Supplementary Material

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

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Study Design

Part C was initiated after the SRC confirmed clinically meaningful inhibition of C5 and complement pathway activity, and favorable risk-benefit assessment in Parts A and B. Clinical activity of cemdisiran monotherapy was defined as clinically meaningful suppression (≤1.5 × upper limit of normal [ULN]) of intravascular hemolysis (LDH assay). These findings determined whether to continue with cemdisiran monotherapy, or to explore whether reduced maintenance eculizumab dosages could prevent residual intravascular hemolysis (maintenance eculizumab dose adjustment was at the discretion of the investigator).

Inclusion criteria

For the Japanese subgroup in Part A, subjects were eligible if (1) parents and all 4 grandparents were Japanese, (2) subjects were born in Japan, (3) had a valid Japanese passport, (4) had resided outside of Japan for <5 years, (5) and were ≥20 years old.

Exclusion criteria

Key exclusion criteria common to Parts A–C included a known or suspected hereditary asymptomatic complement deficiency; history of allergic reaction to oligonucleotides or N-acetylgalactosamine or meningococcal infection; and suspected active viral, bacterial, or fungal infection within 14 days prior to initiation of the study.

Key exclusion criteria specific for Parts A and B included complement activity below reference range using CAP ELISA; an international normalized ratio above reference range at screening; and abnormal liver function (alanine aminotransferase [ALT] or aspartate aminotransferase above normal range and total bilirubin, alkaline phosphatase, or albumin outside the reference range and considered clinically relevant by the investigator at screening and Day 1).

Key exclusion criteria for Part C included a history of venous or arterial thromboembolic events within the previous 12 months and abnormal liver function (ALT >2 x ULN) and considered clinically relevant by the investigator.

Supplementary Table S1. Demographic characteristics of subjects enrolled who received cemdisiran or placebo (3:1 ratio) as single doses in Part A

n (%)	Placebo (n=8)	Cemdisiran Dose Cohort								All Cemdisiran Treated n=24
		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	
Age, years Mean Min, max	26 20, 37	24 20, 26	33 28, 41	22 21, 24	27 22, 32	23 20, 27	30 26, 38	30 22, 38	27 22, 33	27 20, 41
Male sex, %	6 (75)	3 (100)	2 (67)	3 (100)	2 (67)	2 (67)	0	3 (100)	1 (33)	16 (67)
Race, n (%) Asian Black/African American White/Caucasian Other	 3 (37.5) 0 4 (50.0) 1 (12.5)	 0 1 (33.3) 1 (33.3) 1 (33.3	 3 (100) 0 0 0	 0 2 (66.7) 1 (33.3) 0	 3 (100) 0 0 0	 1 (33.3) 0 1 (33.3) 1 (33.3)	 2 (66.7) 0 1 (33.3) 0	 3 (100) 0 0 0	 0 1 (33.3) 2 (66.7) 0	 12 (50.0) 4 (16.7) 6 (25.0) 2 (8.3)
Body weight (kg), mean (SD)	66.1 (9.24)	88.0 (6.40)	61.4 (10.81)	67.4 (2.95)	59.5 (19.04)	64.5 (7.09)	60.2 (3.77)	67.5 (4.21)	70.5 (18.28)	67.4 (12.62)

SD, standard deviation.

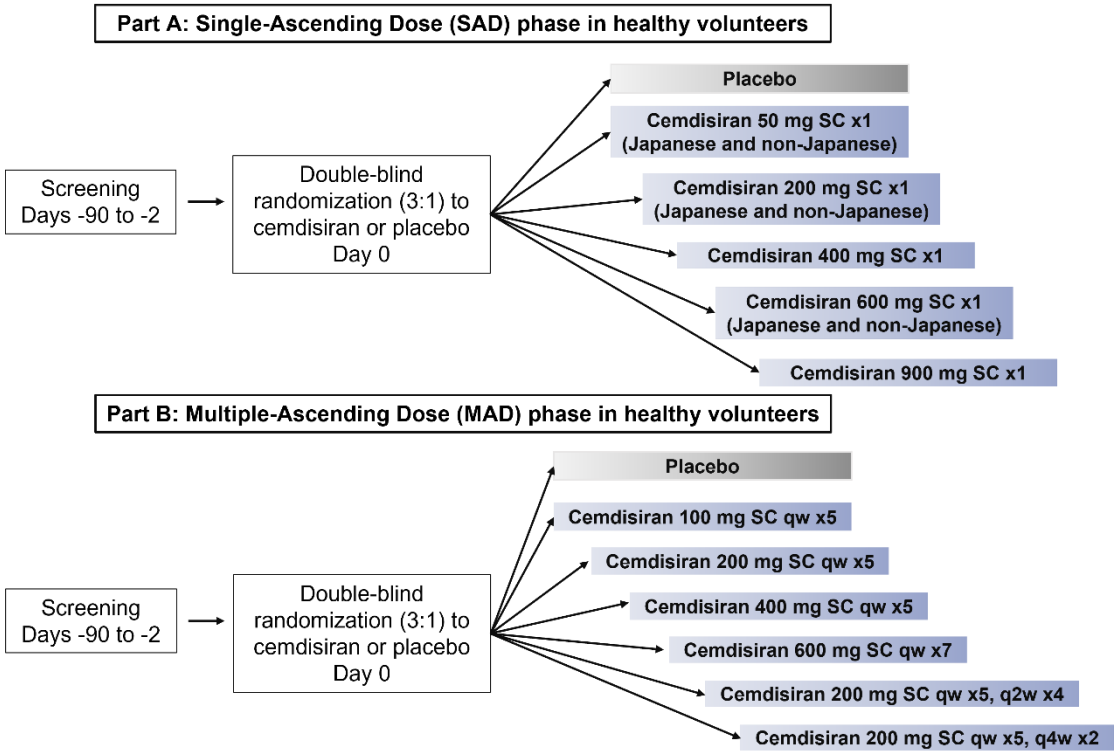
Supplementary Table S2. Demographic characteristics of subjects enrolled who received cemdisiran or placebo (3:1 ratio) as multiple doses in Part B

n (%)	Placebo n=6	Cemdisiran Dose Cohort						All Cemdisiran Treated n=18
		100 mg qw × 5 n=3	200 mg qw × 5 n=3	400 mg qw × 5 n=3	600 mg q2w × 7 n=3	200 mg qw × 5, q2w × 4 n=3	200 mg qw × 5, qm × 2 n=3	
Age, years Mean Min, max	27 20, 38	32 24, 39	29 26, 32	27 25, 30	29 24, 32	26 23, 30	23 19, 30	28 19, 39
Male sex, %	2 (33.3)	2 (66.7)	1 (33.3)	2 (66.7)	2 (66.7)	2 (66.7)	2 (66.7)	11 (61.1)
Race, n (%) White/Caucasian Other	 5 (83.3) 1 (16.7)	 3 (100) 0	 3 (100) 0	 3 (100) 0	 3 (100) 0	 3 (100) 0	 3 (100) 0	 18 (100) 0
Body weight (kg), mean (SD)	71.4 (8.60)	72.3 (12.05)	61.2 (6.85)	75.8 (12.44)	69.9 (7.86)	73.9 (4.82)	82.7 (10.25)	72.6 (10.36)
Median duration of treatment, days (range)	57 (29–85)	29 (29, 29)	29 (29, 29)	29 (29. 29)	85 (71, 85)	85 (85, 85)	85 (85, 85)	—

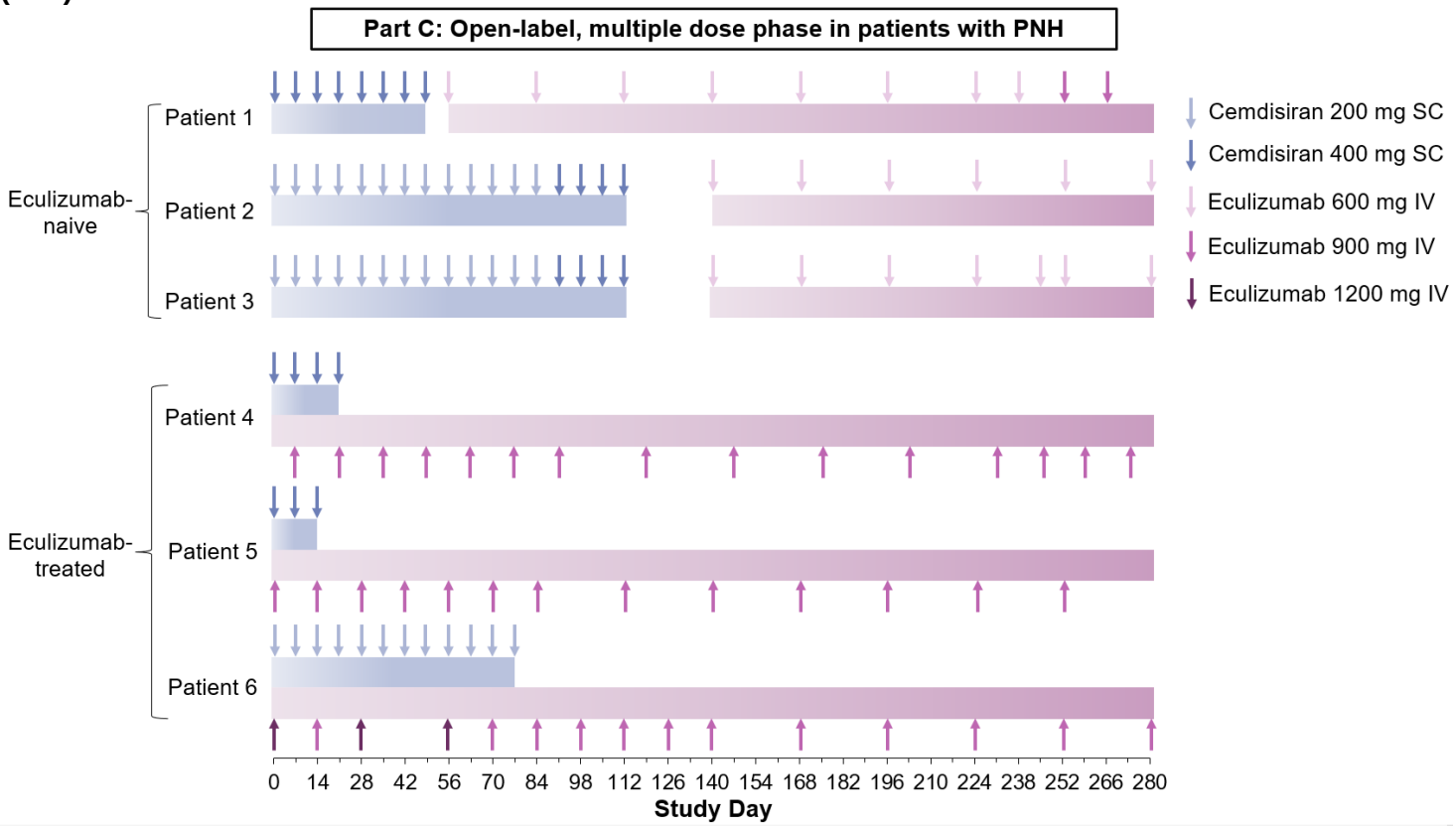
qm, once a month; qw, once weekly; q2w, every other week; SD, standard deviation.

Supplementary Figure S1. Study design: Part A, Single-ascending dose phase in healthy adults; Part B, Multiple ascending dose phase in healthy adults (a); Part C, Open-label, multiple dose phase in patients with PNH (b).

(S1a)



(S1b)



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.
ECU, eculizumab; IV, intravenous; PNH, paroxysmal nocturnal hemoglobinuria; qw, once weekly; q2w, once every 2 weeks or biweekly; q4w, once every 4 weeks or once a month; SC, subcutaneous administration; SRC, Safety Review Committee.