His) that results in impaired eculizumab binding and poor therapeutic response [14]. Because cemdisiran targets a region of C5 mRNA away from the p.Arg885His mutation, it is also expected to silence the mutant version of the C5 gene. Given the mechanism of C5 suppression, cemdisiran has the potential to be used as monotherapy or in combination with other C5-neutralizing agents. This hypothesis is being evaluated in this clinical study by administering cemdisiran with and without eculizumab in eculizumab-naïve PNH patients and PNH patients stable on eculizumab treatment.

In preclinical studies, dose-dependent and prolonged reduction of serum C5 protein was observed in non-human primates (NHPs), with maximum serum C5 reduction of 98% after single- and multiple-dose subcutaneous administration of cemdisiran [15]. Based on the robust C5 lowering seen in preclinical studies, a phase I study was conducted in healthy volunteers (HVs) to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of cemdisiran following a single dose (SD) and multiple doses (MDs) in HVs, and MDs in PNH patients. In this paper, we report the characterization of the PK and PD of cemdisiran and its major active metabolite AS(N-2)3′-cemdisiran, and the incidence of antidrug antibody (ADA). The results of this study form the basis for further clinical evaluation of cemdisiran in late-phase studies in PNH and other complement-mediated diseases.

2 Methods

2.1 Study Design

This was a phase I, randomized, double-blind, placebo-controlled, parallel group study with a sequential design (NCT02352493). In Part A, five groups of eight HVs ($n=32$) were randomized in a 3:1 ratio to receive single ascending doses (SADs) of subcutaneous cemdisiran (50–900 mg) or placebo. Among these, 12 Japanese subjects received cemdisiran SDs of 50, 200, or 600 mg, or placebo. In Part B, four groups of nine HVs ($n=24$) were randomized in a 3:1 ratio to receive multiple ascending doses (MADs) of subcutaneous cemdisiran (100–600 mg) or placebo administered weekly or biweekly, weekly/biweekly, or weekly/monthly for 5–13 weeks (Fig. 1). In both parts, dose escalation proceeded after evaluation of the safety and tolerability data obtained from the preceding cohort.

Part C of the study consisted of an open-label treatment phase (up to 17 weeks) and a monitoring phase (≥ 20 weeks) in PNH patients (Fig. 2). In the treatment phase, cemdisiran was administered as 200 or 400 mg subcutaneous doses every week for varying durations, as monotherapy in eculizumab-naïve PNH patients ($n=3$) or in combination with eculizumab in PNH patients ($n=3$) who were receiving stable doses of eculizumab (900 or 1200 mg every 2 weeks) before the start of the study (referred to as eculizumab-treated patients). In the monitoring phase, cemdisiran dosing was discontinued and patients were followed for safety and ongoing pharmacologic effects of cemdisiran with a sparing regimen (reduced dose and/or frequency) of eculizumab (600 or 900 mg every 4 weeks). The start of Part C and the cemdisiran dose were selected based on the safety, tolerability, and available PD data from Parts A and B.

In all parts of the study, subjects were discharged from the clinical study site following completion of the 24-h postdose follow-up assessments. Subjects were monitored on an outpatient basis for safety, tolerability, PK, and PD through day 70 for Part A, and overtreatment/postdose follow-up period (up to day 140) for Parts B and C. For Parts A and B, PD follow-up visits were conducted every 28 ± 7 days for subjects with serum complement activity below the normal range at the last postdose follow-up visit; monitoring visits occurred until serum complement activity was within the normal reference range for all subjects or until an SRC decision to discontinue monitoring on a case-by-case basis, whichever was sooner.

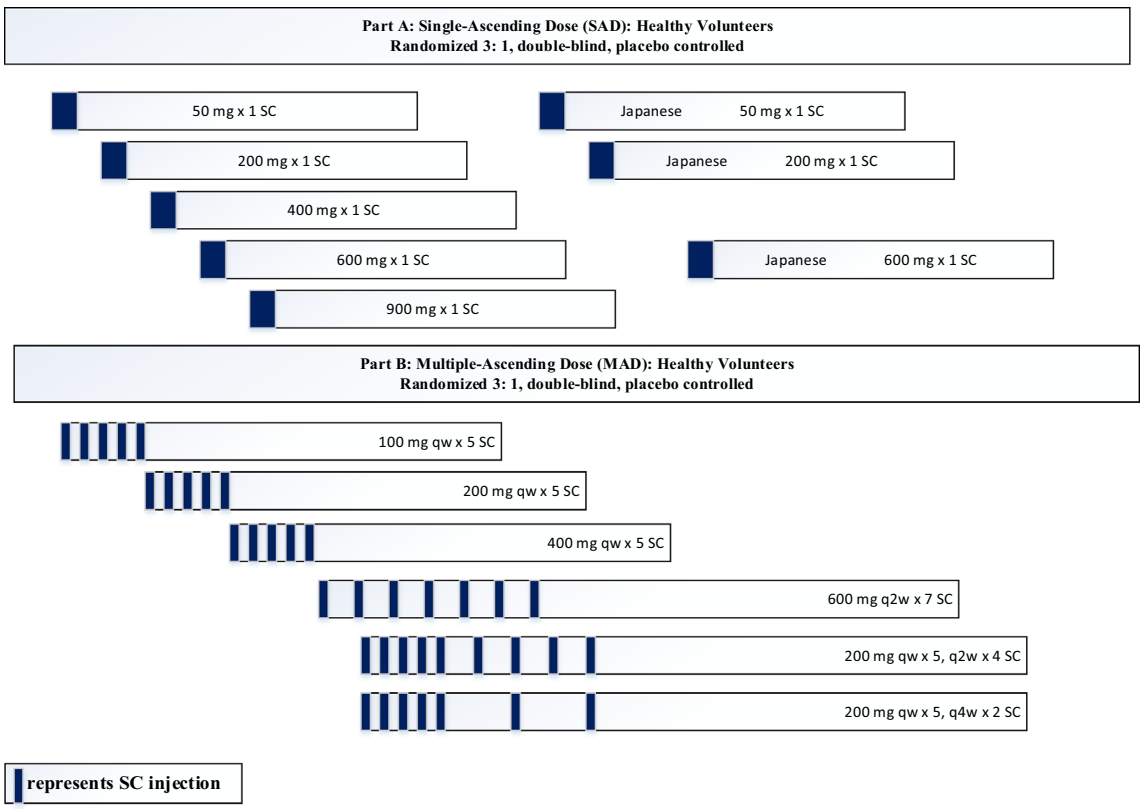

Fig. 1 Study design schematic for cemdisiran administration in healthy subjects (Parts A and B). *SC* subcutaneous administration, *qw* once weekly, *q2w* once every 2 weeks or biweekly, *q4w* once every 4 weeks or once a month

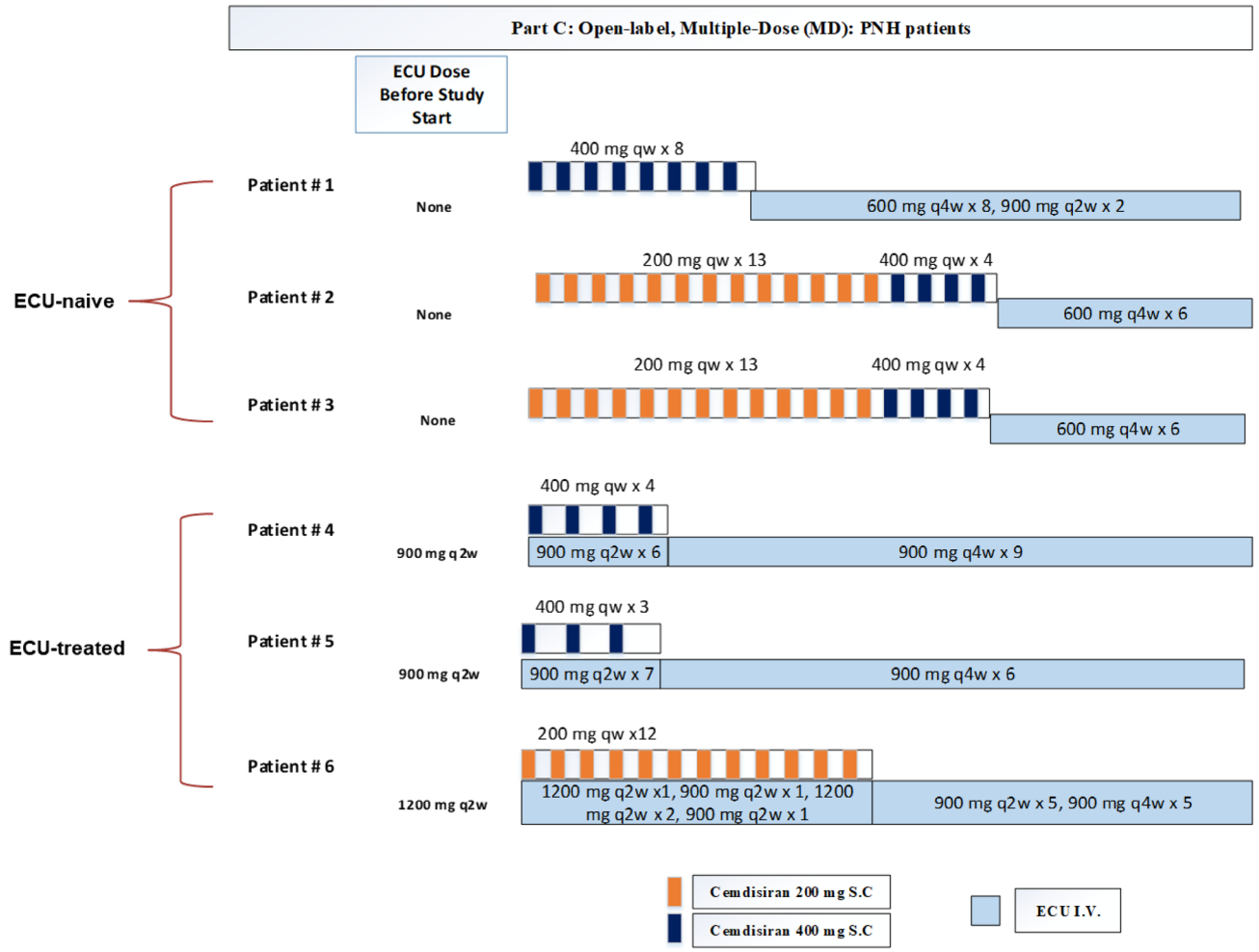

Fig. 2 Study design schematic for cemdisiran with or without eculizumab administration in PNH subjects (Part C). (1) Patients 4 and 5 received a labeled dose of eculizumab for maintenance treatment in PNH. Patient 6 received more than the labeled dose of eculizumab for maintenance in PNH. All patients received a reduced dose and/or frequency of eculizumab compared with a labeled dose for maintenance treatment in PNH following discontinuation of cemdisiran during the monitoring phase. (2) Patient 6 received eculizumab 1200 mg q2w from days 0 to 56, with eculizumab 900 mg on day 14 and eculizumab 900 mg q2w on day 70, with cemdisiran followed by eculizumab monotherapy of 900 mg q2w from days 84 to 140, and eculizumab monotherapy of 900 mg q4w from days 168 to 280. *PNH* paroxysmal nocturnal hemoglobinuria, *SC* subcutaneous administration, *IV* intravenous, *qw* once weekly, *q2w* once every 2 weeks or biweekly, *q4w* once every 4 weeks or once a month, *ECU* eculizumab

2.2 Study Participants

For Parts A and B, men and women aged 18–45 years with a body mass index ≥ 18.0 kg/m^2 and ≤ 30 kg/m^2 were included. Light smokers and users of nicotine (defined as the equivalent of 10 cigarettes per day) were allowed. Subjects were excluded if they had used any over-the-counter or prescription medications (excluding vitamins) within 2 weeks before study drug administration, if they had liver function tests outside the reference range, or had complement activity below the normal reference range (as evaluated by the Weislab Alternative Pathway Assay).

For Part C, adults with granulocyte and monocyte PNH clone $> 1\%$, as documented by medical records, and lactate dehydrogenase (LDH) ≥ 1.5 upper limit of normal (ULN) in the absence of eculizumab, were included. If PNH patients were receiving stable eculizumab therapy, as assessed by the investigator, patients with historical laboratory values documenting elevated LDH levels before administration of the first dose of eculizumab were included.

All participants were vaccinated against *Neisseria meningitides*, and HVs were receiving antibiotic prophylaxis. Participants were excluded if they were hepatitis B/C- or HIV-positive, or if they had known/suspected hereditary asymptomatic complement deficiency.

2.3 Assessments

Blood and 24-h urine samples were collected to measure cemdisiran, AS(N-2)3′-cemdisiran, serum C5 protein, and ADA. Detailed schedules for the collection of blood and urine samples for PK analysis, serum C5, and ADA sampling for Parts A, B, and C of the study are shown in electronic supplementary Table 1.

Cemdisiran and AS(N-2)3′-cemdisiran were quantitated in plasma and urine samples using a validated liquid chromatography mass spectrometry high-resolution method. The lower limit of quantification (LLOQ) for each analyte was 10 ng/mL for both plasma and urine PK sample analyses. Total serum C5 protein was analyzed using a qualified liquid chromatography/tandem mass spectrometry method following protein digestion by Lys-C to a unique peptide and using a labeled peptide as a reference standard. Protein concentration LLOQ was based on sample peptide recovery and was approximately 0.5 µg/mL. ADA samples were analyzed using a validated enzyme-linked immunosorbent assay (ELISA) method, where cemdisiran was covalently bound to the surface of the microtiter plate to capture ADA. Dual-specific human anti-IgG/IgM was used to detect drug-specific ADA and was performed in a tier-wise manner to screen, confirm, and titer with a surrogate rabbit ADA-positive control. The minimum required dilution for the assay was 1/50 and the assay sensitivity was determined to be 395 ng/mL. The ADA and PK assays were validated according to US FDA and European Medicines Agency (EMA) guidelines for immunogenicity and bioanalytical method validation.

In addition to C5 levels, serum complement activity and LDH levels, complement hemolytic activity, safety, and clinical and laboratory evidence of adverse events (AEs) were evaluated in this study and will be presented in a forthcoming publication.

2.4 Pharmacokinetic and Pharmacodynamic Statistical Analyses

The plasma PK parameters of cemdisiran and AS(N-2)3′-cemdisiran were estimated by noncompartmental methods using Phoenix WinNonlin version 7.0 (Certara LP, Princeton, NJ, USA). The maximum plasma concentration (C_{max}) and time to reach C_{max} (t_{max}) were observed from the plasma concentration–time data. Calculated PK parameters included area under the curve from time zero to time of the last measurable concentration (AUC_t), terminal phase elimination rate constant (λz), half-life ($t_{½}$), and percentage excreted in urine ($\%f_e$).

Day 1 C_{max} and AUC of AS(N-2)3′-cemdisiran after an SD for each cohort were evaluated using a power model for dose proportionality. The power model is described as $y = \alpha \times \text{Dose}^{\beta}$, where y, α, and β correspond to the PK variable, proportionality constant, and exponent, respectively. The exponent β in the power model was estimated by regressing the natural log-transformed PK variable on the natural log-transformed dose. Dose proportionality is implied when $\beta = 1$, and was assessed by estimating β (95% confidence interval [CI]) [16, 17].

The dose response assessment was conducted by evaluating the relationship between cemdisiran administered as

Table 1 Demographics of healthy volunteers in single and multiple ascending dose cohorts, and PNH patients in a multiple-dose cohort

Demographic parameter	Single-dose cohort (healthy)		Multiple-dose cohort (healthy)		Multiple-dose cohort (PNH patients)	
	Placebo [$n=8$]	Cemdisiran [$n=24$]	Placebo [$n=6$]	Cemdisiran [$n=18$]	Eculizumab-treated [$n=3$]	Eculizumab-naïve [$n=3$]
Mean age, years (minimum, maximum)	26 (20, 37)	27 (20, 41)	27 (20, 38)	28 (19, 39)	44 (25, 58)	44 (34, 57)
Mean body weight, kg (SD)	66.1 (9.24)	67.4 (12.62)	71.4 (8.60)	72.6 (10.36)	77.6 (2.70)	65.6 (6.15)
Sex [*n* (%)]						
Male	6 (75.0)	16 (66.7)	2 (33.3)	11 (61.1)	2 (66.7)	1 (33.3)
Female	2 (25.0)	8 (33.3)	4 (66.7)	7 (38.9)	1 (33.3)	2 (66.7)
Race [*n* (%)]						
White	4 (50.0)	6 (25.0)	5 (83.3)	18 (100)	3 (100)	3 (100)
Black or African American	0	4 (16.7)	0	0	0	0
Asian	3 (37.5)	12 (50.0)	0	0	0	0
Other	1 (12.5)	2 (8.3)	1 (16.7)	0	0	0
Baseline LDH (IU/L)[a]					270, 172, 803	412, 1644, 1374

PNH paroxysmal nocturnal hemoglobinuria, *SD* standard deviation, *LDH* lactate dehydrogenase

[a]Individual baseline LDH values are reported

SDs and the corresponding serum C5 protein nadir using an inhibitory sigmoid maximum effect (E_{max}) model: $E = E_0 \times (1 - \text{DOSE}^{\gamma}/(\text{ED}_{50}{}^{\gamma} + \text{DOSE}^{\gamma}))$, where E is the estimated serum C5 protein nadir, E_0 is the baseline serum C5 protein level, DOSE is the dose amount (mg), ED_{50} is the dose resulting in one-half of the maximum inhibitory effect, and γ is the hill factor. Phoenix WinNonlin version 7.0 (Certara LP) was used for the model fitting.

Descriptive statistics were provided for demographic, PK and PD, ADA, and safety parameters.

3 Results

3.1 Study Population

The baseline demographic characteristics were generally comparable across treatment/placebo groups and parts (Table 1). The study populations were predominantly male, and mixed race in Part A and all White in Parts B and C.

3.2 Cemdisiran and AS(N-2)3′-Cemdisiran Plasma Pharmacokinetics

3.2.1 Plasma Pharmacokinetics

Following SD cemdisiran in HVs, the median t_{max} of cemdisiran occurred between 0.50 and 1.00 h. Cemdisiran declined rapidly by 8 h postdose, with a corresponding increase in the plasma concentration of the metabolite AS(N-2)3′-cemdisiran (electronic supplementary Fig. 1). AS(N-2)3′-cemdisiran reached peak levels generally within 1–12 h (Fig. 3) and plasma levels were below LLOQ within 48 h. The mean $t_{½}$ of AS(N-2)3′-cemdisiran was approximately 4–7 h (Table 2). AS(N-2)3′-cemdisiran exposures were similar between Japanese and non-Japanese subjects.

Following MDs of cemdisiran in HVs and PNH patients, cemdisiran and AS(N-2)3′-cemdisiran PK were consistent with those observed after an SD in HVs. There was minimal accumulation of AS(N-2)3′-cemdisiran with repeat dosing (Fig. 4 and electronic supplementary Fig. 2 and electronic supplementary Tables 2 and 4).

3.2.2 Dose Proportionality

Over the SD range, plasma C_{max} and AUC_t values of AS(N-2)3′-cemdisiran increased in a slightly greater than dose-proportional manner (Fig. 5). In addition, the power model estimates for the slope (β) [90% CIs] were 1.29 (1.14–1.44) for C_{max} and 1.44 (1.34–1.53) for AUC_t, indicating a slightly greater than dose-proportional increase in C_{max} and AUC_t.

Consistent with SD PK, plasma AS(N-2)3′-cemdisiran C_{max} and AUC_t were slightly greater than dose proportional over the MD range evaluated in HVs and PNH patients (electronic supplementary Tables 2 and 4).

3.2.3 Urine Pharmacokinetics

Following SD and MDs of cemdisiran in HVs, and MDs in PNH patients, the mean percentage of cemdisiran and AS(N-2)3′-cemdisiran in the urine after 24-h urine collection was low, i.e. ≤ 0.12% and 3.72–14.1%, respectively, exhibiting a slight increase with dose (Table 2 and electronic supplementary Tables 3 and 4). Urine PK parameters were similar between Japanese and non-Japanese subjects (Table 2).

3.3 Pharmacodynamics

3.3.1 Single-Dose Pharmacodynamics in Healthy Volunteers

The mean baseline serum C5 protein concentration across all SD cohort subjects was 59 mg/L. Treatment with cemdisiran led to dose-dependent reductions in serum C5 protein levels, while serum C5 concentrations were unchanged over 500 days in placebo-treated subjects (Fig. 6a). Across all dose groups, the serum C5 group nadir was reached between days 28 and 70. Reductions in C5 protein were similar between Japanese and non-Japanese HVs in same dose cohorts. The lowest and highest dose of 50 mg and 900 mg resulted in 78% and 98% maximum C5 protein reductions from baseline, respectively. Maximum C5 suppression reached a plateau at doses ≥ 400 mg, with approximately 97% C5 suppression at 400 mg and only incremental increases in suppression observed at higher doses. These reductions in C5 protein were durable. For example, after administration of cemdisiran 600 mg, a > 90% reduction in C5 protein persisted from day 21 through day 238. Across doses, the interindividual variability (percentage coefficient of variation [%CV]) in C5 nadir was low, ranging from approximately 18% to 40%.

The dose–response relationship adequately described by an inhibitory sigmoid E_{max} model with ED_{50} was estimated to be 14.0 mg (%CV 49.4), and γ was estimated to be 0.79 (%CV 25.7). The model predicted a maximum reduction in C5 protein of 99% inhibition at 600 mg (Fig. 7).

3.3.2 Multiple-Dose Pharmacodynamics

3.3.2.1 Healthy Volunteers Compared with the corresponding dosing groups in SADs, a higher C5 protein reduction with longer duration of suppression was observed after MDs of cemdisiran (Fig. 6b).

Dose-dependent decreases in C5 protein concentrations were observed following treatment with weekly doses of 100, 200, or 400 mg, and a biweekly dose of

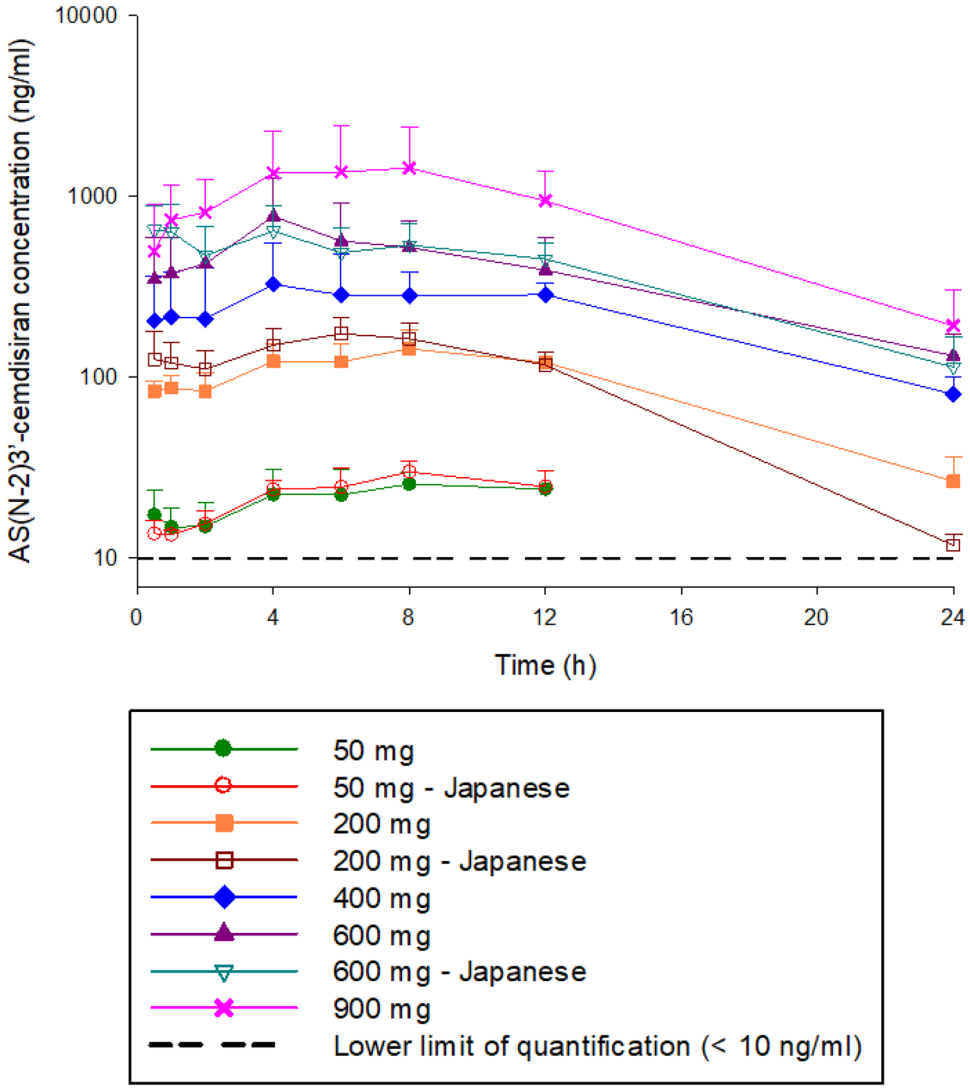

Fig. 3 Mean AS(N-2)3′-cemdisiran plasma concentration profiles following single subcutaneous doses. Error bars represent standard deviations. Plasma concentrations below the limit of quantification are not shown in the plot

600 mg cemdisiran. Following administration of weekly doses (100, 200, and 400 mg), a reduction of approximately 35–56% was seen in the C5 protein within the first week of dosing, and subsequently continued, resulting in an 89–99% C5 reduction being observed after the administration of five total doses. Treatment with cemdisiran achieved a maximum 98.7% reduction in C5 protein relative to baseline in the 600 mg biweekly cohort. Reductions in C5 protein were durable, with > 90% suppression of C5 beginning on day 28 and persisting through day 308 for the 600 mg biweekly dosing. Similarly, the maximum reductions in C5 protein were 98.6% and 96.7% in the 200 mg weekly/biweekly cohort and 200 mg weekly/monthly cohort, respectively.

Across all dose groups, the serum C5 group nadir was reached between days 56 and 98. The intersubject variability (%CV) in serum C5 nadir ranged from approximately 15–39% in the 100–400 mg weekly and 600 mg biweekly dosing regimens, while that in the 200 mg weekly/biweekly and 200 mg weekly/monthly dosing regimens was approximately 28% and 87%, respectively.

3.3.2.2 Paroxysmal Nocturnal Hemoglobinuria Patients All six PNH patients, eculizumab-naïve and eculizumab-treated, showed substantial and persistent C5 reduction, with a maximum C5 reduction of approximately 93–99% achieved between days 42 and 112. In eculizumab-treated patients, the total C5 levels, which include both free C5 and eculizumab-bound C5, were, as expected, markedly higher at study baseline (Fig. 8b) compared with the eculizumab-naïve patients (Fig. 8a) and HVs in Parts A and B (Fig. 6a, b, respectively). In most patients, the C5-lowering effect of cemdisiran was long-lasting (6–10 months), with a > 84% and > 53% reduction maintained after the last dose of cemdisiran in the eculizumab-naïve and eculizumab-treated patients,

Table 2 Mean (SD) plasma and urine pharmacokinetic parameters of AS(N-2)3′-cemdisiran after a single subcutaneous dose of cemdisiran

Parameter	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 [$n=3$]
Plasma pharmacokinetics								
C_{max}, ng/mL	27.2 (4.35)	30.4 (4.21)	144 (39.1)	178 (38.1)	384 (183)	787 (473)	710 (250)	1496 (966)
Dose-normalized C_{max} (ng/mL/mg)	0.54 (0.09)	0.61 (0.08)	0.72 (0.20)	0.89 (0.19)	0.96 (0.46)	1.31 (0.79)	1.18 (0.42)	1.66 (1.07)
T_{max}, h[a]	8.0 (6.0, 12.0)	8.0 (4.0, 8.0)	8.0 (8.0, 8.0)	6.0 (6.0, 8.0)	12.0 (4.0, 12.0)	4.0 (4.0, 8.0)	1.0 (0.5, 12.0)	6.0 (4.0, 8.0)
AUC_t, h·ng/mL	257 (58.3)	277 (41.1)	2136 (278)	2237 (452)	5174 (1510)	9383 (3057)	9179 (1869)	19,500 (8291)
Dose-normalized AUC_t, (h·ng/mL/mg)	5.14 (1.17)	5.54 (0.82)	10.7 (1.39)	11.2 (2.26)	12.9 (3.78)	15.6 (5.09)	15.3 (3.12)	21.7 (9.21)
$t_{½}$, h	NC	NC	NC	4.29 (0.289)	NC	7.05 (1.23)	5.59 (1.43)	6.37 (3.61)
CL/F, L/h	NC	NC	NC	92.2 (25.5)	NC	63.9 (21.6)	57.0 (8.33)	46.4 (14.9)
Urine pharmacokinetics								
fe, %	6.19 (3.37)	5.78 (1.37)	5.30 (2.76)	7.53 (0.61)	7.12 (1.74)	7.99 (2.63)	8.74 (1.58)	9.27 (1.54)

AUC_t area under the curve from time zero to the last measurable concentration, *C_{max}* maximum concentration, *$t_{½}$* terminal half-life, *T_{max}* time to maximum concentration, *fe* fraction of dose excreted in urine, *NC* not calculated due to a lack of concentrations in the terminal phase of the curve, *SD* standard deviation, *CL/F* apparent clearance

[a]Median (minimum, maximum)

respectively, with reduced dose and/or frequency of eculizumab relative to the eculizumab label maintenance dose.

3.4 Antidrug Antibody

The incidence of ADA was low and transient. Of the 48 volunteers/patients treated with cemdisiran, one HV (2%) in the 200 mg ALN-CC5 cohort in Part A was ADA-positive on day 14, with a low titer of 50, and subsequently became ADA-negative on day 70, with no impact on PK or PD. One of the 14 subjects in the placebo arm (7%) tested positive for ADA at baseline, with a titer of 100, and remained ADA-positive through day 70. None of the subjects in Parts B and C were confirmed positive for ADA during the study.

3.5 Safety and Efficacy

Brief summaries of the safety and efficacy results are presented below and will be discussed in detail in a separate forthcoming publication.

3.5.1 Safety

Cemdisiran was generally well tolerated in the 56 HVs and 6 PNH patients following an SD or MDs. The percentages of HVs with AEs and changes in serum biochemistry, hematology, coagulation, and urinalysis parameters from baseline were similar in the placebo and cemdisiran groups. All AEs were mild and moderate in severity. The frequency and nature of AEs were similar between Japanese and non-Japanese subjects. In Part C, one patient treated with cemdisiran 200 mg weekly in addition to eculizumab had a severe AE of increased transaminases, which was considered possibly related to treatment with cemdisiran and eculizumab and led to study drug interruption. While C5 protein was suppressed by cemdisiran during the recovery period, this AE resolved within 120 days of onset. Two patients in Part C who received cemdisiran 400 mg weekly (one eculizumab-naive and one eculizumab-treated) had transient and isolated elevations in total bilirubin $> 3 \times$ ULN and $\leq 5 \times$ ULN. Both patients had elevated bilirubin at baseline, consistent with the natural history of PNH disease. One eculizumab-treated patient showed mild injection site reaction. No other HVs or patients had clinically significant elevations in LFTs $> 3 \times$ ULN during the study. There were no deaths, serious AEs (SAEs), or AEs leading to discontinuation of study drug or withdrawal from the study.

3.5.2 Efficacy

Maximal reductions in LDH, an exploratory objective, of 37–50% were observed in eculizumab-naïve patients, and

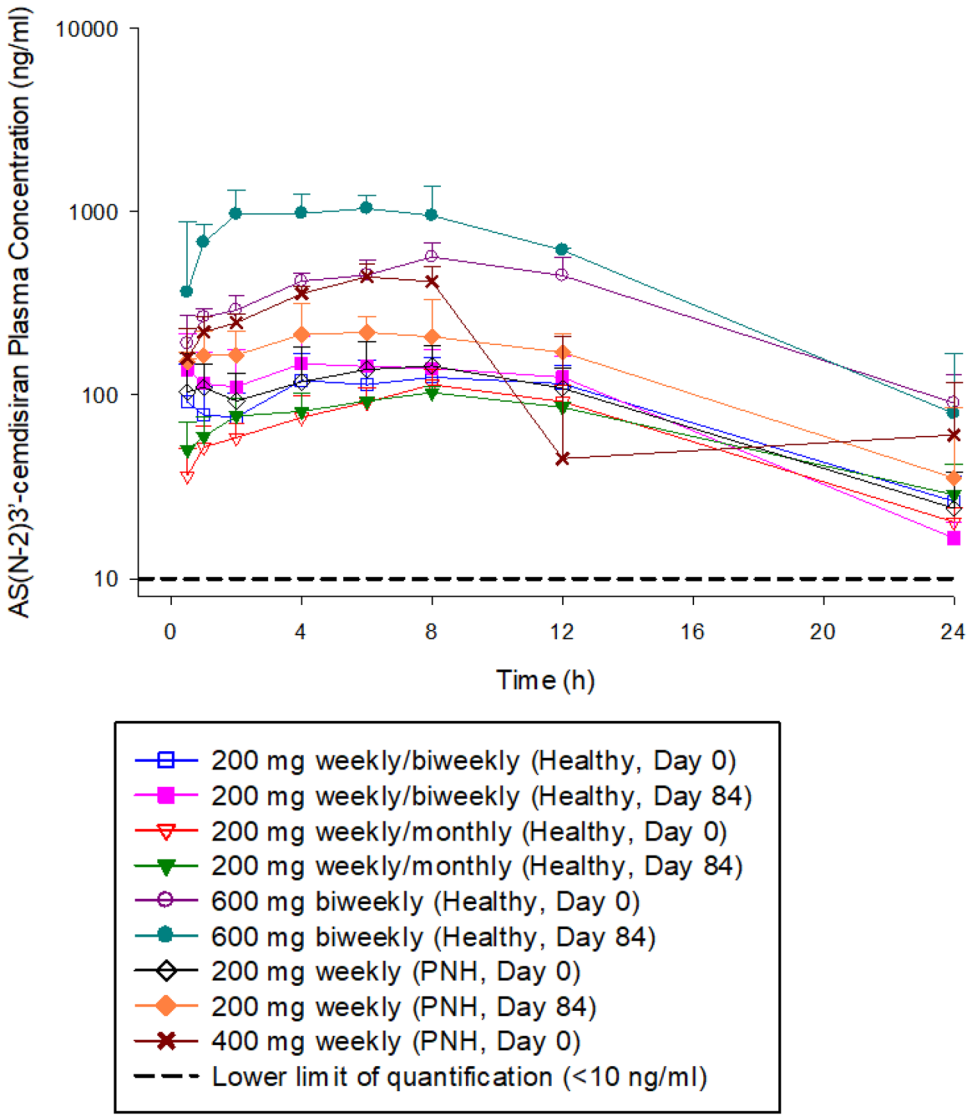

Fig. 4 Mean AS(N-2)3′-cemdisiran plasma concentration profiles on days 0 and 84 following multiple subcutaneous doses of cemdisiran. Plasma concentrations below the limit of quantification are not shown in the plot. *PNH* paroxysmal nocturnal hemoglobinuria

LDH levels remained above the goal of < 1.5 × ULN. In two eculizumab-treated patients receiving maintenance eculizumab doses, LDH levels were within normal limits at baseline and were maintained near or within normal range with cemdisiran treatment. The third eculizumab-treated patient had symptoms of PNH that were historically not well managed on eculizumab 900 mg every 2 weeks, and. at the time of entry into the study, this patient was receiving eculizumab 1200 mg every 2 weeks (higher than the labeled eculizumab maintenance dose in PNH) with episodes of breakthrough hemolysis. This patient had markedly elevated LDH at study entry (803 IU/L), which decreased to within the normal range with the addition of cemdisiran treatment. All patients receiving cemdisiran achieved LDH < 1.5 × ULN on reduced doses and/or frequency of eculizumab, including the patient with prior inadequate eculizumab response.

4 Discussion

Cemdisiran is currently under development for the treatment of complement-mediated diseases by suppressing liver production of C5 protein. The purpose of this study was to characterize the single and multiple subcutaneous dose PK, PD, and safety profile of cemdisiran in HVs and PNH patients in order to support dose selection of cemdisiran for late-stage clinical trials.

Following administration of SDs, cemdisiran exposures peaked at 0.5–1 h, and declined rapidly to values below the LLOQ in approximately 8 h as it is rapidly converted to AS(N-2)3′-cemdisiran by cleavage of two oligonucleotides (dTdT) from the 3′-terminus of the AS strand. This conversion is mediated by the ubiquitously present endo- and exonucleases. AS(N-2)3′-cemdisiran, which is equipotent to cemdisiran based on in vitro potency evaluation, was the

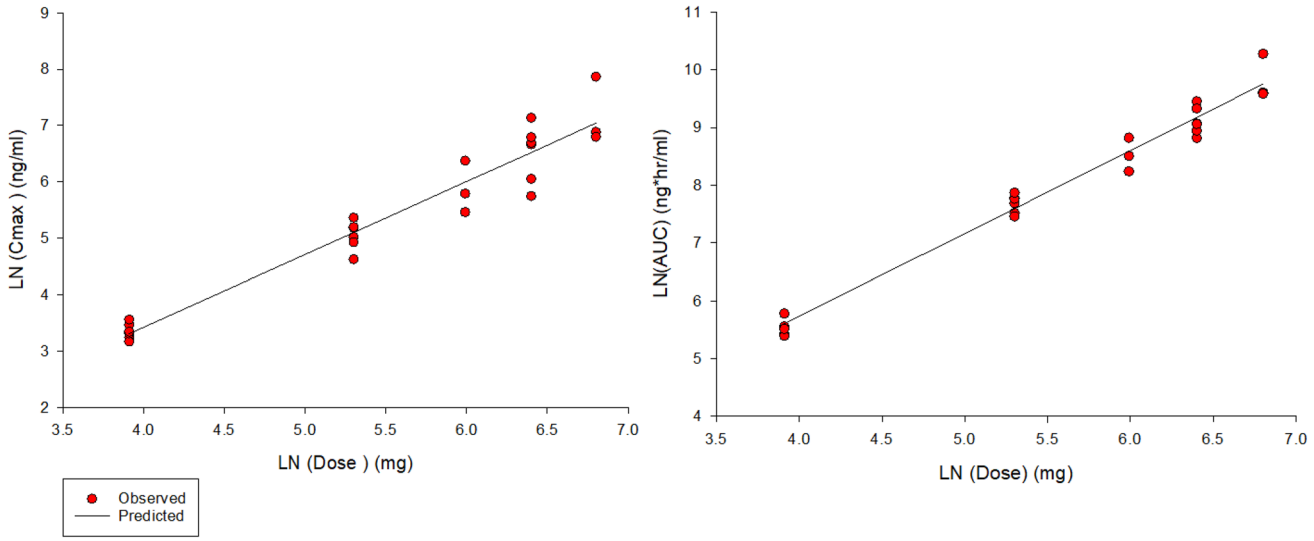

Fig. 5 Cemdisiran dose versus C_{max} and AUC_t for AS(N-2)3′-cemdisiran on a logarithmic scale. C_{max} and AUC (AUC_t) in the plot follow a single subcutaneous dose of cemdisiran. The power model estimates for the slope (β) [95% confidence intervals] were 1.29 (1.14–1.44) and 1.44 (1.34–1.53) for C_{max} and AUC_t, respectively. AUC_t area under the curve from time zero to the last measurable concentration, C_{max} maximum concentration, *LN* natural logarithm

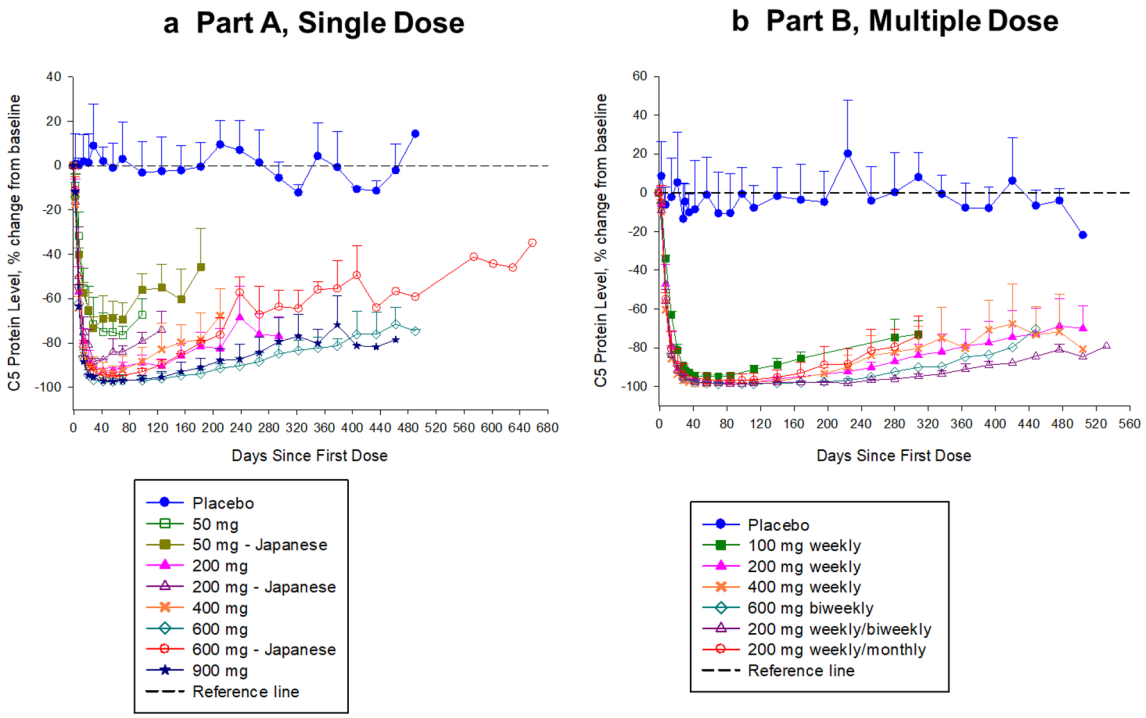

Fig. 6 Mean percentage change from baseline in serum C5 protein following **a** single doses and **b** multiple doses of cemdisiran administered subcutaneously. *C5* complement protein

major circulating entity and is largely responsible for serum C5 lowering. The rapid decline in AS(N-2)3′-cemdisiran plasma concentrations was attributable to efficient GalNAc-mediated uptake into hepatocytes, the site of RNAi activity. The plasma clearance of GalNAc-siRNA molecules is primarily influenced by ASGPR-mediated uptake into the liver [18]. ASGPR, which is abundantly and primarily expressed on the surface of hepatocytes, up to 0.5 million per hepatocyte, is capable of efficiently internalizing GalNAc-siRNA. However, as the cemdisiran dose increases,

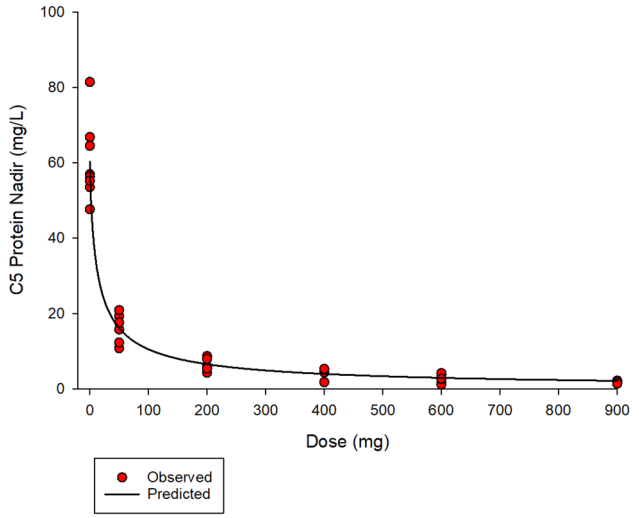

Fig. 7 Relationship between dose and maximum C5 protein suppression after a single subcutaneous dose of cemdisiran. The dose–response relationship in the plot is described by an inhibitory sigmoid E_{max} model ($E = E_0 \times (1 - \mathrm{DOSE}^{\gamma}/(\mathrm{ED}_{50}{}^{\gamma} + \mathrm{DOSE}^{\gamma}))$, where E is the estimated serum C5 protein nadir, E_0 is the baseline serum C5 protein level, DOSE is the dose amount (mg), ED_{50} is the dose resulting in one-half of the maximum inhibitory effect, and γ is the hill factor. ED_{50} was estimated to be 14.0 mg (%CV 49.4) and γ was estimated to be 0.79 (%CV 25.7). The model predicted maximum reduction in C5 protein of 99% inhibition at 600 mg. *C5* complement 5, E_{max} maximum effect, *%CV* percentage coefficient of variation

the AS(N-2)3′-cemdisiran plasma concentrations seem to transiently saturate ASGPR, resulting in slightly more than dose proportional plasma exposure increases. The transient nature of saturation is attributable to the rapid recycling of ASGPR back to the surface of the hepatocyte to engage with new GalNAc conjugates, resulting in plasma concentrations declining below the LLOQ within 48 h after dosing. The similar PK profiles of cemdisiran between Japanese and non-Japanese subjects is consistent with similar metabolic and clearance properties of siRNAs across the races. To date, there have been no reports of differences in expression and activity of ASGPR or endo- and exonucleases between Japanese and non-Japanese subjects. In addition, cemdisiran and AS(N-2)3′-cemdisiran plasma PK were similar between HVs and PNH patients.

The mean percentage of cemdisiran excreted in the urine was negligible (≤ 0.12%), while 3.72–14.1% was recovered in urine as AS(N-2) 3′-cemdisiran in HVs and PNH patients. The percentage of urine excretion increases with dose, suggesting that transiently higher plasma concentrations due to ASGPR saturation results in a slightly greater amount of AS(N-2) 3′-cemdisiran available for filtration by the kidneys. Even at the highest SD of 900 mg, urine recovery was low (9.27%), indicating that the rate of hepatic uptake of siRNA through ASGPR far exceeds the glomerular filtration rate. Thus, since the renal route is not a major elimination pathway, renal impairment is not anticipated to have a major impact on the PK of cemdisiran and AS(N-2) 3′-cemdisiran.

In the current study, SD and MD administration of cemdisiran in HVs led to dose-dependent reductions in C5 protein, with low variability in C5 nadir across doses. Residual C5 levels achieved with cemdisiran in these HVs were comparable with free C5 levels in aHUS patients taking eculizumab [19]. At doses ≥ 200 mg, C5 protein reduction was rapid, with a more than 80% reduction in C5 protein achieved by week 2, and a higher reduction of > 90% achieved between weeks 3 and 4. In addition, this C5 protein reduction achieved was maintained for 10–13 months in the 600 mg SD and biweekly MD cohorts. The C5 reductions were similar between Japanese and non-Japanese subjects. The dose response analysis indicated that the dose required to reduce C5 protein by 50% was 14 mg, indicating a steep dose–response relationship, with a maximum C5 reduction of 99% at 600 mg and plateauing of C5 reduction at doses of ≥ 400 mg.

The prolonged cemdisiran-mediated C5 protein suppression in HVs, lasting up to 13 months, is particularly noteworthy given the short plasma $t_{½}$ of cemdisiran and its metabolite. The long duration of C5 protein suppression following cemdisiran SD indicates that AS(N-2)3′-cemdisiran has a long $t_{½}$ in the liver, enabling it to exert its inhibitory effect. This is consistent with the observations in NHPs where despite a short plasma $t_{½}$ of 5–6 h, sustained reduction in circulating C5 was achieved for over 2 months after an SD [15]. An in vitro study in rat liver tritosomes and cytosol showed minimal degradation after 24 h of incubation with siRNA molecules of similar chemistry as cemdisiran, suggesting that siRNAs exhibit long residence times within hepatocytes. This long residence time leading to stable and extended duration is enabled by the slow turnover of the hepatocytes, with a lifespan that is reported to range from 180 to 400 days in HVs [20, 21]. Therefore, the long duration of action of cemdisiran in the current study can likely be attributed to the metabolic stability of siRNA, long hepatocyte residence times, and the slow turnover rate of human hepatocytes.

Lowering of free C5 levels is a clinically validated approach to treat complement-mediated diseases, and the on-target safety is supported by the marketed anti-C5 monoclonal antibodies eculizumab and ravulizumab-cwvz [22–26]. Because of the high circulating levels of free C5 in untreated patients (80–110 mg/L) [27, 28], a high degree of C5 suppression is required to maintain therapeutic effect in complement-mediated diseases. In the ravulizumab phase III studies in PNH patients, mean steady-state trough concentrations (C_{trough}) of 212.6–263.7 mg/L for eculizumab and 450.2–500.8 mg/L for ravulizumab have been shown to achieve high C5 suppression, leading to LDH lowering of 76.84% with ravulizumab and 76.02% with eculizumab

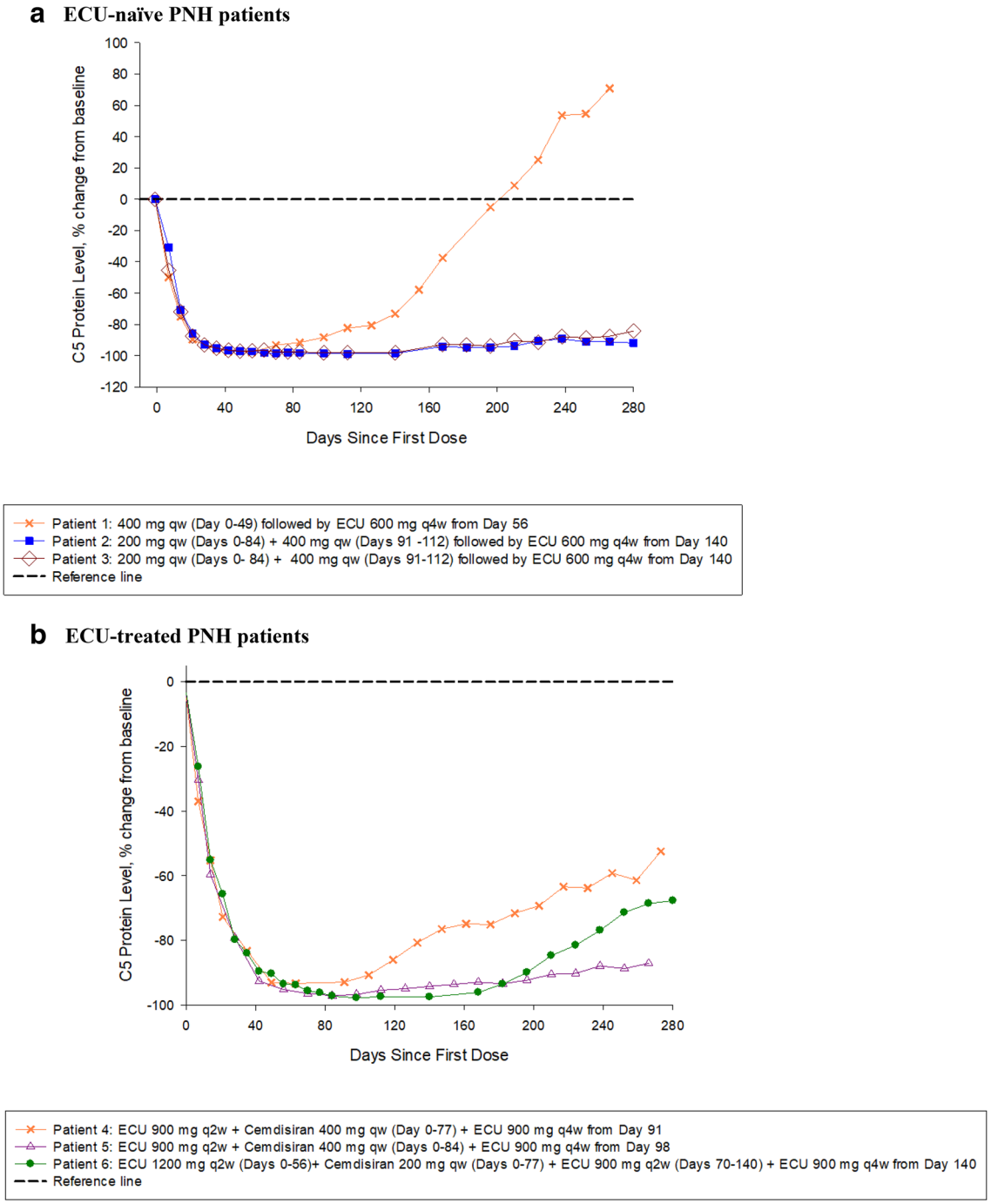

Fig. 8 Mean percentage change from baseline in C5 protein following multiple doses of cemdisiran in representative **a** eculizumab-naïve PNH patients and **b** eculizumab-treated PNH patients. Patient 6 received eculizumab 900 mg on day 14 instead of eculizumab 1200 mg. *C5* complement 5, *qw* every week, *q2w* every 2 weeks, *q4w* every 4 weeks, *ECU* eculizumab

in C5 inhibitor-naïve patients [13, 29]. These concentrations are achieved with a maintenance dosing regimen of every 2 weeks and every 8 weeks of intravenous infusions of 900 mg eculizumab and 3000–3600 mg ravulizumab, respectively [12, 13, 29]. Cemdisiran can reduce the circulating of free C5 protein in plasma by up to 99% for an extended period of time. These reduced C5 levels can be completely suppressed with lower concentrations of concomitantly administered anti-C5 antibody, allowing for lower or infrequent dosing with anti-C5 antibody. This hypothesis was evaluated in the current study by administering cemdisiran

with and without eculizumab in eculizumab-naïve and eculizumab-treated PNH patients.

In eculizumab-naïve PNH patients, where free C5 levels can be measured, administration of cemdisiran monotherapy resulted in a similar magnitude of C5 suppression of up to 99%, as observed in HVs (Figs. 6, 8a). In eculizumab-treated patients, only total C5 levels (free C5 + eculizumab bound C5) are measurable since the C5 assay cannot differentiate between the free and eculizumab-bound C5. In these patients, where nearly all the circulating C5 is bound to eculizumab, administration of cemdisiran decreased total C5 levels of up to 98% relative to baseline (Fig. 8b). A prolonged and sustained effect of cemdisiran on C5 reduction (> 50%) was observed up to 6–10 months after the last dose of cemdisiran in most PNH patients, during which time a lower dose and/or frequency of eculizumab 600–900 mg every 4 weeks was able to maintain C5 suppression similar to that observed with the labeled eculizumab regimen**.** In combination with cemdisiran, the total cumulative yearly maintenance dose of eculizumab can potentially be reduced to approximately 70% relative to the labeled dose of 900 mg every 2 weeks. These results support further evaluation of cemdisiran as monotherapy or in combination with a complement inhibitor antibody in PNH patients.

Cemdisiran is being considered for multiple complement-mediated indications, where cemdisiran can be administered as monotherapy or in combination with other C5 inhibitors depending on the therapeutic context. An appropriate dosing regimen for each indication will be evaluated in clinical trials.

Although the PK, PD, safety, and efficacy results are encouraging, the limitation of this study is that PD and efficacy data are available in a small number of PNH patients. These findings need to be confirmed in a larger and more diverse population of PNH patients.

Currently, cemdisiran is being evaluated in a phase II study for the treatment of IgAN at a monthly dose of 600 mg (NCT03841448).

5 Conclusions

Consistent with the PK/PD properties of GalNac conjugates, plasma concentrations of cemdisiran and its active metabolite AS(N-2)3′-cemdisiran, declined below the LLOQ within 48 h due to efficient and rapid uptake into hepatocytes while showing a rapid, robust, dose-dependent C5 suppression maintained up to 13 months following SD and MDs. Renal excretion was not a major elimination pathway. The long PD duration of action in the liver, low immunogenicity, and acceptable safety profiles enables a low, infrequent subcutaneous dosing schedule and supports further evaluation of cemdisiran in complement-mediated diseases as monotherapy or in combination with an anti-C5 antibody.

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Declarations

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Conflict of interest Prajakta Badri, Jae Kim, Xuemin Jiang, Anna Borodovsky, Nader Najafian, Valerie A. Clausen, Varun Goel, Bahru Habtemariam, and Gabriel J. Robbie are/were employees of Alnylam Pharmaceuticals Inc. and may hold Alnylam stocks or options.

Ethical Approval This study was conducted in accordance with the Good Clinical Practice Guideline as defined by the International Conference on Harmonisation, the Declaration of Helsinki, and all applicable federal and local regulations. The study was approved by independent Institutional Review Boards.

Consent to participate Written informed consent was obtained from each subject before any study related procedures were performed.

Consent for publication The authors, jointly and severally, give the Publisher the permission to publish the Work.

Availability of data and material The authors declare that [the/all other] data supporting the findings of this study are available within the article [and its supplementary information files].

Code availability Not applicable.

Informed Consent Written informed consent was obtained from each subject before any study-related procedures were performed.

Author contributions Prajakta Badri contributed to the data analyses for this manuscript, interpretation of results, writing and reviewing of the manuscript. Xuemin Jiang, Anna Borodovsky, Nader Najafian, Jae Kim, Valerie A. Clausen, Varun Goel, Bahru Habtemariam and Gabriel J. Robbie contributed to the study designs, interpretation of results, and writing and reviewing of the manuscript.

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