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Terminal complement inhibition and control of hemolysis in patients with paroxysmal nocturnal hemoglobinuria who switched from high-dose eculizumab to ravulizumab: a phase IV, single-arm clinical trial

by Morag Griffin, Shreyans Gandhi, Richard J. Kelly, Talha Munir, Roochi Trikha, Eden Hicks, Deepak Jain, Masayo Ogawa, Ji Yu, Petra Muus, and Austin G. Kulasekararaj

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Terminal complement inhibition and control of hemolysis in patients with paroxysmal nocturnal hemoglobinuria who switched from high-dose eculizumab to ravulizumab: a phase IV, single-arm clinical trial

Morag Griffin,[1] Shreyans Gandhi,[2] Richard J. Kelly,[1] Talha Munir,[1] Roochi Trikha,[2] Eden Hicks,[3] Deepak Jain,[3] Masayo Ogawa,[3] Ji Yu,[3] Petra Muus,[1] and Austin G. Kulasekararaj[2,4]

[1]St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK

[2]King's College Hospital, National Institute for Health and Care Research (NIHR) Wellcome Trust King's Clinical Research Facility, London, UK

[3]Alexion, AstraZeneca Rare Disease, Boston, MA, USA

[4]King's College London, London, UK

Running head: High-dose eculizumab to ravulizumab switch in PNH

Correspondence: M. GRIFFIN - m.griffin@nhs.net

Data-sharing statement

Alexion, AstraZeneca Rare Disease will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods like data de-identification, pseudonymization, or anonymization (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at https://www.alexionclinicaltrialtransparency.com/data-requests/

Trial registration

ClinicalTrials.gov identifier: NCT04320602

EudraCT number: 2019-003440-74

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Author ORCID ID details

Morag Griffin	0000-0002-4287-0595
Shreyans Gandhi	0000-0003-3532-231X
Richard J Kelly	0000-0002-3318-9482
Talha Munir	0000-0002-2901-0769
Roochi Trikha	-
Eden Hicks	0000-0002-4975-4407
Deepak Jain	-
Masayo Ogawa	-
Ji Yu	-
Petra Muus	0000-0002-2560-3882
Austin G. Kulasekararaj	0000-0003-3180-3570

Disclosures

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Author contributions

MG, SG, RK, TM, PM, RT, and AK recruited patients, collected data, analyzed and interpreted the data, contributed to the manuscript, and approved the final version. EH, DJ, MO, and JY developed the protocol, analyzed and interpreted the data, contributed to the manuscript, and approved the final version.

Letter to the Editor

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, chronic, hematological disorder characterized by uncontrolled terminal complement activation, intravascular hemolysis (IVH), and potentially life-threatening thromboses, leading to early mortality.[1,2] The complement component 5 (C5) inhibitors eculizumab and its analog ravulizumab (the current standard of care) are approved treatments for PNH. Both treatments inhibit IVH, reduce incidence of thrombosis, and are associated with improvements in anemia, transfusion dependence, quality of life, and survival when administered at their respective 2-week (eculizumab) and 8-week (ravulizumab) dosing intervals.[3-9] Some patients treated with eculizumab at the approved fixed-dose regimen of 900 mg every 2 weeks (Q2W) experience IVH toward the end of the fixed-dosing interval.[6,10] This can be managed by shortening the dosing interval, which may increase the treatment burden for both patients and healthcare providers,[7,11,12] or by using a higher than approved dose.[6,10]

Ravulizumab offers immediate, complete, and sustained inhibition of complement-mediated IVH at 8-week dosing intervals.[7,11,12] In clinical trials, weight-based doses of ravulizumab demonstrated non-inferiority and a comparable safety profile to approved fixed-dose eculizumab in patients with PNH,[11,12] with durable efficacy and tolerance for up to 4 years following switch from fixed-dose eculizumab.[7] Although a single case describing treatment switch from high-dose eculizumab to standard weight-based ravulizumab has been reported,[13] there are currently no clinical trial data reporting the feasibility and safety of this switch in patients with PNH.

Here, we report findings from study 401 (NCT04320602), a phase IV, single-arm, two-center trial conducted in the UK between April 2021 and December 2022 that was designed to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of switching treatment from high-dose intravenous (IV) eculizumab (1200 mg Q2W) to weight-based IV ravulizumab Q8W in patients with PNH. Included patients were aged ≥18 years with a documented diagnosis of PNH, who had received high-dose IV eculizumab for ≥3 months prior to screening and had lactate dehydrogenase (LDH) levels ≤2 × upper limit of normal (ULN; 281.0 U/L, central laboratory assessment) at screening. All patients had received meningococcal vaccines A/C/Y/W-135 conjugate and B within 3 years prior to study start. Key exclusion criteria were body weight <40 kg at screening, history of major adverse vascular events (MAVEs) within 6 months prior to enrollment, bone marrow transplantation,

malignancy within 5 years prior to enrollment, platelet count <30 × 10^9/L, and neutrophil count <0.5 × 10^9/L. Ethical approval for this study was received from Yorkshire and the Humber – Leeds East Research Ethics Committee (reference: 20/YH/0105). Patients consented to study participation and could withdraw at any time.

During the 3-month pre-baseline period, patients continued to receive stable doses of eculizumab 1200 mg Q2W; LDH, free C5, and hemoglobin (Hb) levels were measured on day −85 [LDH and Hb only], day −57, and day −15, immediately before eculizumab infusion. On day 1 (baseline), patients switched treatment to ravulizumab, receiving an initial loading dose (patients weighing ≥40-<60 kg: 2400 mg; patients weighing ≥60-<100 kg: 2700 mg; patients weighing ≥100 kg: 3000 mg), followed by a maintenance dose on day 15 and Q8W thereafter (patients weighing ≥40-<60 kg: 3000 mg; patients weighing ≥60-<100 kg: 3300 mg; patients weighing ≥100 kg: 3600 mg) up to day 351 (end of study).

The primary endpoint was the proportion of patients who experienced free C5□associated breakthrough IVH (also called breakthrough hemolysis [BTH]). BTH was defined as the presence of at least one new or worsening PNH symptom or sign of IVH, with LDH ≥2 × ULN and free C5 concentration ≥0.5 μg/mL. Secondary endpoints included LDH percentage change, proportion of patients who received a transfusion, and proportion of patients with stabilized Hb (avoidance of a ≥2 g/dL decrease in Hb concentration in the absence of transfusion). Safety endpoints included proportion of patients with treatment-emergent adverse events (TEAEs) and serious TEAEs, and proportion of patients who developed antidrug antibodies to ravulizumab.

Overall, 18 patients were screened and enrolled into the study, all of whom completed study treatment up to day 351. Baseline characteristics of the study population are presented in Table 1. Two patients had low red blood cell clone sizes (5%) although their monocyte clone size was 24% and 71%, respectively.

Per-patient laboratory values are available in *Online Supplementary Table S1*. Throughout the study period, individual serum free C5 concentrations were <0.5 μg/mL in all participants (Figure 1A). One instance of BTH was reported in a patient on day 61 (symptoms: abdominal pain, fatigue, macroscopic hemoglobinuria, and shortness of breath), which was considered related to vaccinations for COVID-19 and influenza received the day prior to the event. At the study time point prior to the BTH event (day 15), LDH level was ≤1 × ULN, free C5

concentration was 0.0192 μg/mL, and Hb level was 12.0 g/dL. At 4 days post-event, the local laboratory-reported LDH level was 2 × ULN, while the free C5 concentration was 0.11 μg/mL and the Hb level was 11.5 g/dL. The patient continued ravulizumab treatment without altering the dose or dosing interval, and on day 127 their LDH level was ≤1 × ULN.

Central laboratory LDH levels were ≤1.5 × ULN for all patients (Figure 1B). Median Hb levels ranged from 10.6-11.3 g/dL during the study (*Online Supplementary Figure S1 and Table S1*), with eleven patients maintaining stable Hb (avoidance of a ≥2 g/dL decrease in Hb in the absence of transfusion) up to day 351. Six patients (33.3%) required a total of 10 transfusions during the ravulizumab treatment period. Of these patients, two had received transfusions within 12 months prior to enrollment (one of whom required a transfusion during the pre-baseline period [day −14]). Hb levels prior to transfusion ranged from 4.6 g/dL to 8.0 g/dL; investigator-recorded reasons for transfusion other than low Hb (*n*=7) included COVID-19 infection (*n*=1), chest infection (*n*=1), and extravascular hemolysis (*n*=1); see *Online Supplementary Figure S2* for details.

In total, 16 patients (88.9%) reported 63 TEAEs during the ravulizumab treatment period, which were predominantly mild (27.8%) or moderate (44.4%) in severity; none led to death or study withdrawal. Five patients (27.8%) experienced TEAEs considered to be treatment-related (nine events, comprising fatigue, non-cardiac chest pain, headache, asthenia, and nail ridging; Table 2). Serious TEAEs were reported in three patients (16.7%; comprising pneumonia, urinary tract infection, retinal hemorrhage, pyrexia, and headache), none of which were deemed related to treatment. One extravascular hemolysis event was reported as an explanation for why a patient required transfusion; it is possible that other patients experienced some degree of extravascular hemolysis which was not reported as an adverse event (hemoglobin and reticulocyte count data for individual patients are shown in *Online Supplementary Table S1*). There were no MAVEs, meningococcal infections, or clinical signs of antidrug antibodies to ravulizumab. Following study completion, one subclavian vein thrombosis event was reported on day 461; no known complement-activating events were identified in this patient.

This clinical trial was the first to investigate the feasibility of switching treatment from high-dose eculizumab to weight-based ravulizumab in patients with PNH who required a higher than approved dose of eculizumab for complete C5 inhibition over the 14-day dosing interval. Switching treatment to weight-based ravulizumab Q8W maintained complete and sustained

inhibition of terminal complement activity and complement-mediated IVH. Free C5 concentrations were <0.5 μg/mL at all study time points, indicating appropriate suppression of C5 activity, thereby satisfying the primary outcome for this study. Hb levels were also well controlled, with the majority of patients avoiding transfusion during the study. Therefore, despite needing a higher dose of eculizumab, approved weight-based dosing of ravulizumab was sufficient for PNH disease control in these patients, and there was no need to shorten the 8-week dosing interval.

No new ravulizumab-associated safety signals were identified and adverse events were comparable to those previously reported in adults with PNH.[7,11,12] Importantly, there were no meningococcal infections or MAVEs, and no TEAEs that led to death or study withdrawal. The subclavian vein thrombosis reported post-study occurred in a patient whose weight was at the upper limit of the 60–100 kg weight range for their ravulizumab dose, suggesting that they may have required the higher weight-based dose of ravulizumab. However, as the patient had sufficient disease control during the study period, further investigation is required.

Over the treatment period, 12/18 patients (66.7%) avoided transfusion. In previous trials of ravulizumab in patients with PNH, transfusion avoidance levels of 76.6% and 86.5% were reported following 1 year of treatment;[8,9] the lower proportion in this study may be owing to the smaller sample size, the shorter follow-up and differences in the patient populations.[8,9]

The main limitation of this study is the small sample size, which precludes formal statistical comparisons; this was to be expected given that this study was based on a subpopulation of patients with a rare disease receiving a dose above the approved fixed-dose regimen. In addition, the study recruited patients from two referral centers in a single country; consequently, the findings should be interpreted with caution and may not be generalizable to the wider PNH population. Finally, only patients receiving eculizumab 1200 mg Q2W were included in the study, so findings may not be applicable to the small proportion of patients requiring even higher doses of eculizumab.

In summary, switching treatment from high-dose IV eculizumab (1200 mg Q2W) to standard, weight‐based IV ravulizumab demonstrated minimal changes in laboratory measures at an improved dosing interval, with no new safety signals reported. Our findings support the use of weight-based ravulizumab as a suitable and well-tolerated alternative to eculizumab, even

for patients who had experienced pharmacokinetic BTH during standard dose eculizumab treatment.

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Tables

Table 1. Patient baseline demographics and clinical characteristics (*N*=18).

	Total (*N*=18)
Age, median (range),[a] years	58.0 (22–73)
Age at PNH diagnosis, median (range), years	41.0 (18–62)
Male, *n* (%)	12 (66.7)
Weight, median (range),[b] kg	81.70 (49.5–114.0)
Weight category,[b] *n* (%)	
≥40 kg to <60 kg	2 (11.1)
≥60 kg to <100 kg	13 (72.2)
≥100 kg	3 (16.7)
Total RBC PNH clone size at screening, median (range), %	85.5 (5–99)
Granulocyte clone size at screening, median (range), %	98.5 (7–100)
Monocyte clone size at screening, median (range), %	98.0 (24–99)
LDH level, median (range),[c] U/L	230.05 (158.5–343.0)
LDH ≤1 × ULN[c,d]	17 (94.4)
Hb concentration, median (range),[b] g/dL	11.1 (7.8–14.1)
Free C5 concentration, median (range),[b] μg/mL	0.0092 (0.0092–0.0483)
Received pRBC/transfusions during 3-month pre-baseline period, *n* (%)	1 (5.6)
History of aplastic anemia, *n* (%)	7 (38.9)
History of any conditions associated with MAVE, *n* (%)[e]	8 (44.4)
Hepatic/portal vein thrombosis (Budd–Chiari syndrome)	3 (16.7)
Thrombophlebitis/deep vein thrombosis	2 (11.1)
Mesenteric/visceral arterial thrombosis or infarction	1 (5.6)
Myocardial infarction	1 (5.6)
Cerebral vein thrombosis	1 (5.6)
Transient ischemic attack	1 (5.6)
Other[f]	5 (27.8)

[a]At the time of informed consent.

[b]Considered the most recent value captured prior to the first ravulizumab infusion. Free C5 concentration <0.00915 μg/mL was utilized as the lower limit of quantification.

[c]Calculated using the average of all screening assessments (day −85, day −57, and day −29) captured prior to the first ravulizumab infusion.

[d]LDH ULN: 281.0 U/L.

[e]*n* is the number of participants with at least one event in the category; three patients had findings in more than one category.

[f]Additional findings reported by investigator: extravascular hemolysis (*n*=1), minor myocardial damage (*n*=1), leg swelling (suspected deep vein thrombosis; *n*=1), sub-clinical pulmonary embolism (*n*=1), and thrombosis (chest; *n*=1).

C5: complement component 5; Hb: hemoglobin; LDH: lactate dehydrogenase; MAVE: major adverse vascular event; PNH: paroxysmal nocturnal hemoglobinuria; pRBC: packed red blood cell; RBC: red blood cell; ULN: upper limit of normal.

Table 2. Summary of TEAEs in patients with PNH who switched treatment from high-dose eculizumab to weight-based ravulizumab (*N*=18).

	Total (*N*=18)	
	***n* (%)**	**Number of events**
Any TEAE	16 (88.9)	63
Any serious TEAE	3 (16.7)	5
Infections and infestations	2 (11.1)	2
Pneumonia	1 (5.6)	1
Urinary tract infection	1 (5.6)	1
Eye disorders	1 (5.6)	1
Retinal hemorrhage	1 (5.6)	1
General disorders and administration site conditions	1 (5.6)	1
Pyrexia	1 (5.6)	1
Nervous system disorders	1 (5.6)	1
Headache	1 (5.6)	1
Any TEAE leading to death	0	–
Any TEAE leading to study withdrawal	0	–
TEAE by maximum CTCAE grade		
Grade 1: mild	5 (27.8)	–
Grade 2: moderate	8 (44.4)	–
Grade 3: severe	3 (16.7)	–
Grade 4: life-threatening	0	–
Grade 5: fatal	0	–
TEAE considered to be a MAVE	0	–
Any TEAE related to study drug	5 (27.8)	9
General disorders and administration site conditions	4 (22.2)	6
Fatigue	3 (16.7)	3
Non-cardiac chest pain	2 (11.1)	2
Asthenia	1 (5.6)	1
Nervous system disorders	2 (11.1)	2
Headache	2 (11.1)	2
Skin and subcutaneous tissue disorders	1 (5.6)	1
Nail ridging	1 (5.6)	1

CTCAE: Common Terminology Criteria for Adverse Events; MAVE: major adverse vascular event; PNH: paroxysmal nocturnal hemoglobinuria; TEAE: treatment-emergent adverse event.

Figure legend

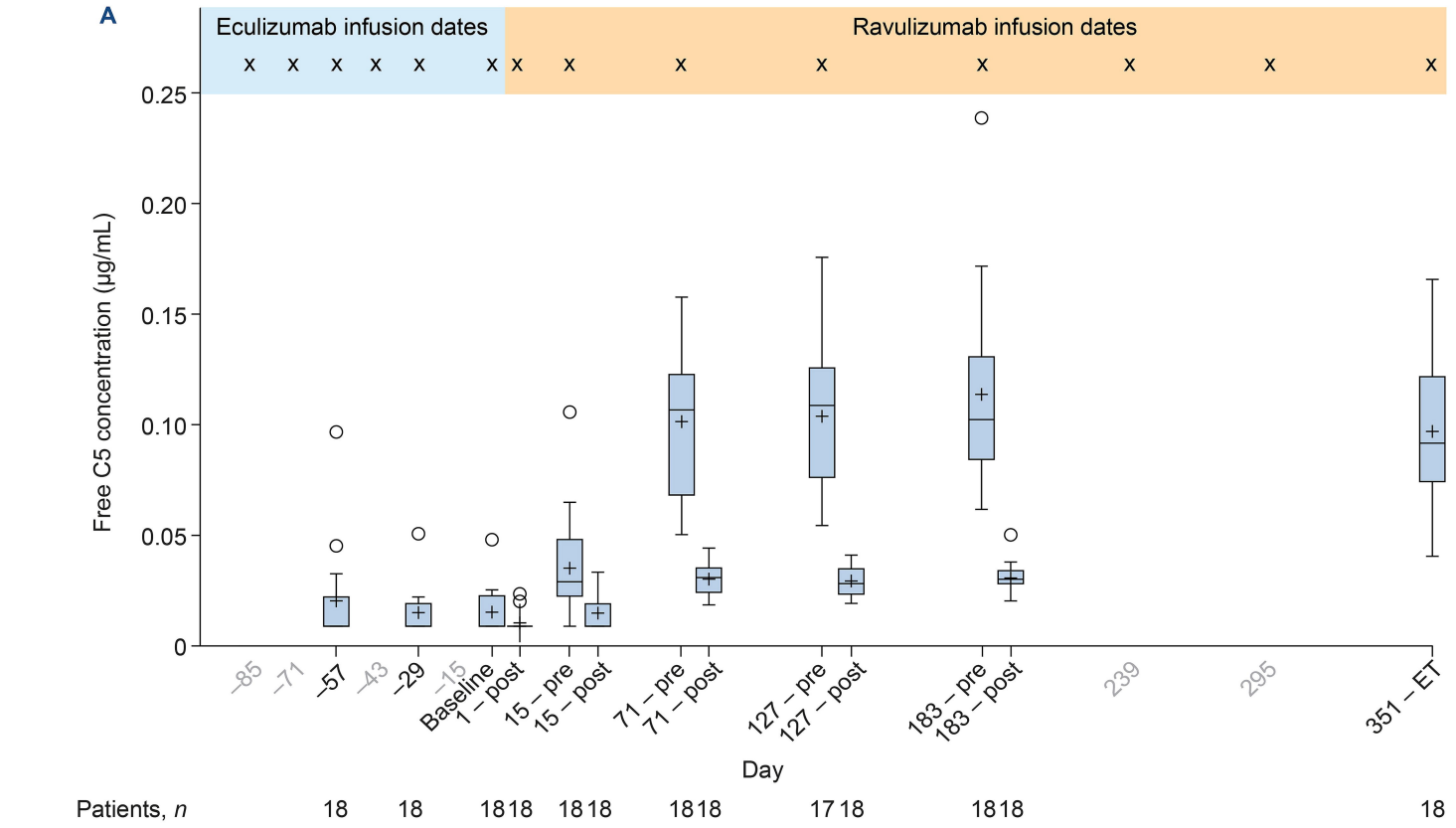
Figure 1. Laboratory measures over the study period. (A) Free C5 concentration and (B) mean (95% CI) LDH level.

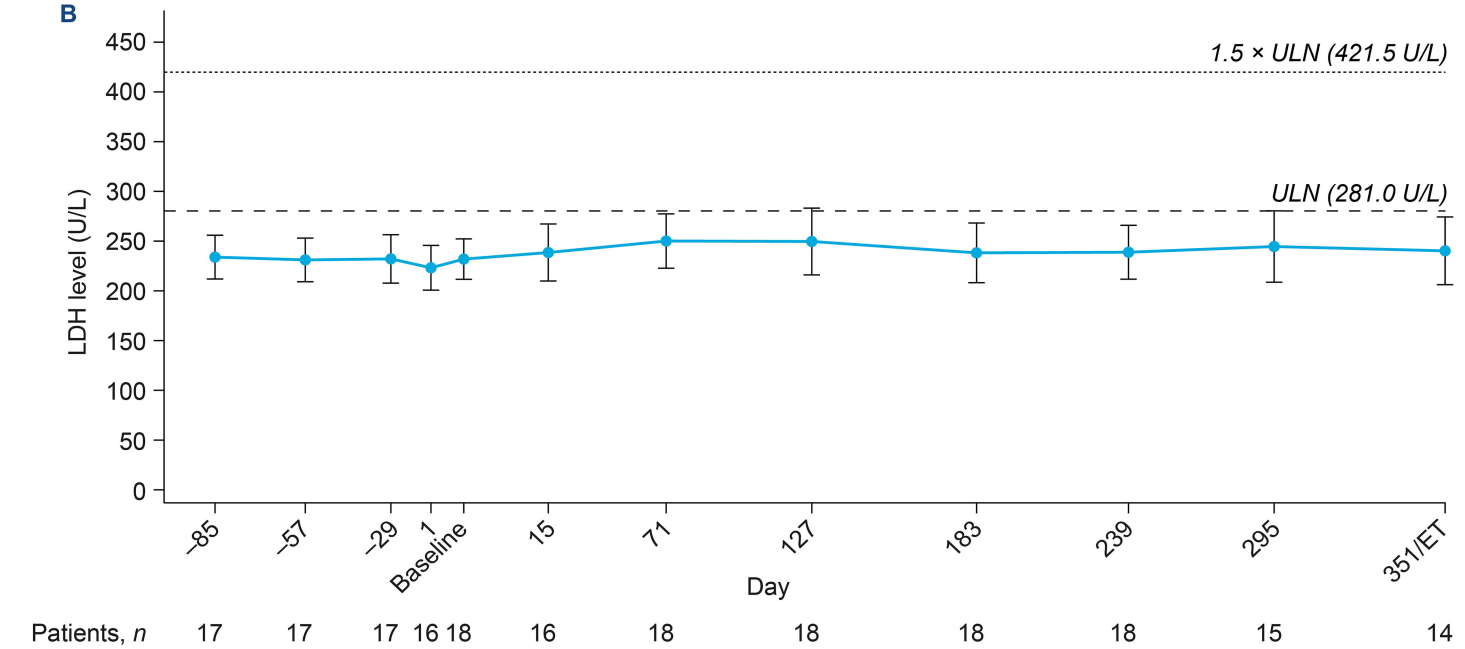
A free C5 level of <0.5 μg/mL indicates effective suppression of C5. Free C5 concentration <0.00915 μg/mL was utilized as the lower limit of quantification.

Baseline: the last non-missing value prior to the first study drug administration.

For box and whisker plots, cross (+) indicates arithmetic mean, horizontal line indicates median, upper and lower lines of box indicate 1st and 3rd quartiles (25th and 75th percentile), whiskers represent fences of 1.5 × IQR or minimum/maximum range if <1.5 × IQR and circles (o) indicate outliers.

C5: complement component 5; CI: confidence interval; ET: end of trial; IQR: interquartile range; LDH: lactate dehydrogenase; post: after ravulizumab infusion; pre: before ravulizumab infusion; ULN: upper limit of normal.


A
Eculizumab infusion dates
Ravulizumab infusion dates
Free C5 concentration (µg/mL)
0.25
0.20
0.15
0.10
0.05
0
–85
–71
–57
–43
–29
–15
Baseline
1 – post
15 – pre
15 – post
71 – pre
71 – post
127 – pre
127 – post
183 – pre
183 – post
239
295
351 – ET
Day
Patients, n
18
18
18 18
18 18
18 18
17 18
18 18
18


B
LDH level (U/L)
450
400
350
300
250
200
150
100
50
0
1.5 × ULN (421.5 U/L)
ULN (281.0 U/L)
–85
–57
–29
1
Baseline
15
71
127
183
239
295
351/ET
Day
Patients, n
17
17
17
16 18
16
18
18
18
18
15
14

Supplementary material

Table S1. Per-patient laboratory values throughout the study period (*N*=18).

	Patients, *N*=18																	
	01	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Patient sex **Age** **Weight**	**Male** **50 years** **108.0 kg**	**Female** **64 years** **85.9 kg**	**Male** **62 years** **80.4 kg**	**Female** **65 years** **93.1 kg**	**Female** **22 years** **49.5 kg**	**Female** **51 years** **89.3 kg**	**Male** **57 years** **70.1 kg**	**Male** **46 years** **72.0 kg**	**Female** **45 years** **71.5 kg**	**Male** **64 years** **114.0 kg**	**Male** **60 years** **82.3 kg**	**Male** **65 years** **71.6 kg**	**Male** **58 years** **78.1 kg**	**Male** **59 years** **97.6 kg**	**Female** **73 years** **56.6 kg**	**Male** **58 years** **81.1 kg**	**Male** **57 years** **90.1 kg**	**Male** **46 years** **101.0 kg**
LDH, U/L																		
Day −85*	240	344	245	294	191	255	233	206	203	252	223	211	248	151	245	216	233	–
Day –57*	246	327	215	278	174	255	233	227	276	213	240	191	239	166	170	–	242	251
Day –29*	202	358	226	291	213	235	265	251	249	224	223	188	–	163	160	234	251	227[a]
Day 1#	229	–	267	273	173	251	264	223	195	216	204	195	277	154	163	–	281	221
Baseline	229.25	343	238.25	284	187.75	249	248.75	226.75	230.75	226.25	222.5	196.25	254.67	158.5	184.5	225	251.75	232.5
Day 15#	174	–	247	381	226	–	244	228	214	206	220	229	266	156	197	302	263	275
Day 71#	179	314	271	317	212	246	208	238	198	284	229	190	378	181	272	233	300	262
Day 127#	166	271	251	451	292	269	221	225	306	205	239	197	311	183	173	236	280	228
Day 183#	171	394	208	284	231	266	197	277	256	211	226	181	338	186	167	198	257	253
Day 239#	161	276	258	320	185	250	225	227	219	179	229	201	371	214	184	240	275	298
Day 295#	143	–	248	305	218	–	171	236	273	187	236	243[b]	410	202	–	243	260	303
Day 351#	172	–	283	–	–	255	287	234	–	203	241	172	327	171	179	245	251	353
Hb, g/dL																		
Day –85*	12.4	12.8	–	9.9	–	12.1	11.2	10.9	12.9	12.0	–	9.1	–	12.6	8.7	9.0	11.2	–
Day –57*	10.3	12.4	10.1	–	11.3	11.0	10.9	10.3	13.3	12.5	–	9.1	14.1	13.0	9.0	8.7	11.9	–
Day –29*	11.0	11.1	8.9	9.2	11.2	–	10.0	9.4	12.9	12.5	11.1	9.4	–	13.3	9.3	8.2	11.6	–
Day 1#	11.8	11.5	10.0	9.3	10.4	–	10.6	10.8	13.0	12.4	–	9.3	–	13.6	8.9	7.8	11.4	12.8
Day 15#	10.6	11.4	9.6	–	10.2	10.9	10.6	10.5	12.7	12.0	–	8.7	–	13.5	8.6	10.2	10.7	13.2

	Patients, *N*=18																	
	01	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Patient sex **Age** **Weight**	**Male** **50 years** **108.0 kg**	**Female** **64 years** **85.9 kg**	**Male** **62 years** **80.4 kg**	**Female** **65 years** **93.1 kg**	**Female** **22 years** **49.5 kg**	**Female** **51 years** **89.3 kg**	**Male** **57 years** **70.1 kg**	**Male** **46 years** **72.0 kg**	**Female** **45 years** **71.5 kg**	**Male** **64 years** **114.0 kg**	**Male** **60 years** **82.3 kg**	**Male** **65 years** **71.6 kg**	**Male** **58 years** **78.1 kg**	**Male** **59 years** **97.6 kg**	**Female** **73 years** **56.6 kg**	**Male** **58 years** **81.1 kg**	**Male** **57 years** **90.1 kg**	**Male** **46 years** **101.0 kg**
Day 71[#]	11.9	11.9	–	9.2	10.4	10.7	10.6	10.0	12.9	11.5	11.2	9.8	–	14.3	8.3	9.0	11.3	12.5
Day 127[#]	11.1	11.0	8.5	8.6	10.6	11.3	11.3	10.7	11.6	12.4	–	9.5	13.5	14.1	8.3	9.6	10.8	12.9
Day 183[#]	10.9	11.3	10.1	9.6	10.6	11.8	11.0	10.4	12.8	12.3	10.9	9.5	12.5	13.4	8.0	11.4	11.5	12.8
Day 239[#]	10.7	12.1	9.6	9.4	10.4	11.9	10.9	10.5	13.1	12.1	–	9.4	12.9	13.8	7.4	8.9	11.4	11.6
Day 295[#]	11.3	12.3	8.9	9.5	–	12.6	12.5	10.5	12.8	12.1	11.0	9.4	11.9	13.8	8.7	9.0	10.6	12.0
Day 351[#]	12.1	12.0	8.2	7.8	–	12.0	11.1	10.1	11.1	11.9	11.1	10.0	11.3	13.3	7.2	8.1	10.9	11.4
Free C5, µg/mL																		
Day –57[*]	0.0455	0.0244	<0.0183	<0.0183	<0.0183	<0.0183	<0.0183	0.0224	<0.0183	<0.0183	<0.0183	<0.0183	0.0970	0.0329	<0.0183	0.0203	0.0185	0.0190
Day –29[*]	0.0510	0.0223	<0.0183	<0.0183	<0.0183	<0.0183	<0.0183	0.0222	<0.0183	0.0190	<0.0183	<0.0183	<0.0183	0.0224	<0.0183	0.0194	<0.0183	0.0189
Day 1[#] Pre-dose Post-dose	 0.0483 0.0238	 0.0229 <0.0183	 <0.0183 <0.0183	 <0.0183 <0.0183	 <0.0183 <0.0183	 <0.0183 <0.0183	 <0.0183 <0.0183	 0.0256 <0.0183	 <0.0183 <0.0183	 <0.0183 <0.0183	 <0.0183 <0.0183	 <0.0183 <0.0183	 <0.0183 <0.0183	 0.0250 0.0204	 <0.0183 <0.0183	 0.0251 <0.0183	 <0.0183 <0.0183	 0.0229 <0.0183
Day 15[#] Pre-dose Post-dose	 0.1060 0.0336	 0.0492 0.0233	 0.0257 <0.0183	 0.0321 <0.0183	 <0.0183 <0.0183	 0.0281 <0.0183	 0.0280 <0.0183	 0.0652 0.0248	 <0.0183 <0.0183	 0.0295 0.0192	 0.0228 <0.0183	 <0.0183 <0.0183	 0.0290 <0.0183	 0.0484 0.0193	 <0.0183 <0.0183	 0.0591 0.0218	 0.0310 0.0191	 0.0469 0.0191
Day 71[#] Pre-dose Post-dose	 0.1580 0.0445	 0.1430 0.0405	 0.0897 0.0320	 0.1130 0.0318	 0.0602 0.0227	 0.0888 0.0263	 0.1230 0.0428	 0.1490 0.0311	 0.0533 0.0202	 0.1050 0.0369	 0.0685 0.0245	 0.0506 0.0198	 0.1210 0.0312	 0.1070 0.0310	 0.0537 0.0188	 0.1320 0.0355	 0.1080 0.0321	 0.1070 0.0267
Day 127[#] Pre-dose Post-dose	 0.1760 0.0413	 0.1580 0.0371	 0.0902 0.0284	 0.1330 0.0351	 0.0547 0.0195	 0.0942 0.0285	 0.1270 0.0411	 – 0.0196	 0.0715 0.0278	 0.0834 0.0326	 0.0765 0.0269	 0.0706 0.0222	 0.1300 0.0237	 0.1100 0.0334	 0.0676 0.0218	 0.1260 0.0368	 0.1120 0.0319	 0.1090 0.0256
Day 183[#] Pre-dose Post-dose	 0.2390 0.0505	 0.1720 0.0352	 0.0909 0.0304	 0.108 0.031	 0.0620 0.0211	 0.0833 0.0284	 0.0130 0.0382	 0.1620 0.0345	 0.0654 0.0231	 0.0972 0.0341	 0.0878 0.0304	 0.0777 0.0270[c]	 0.1500 0.0296	 0.1090 0.0306	 0.0846 0.0206	 0.1310 0.0296	 0.1150 0.0343	 0.0873 0.0291
Day 351[#]	0.1660	0.1630	0.0864	0.1090	0.0408	0.0706	0.1330	0.1220	0.0496	0.0886	0.0607	0.0746	0.1220	0.1020	0.0754	0.1250	0.0953	0.0868

	Patients, *N*=18																	
	01	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Patient sex **Age** **Weight**	**Male** **50 years** **108.0 kg**	**Female** **64 years** **85.9 kg**	**Male** **62 years** **80.4 kg**	**Female** **65 years** **93.1 kg**	**Female** **22 years** **49.5 kg**	**Female** **51 years** **89.3 kg**	**Male** **57 years** **70.1 kg**	**Male** **46 years** **72.0 kg**	**Female** **45 years** **71.5 kg**	**Male** **64 years** **114.0 kg**	**Male** **60 years** **82.3 kg**	**Male** **65 years** **71.6 kg**	**Male** **58 years** **78.1 kg**	**Male** **59 years** **97.6 kg**	**Female** **73 years** **56.6 kg**	**Male** **58 years** **81.1 kg**	**Male** **57 years** **90.1 kg**	**Male** **46 years** **101.0 kg**
Reticulocyte count, × 10^9/L																		
Day –85[*]	91.4	354.8	–	278.6	–	120.6	195.6	269.6	92.7	260.8	–	321.1	–	131.2	230.5	234.5	326.0	–
Day 1[#]	112.6	247.2	207.8	263.3	62.1	–	199.2	220.5	61.0	264.5	–	308.5	–	132.0	223.4	282.7	329.0	374.7
Day 351[#]	131.6	264.5	244.5	299.4	–	128.3	225.6	225.0	50.6	227.1	–	274.6	476.5	118.7	220.2	321.1	335.2	453.2

Shaded cells represent study visits following a transfusion.

Patient numbers align with those in *Online Supplementary Figure S2*.

[*]Eculizumab infusion day.

[#]Ravulizumab infusion day.

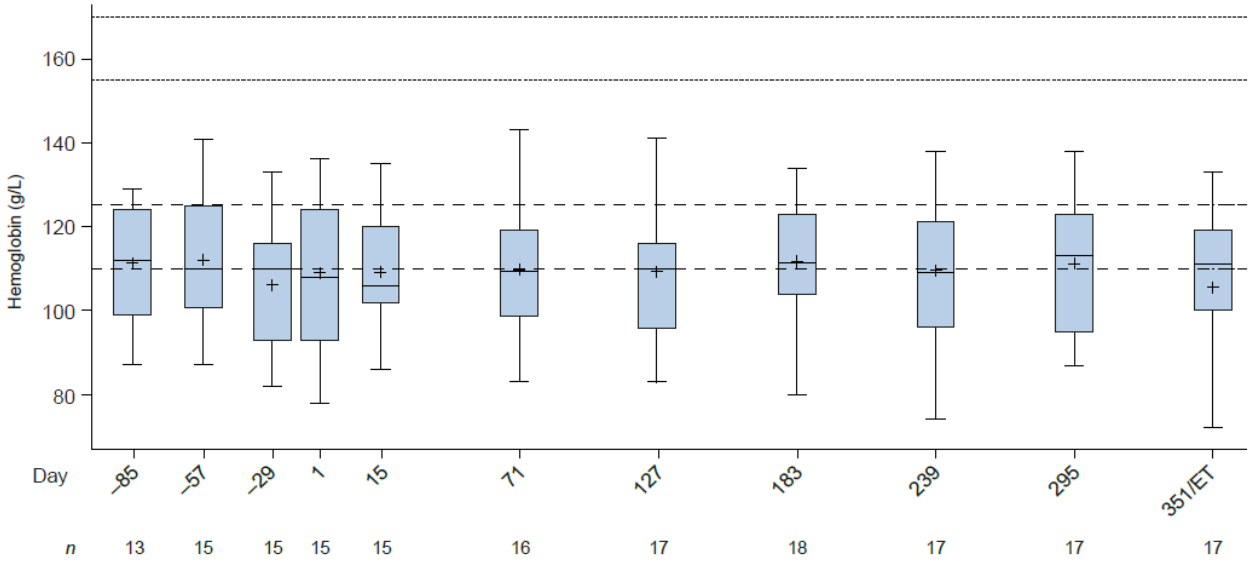
[a]One unscheduled visit was reported on day –1 (LDH recorded as 231 U/L).

[b]One unscheduled visit was reported on day 319 (LDH recorded as 202 U/L).

[c]One unscheduled visit was reported on day 319 (free C5 recorded as 0.0484 µg/dL).

C5: complement component 5; Hb: hemoglobin; LDH: lactate dehydrogenase.

Figure S1. Hemoglobin concentration over time, measured during pre-baseline and ravulizumab treatment period (*N*=18).



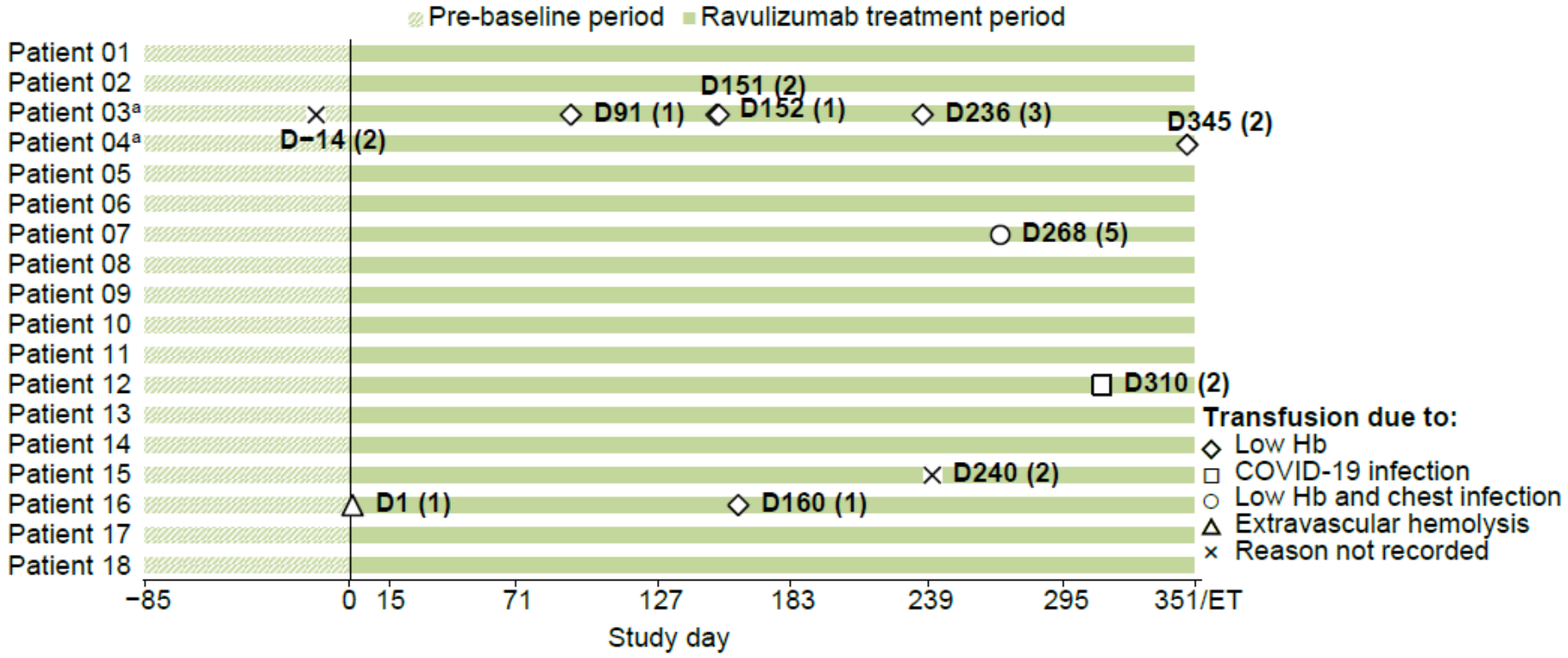
Data are irrespective of transfusions.

Box and whisker plots: cross (+), arithmetic mean; horizontal line, median; box, 1st and 3rd quartiles (25th and 75th percentile); whiskers, fences of 1.5 × IQR or minimum/maximum range if <1.5 × IQR.

Dashed horizontal lines indicate lower normal value (110 g/L for women and 125 g/L for men). Dotted horizontal lines indicate upper normal value (155 g/L for women and 170 g/L for men).

ET: end of trial; IQR: interquartile range.

Figure S2. Transfusions during the 3 month pre-baseline period and ravulizumab treatment period (*N*=18).



The values in parentheses indicate the number of units of packed red blood cells transfused.

Patient numbers align with those in Table S1.

[a]Patients with a history of transfusion in the 12 months prior to screening.

D: day; ET: end of trial; Hb: hemoglobin.