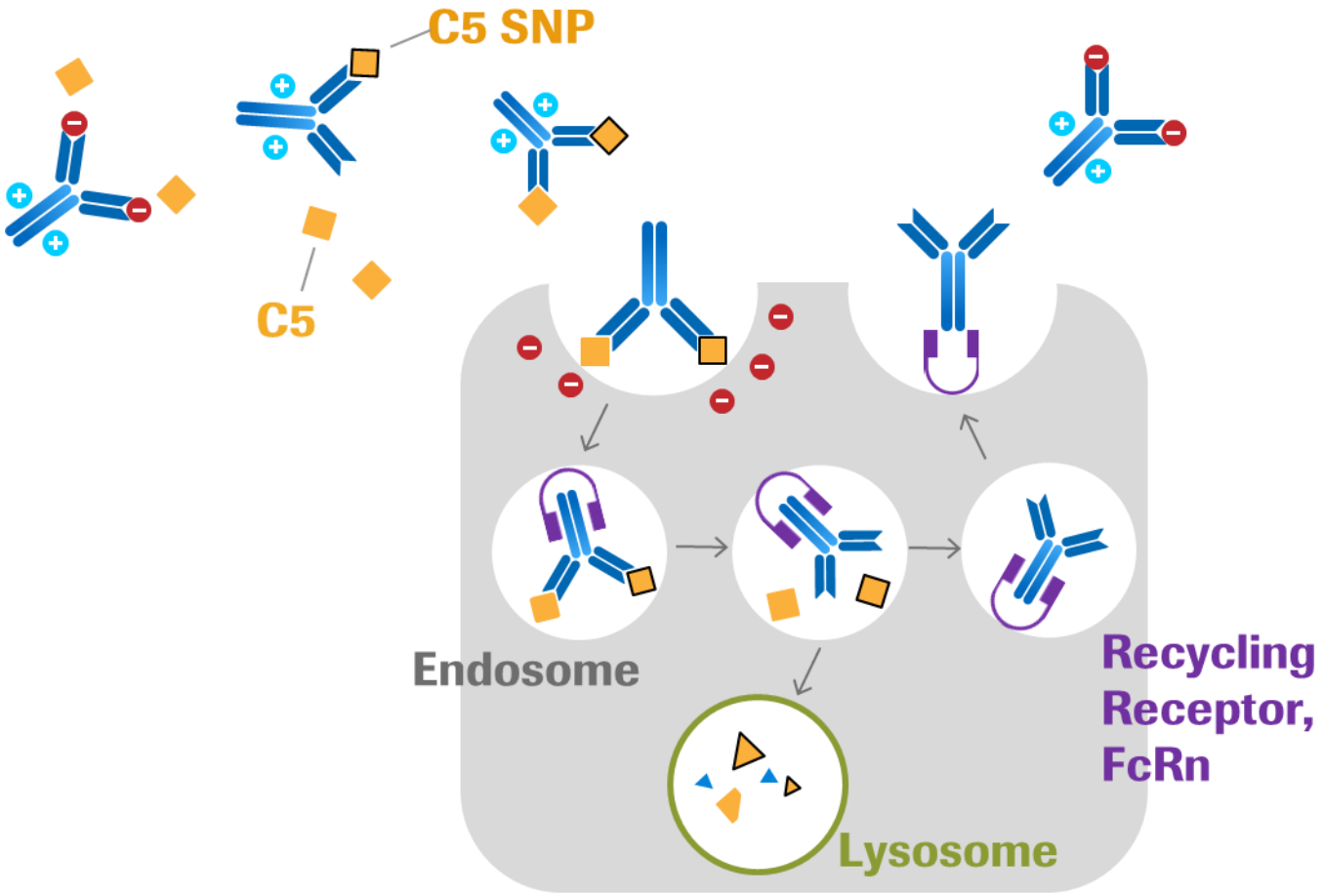


Figure S 1 **Crovalimab Mode of Action**

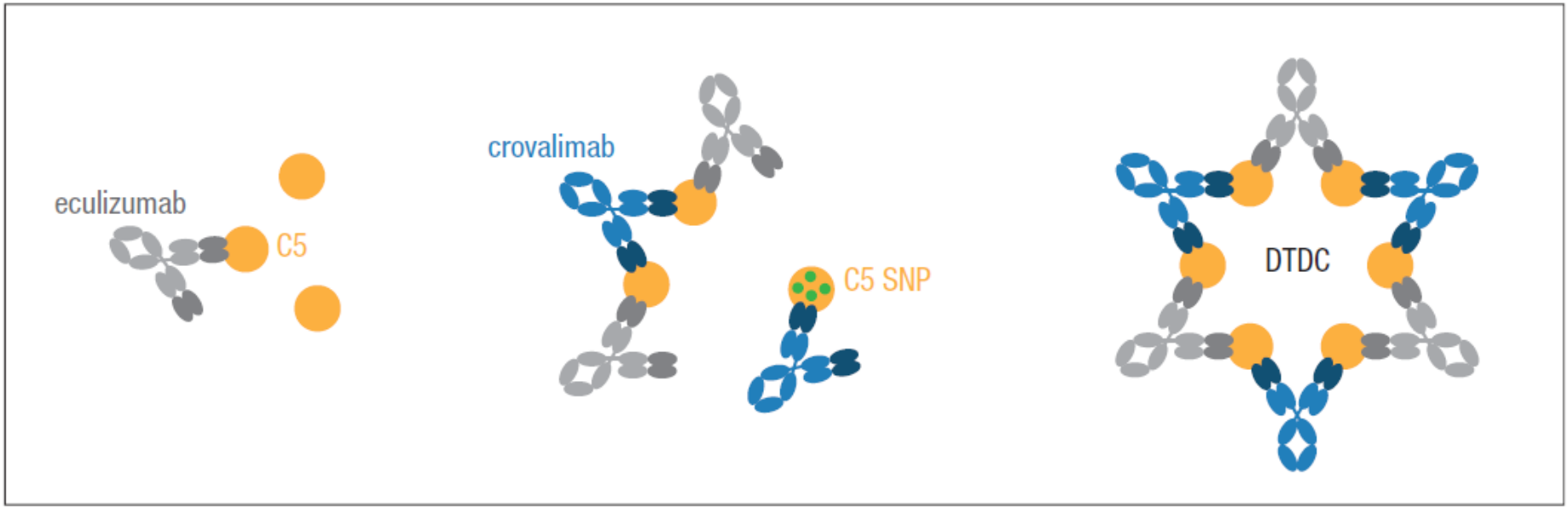


Figure S 2 Formation of Drug Target Drug Complexes (DTDC)

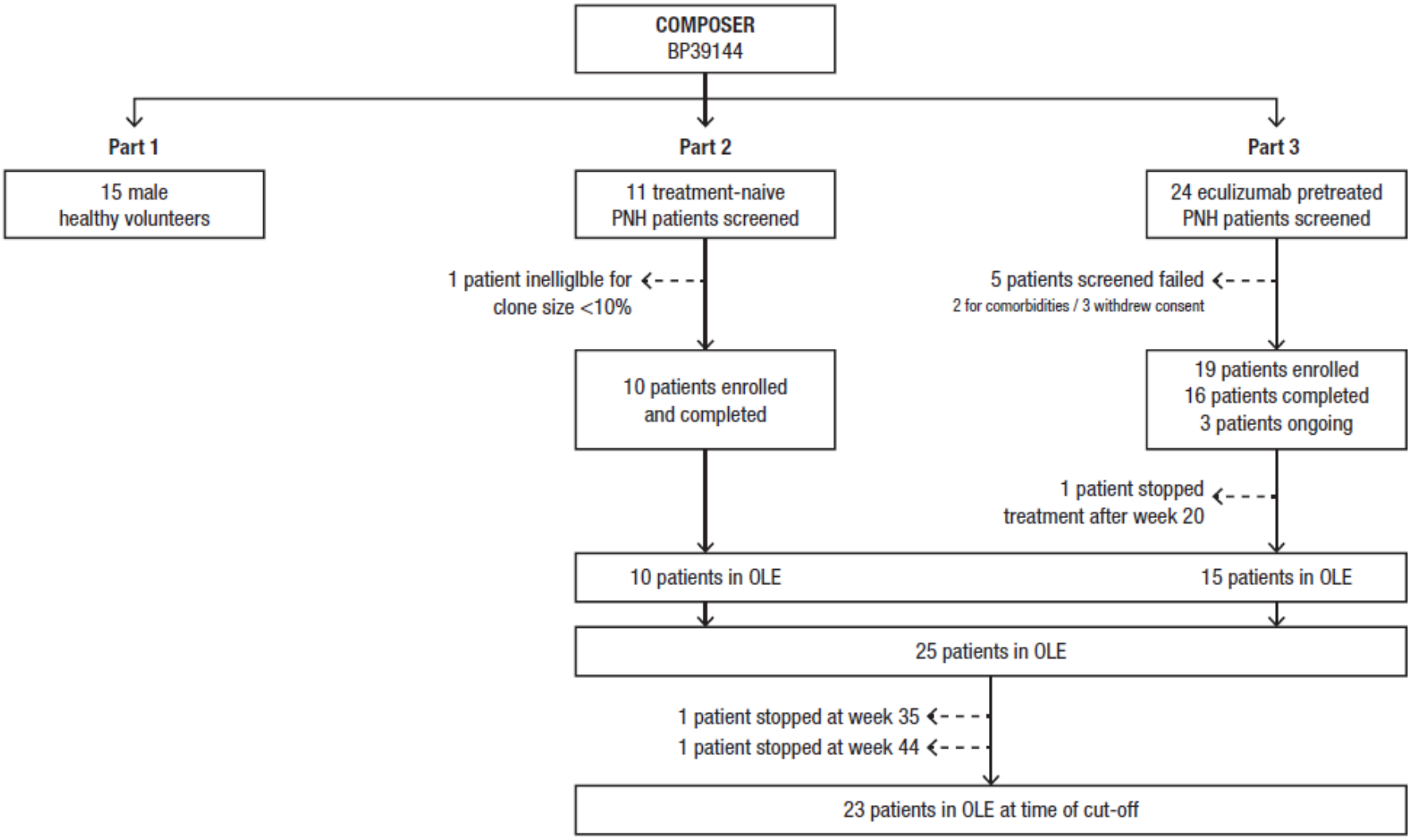


Figure S 3 Patient Disposition

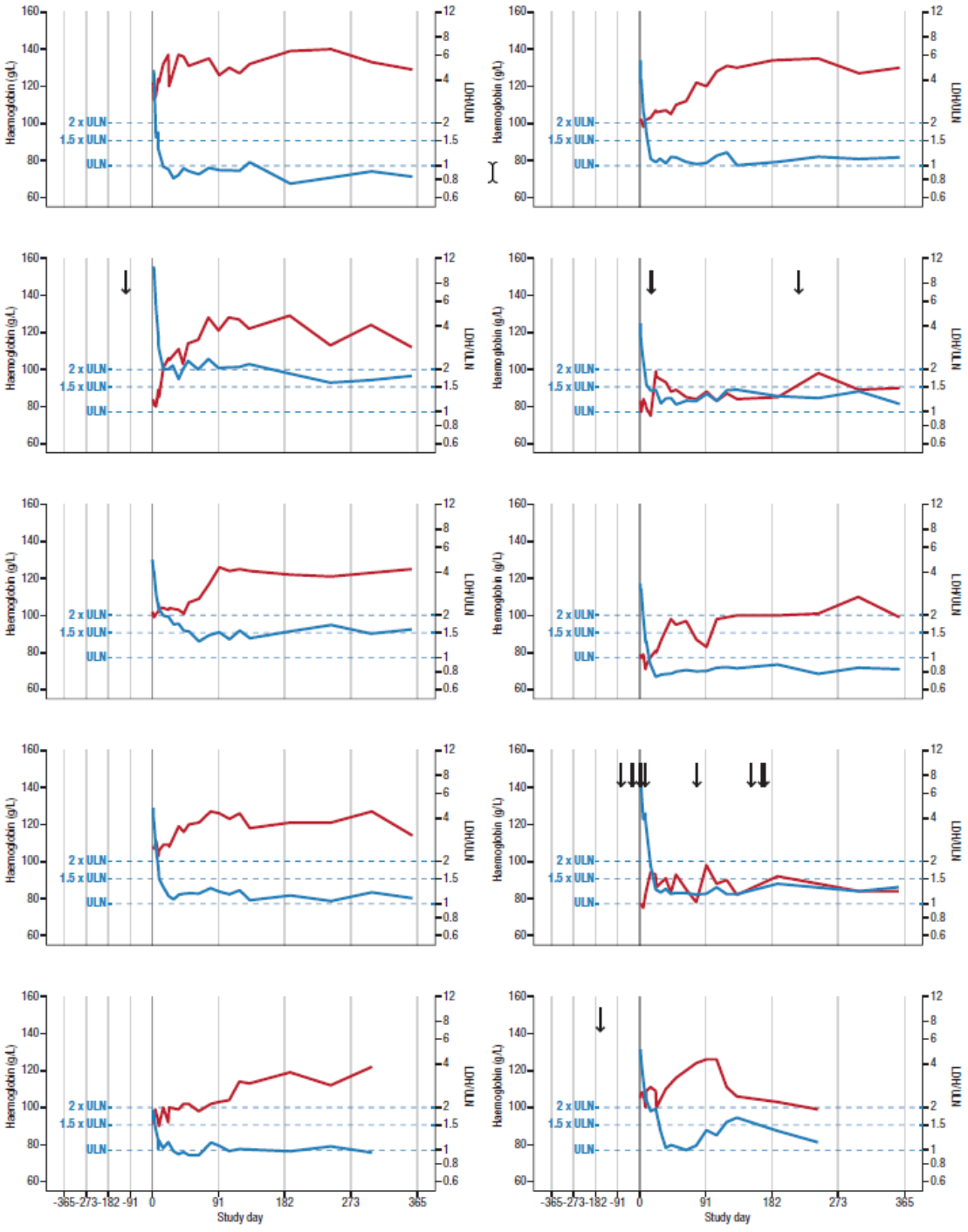
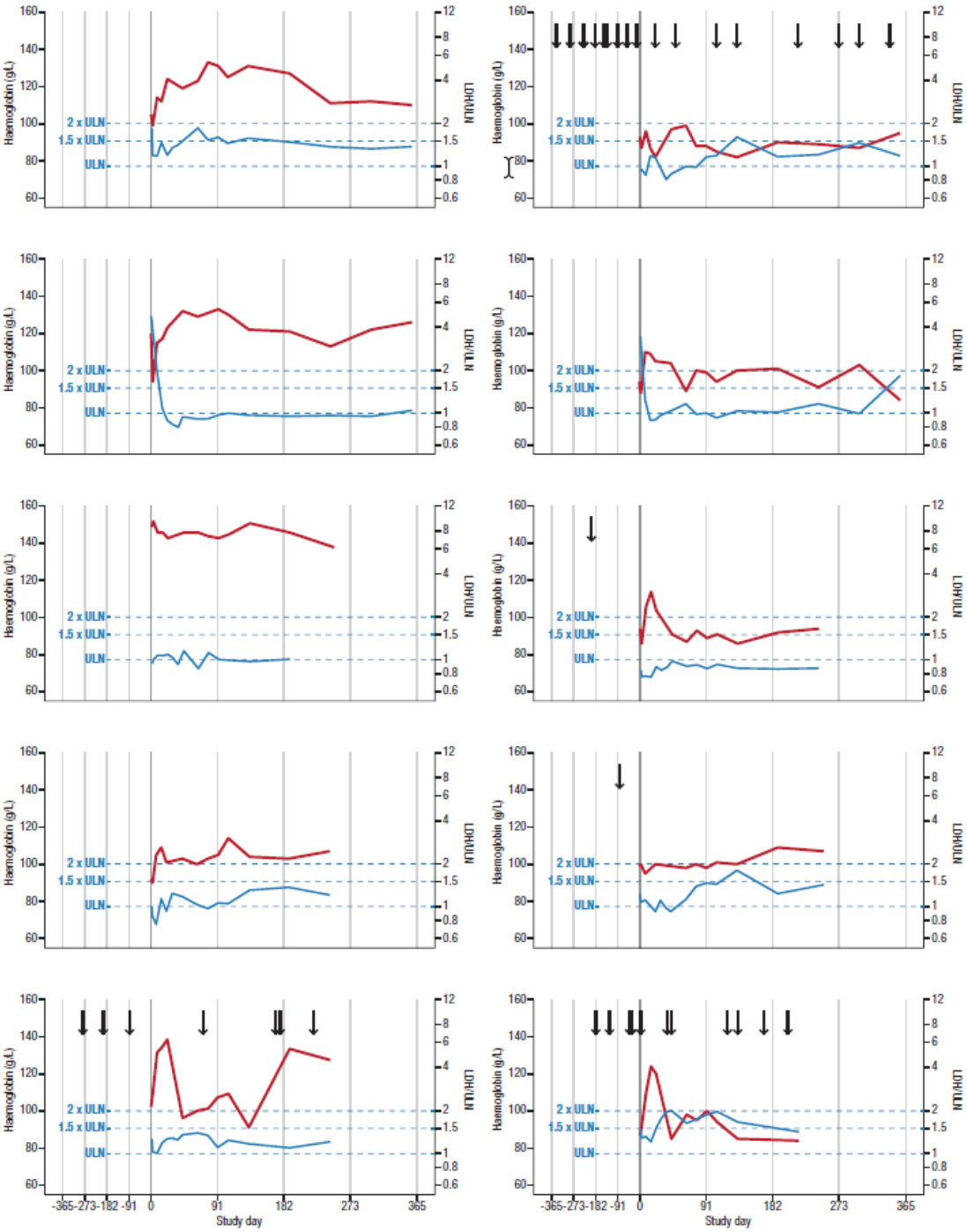


Figure S 4 Hemoglobin (red) and LDH (blue) evolution over time in patients participating in Part 2. Arrows mark blood transfusions


Haemoglobin (g/L)
LOW/ULN
2 x ULN
1.5 x ULN
ULN
Study day
-365 -273 -182 -91 0 91 182 273 365

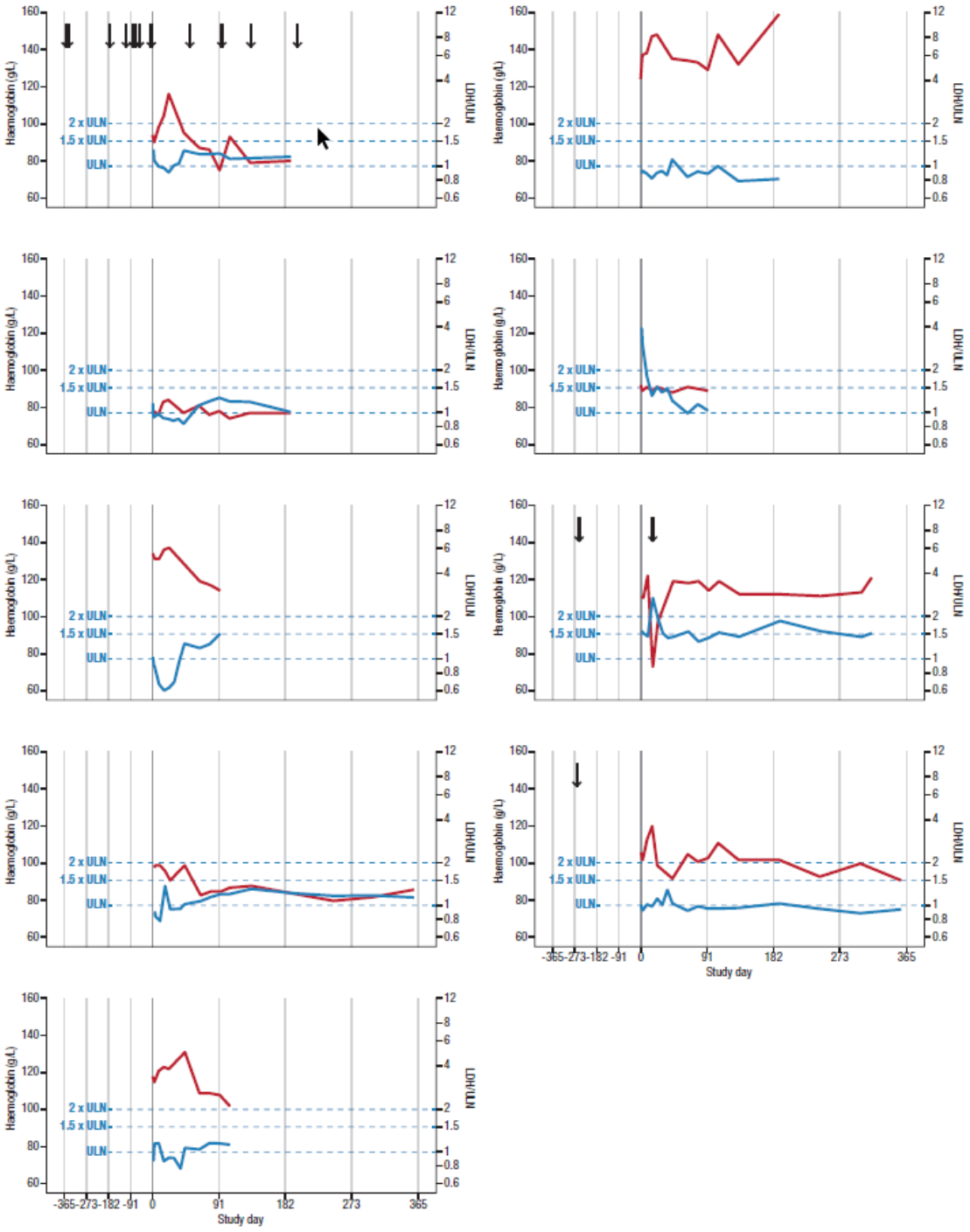


Figure S 5 Hemoglobin (red) and LDH (blue) evolution over time in patients participating in Part 3. Arrows mark blood transfusions

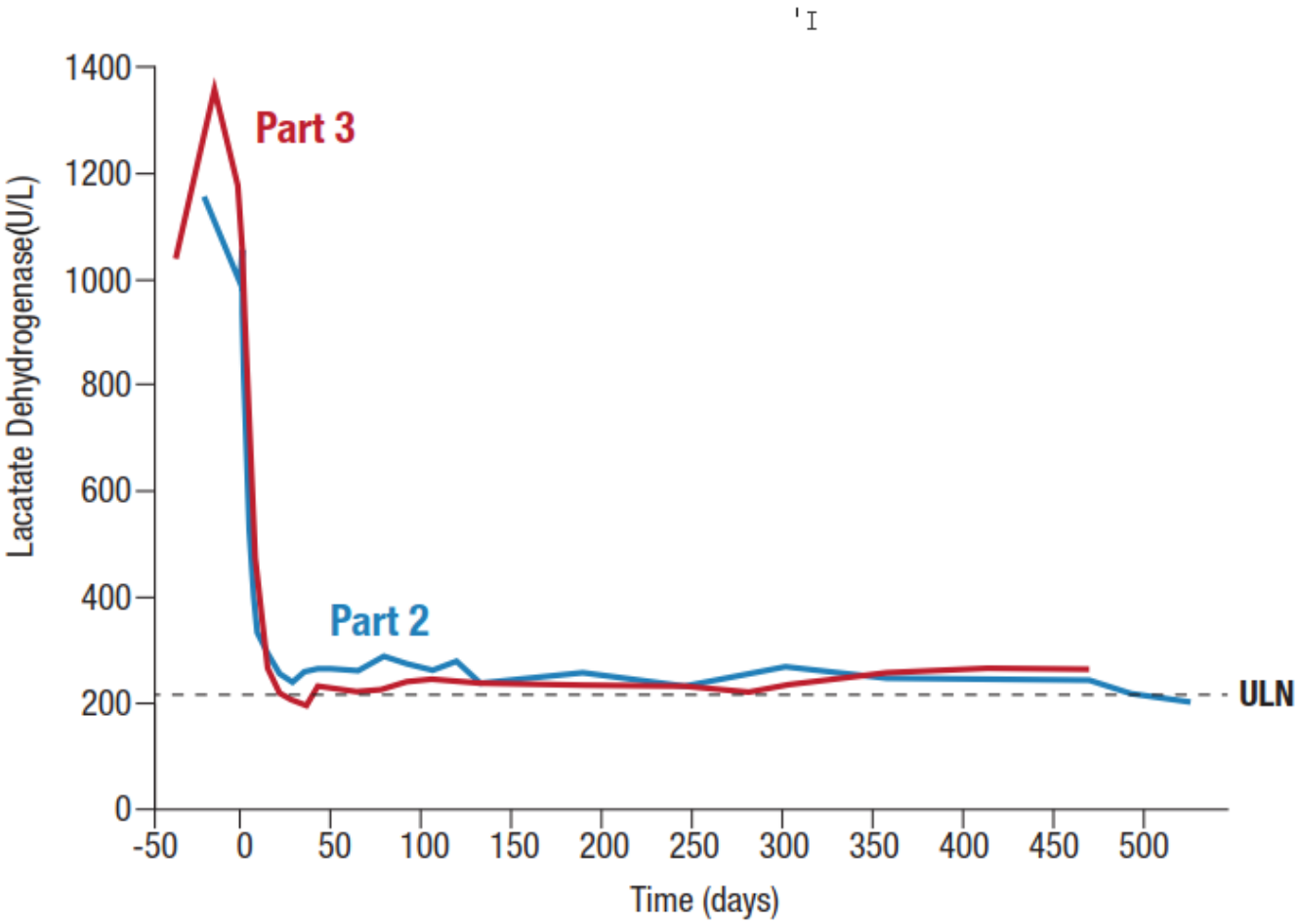


Figure S 6 LDH results of C5 SNP patients, blue Part 2; red Part 3

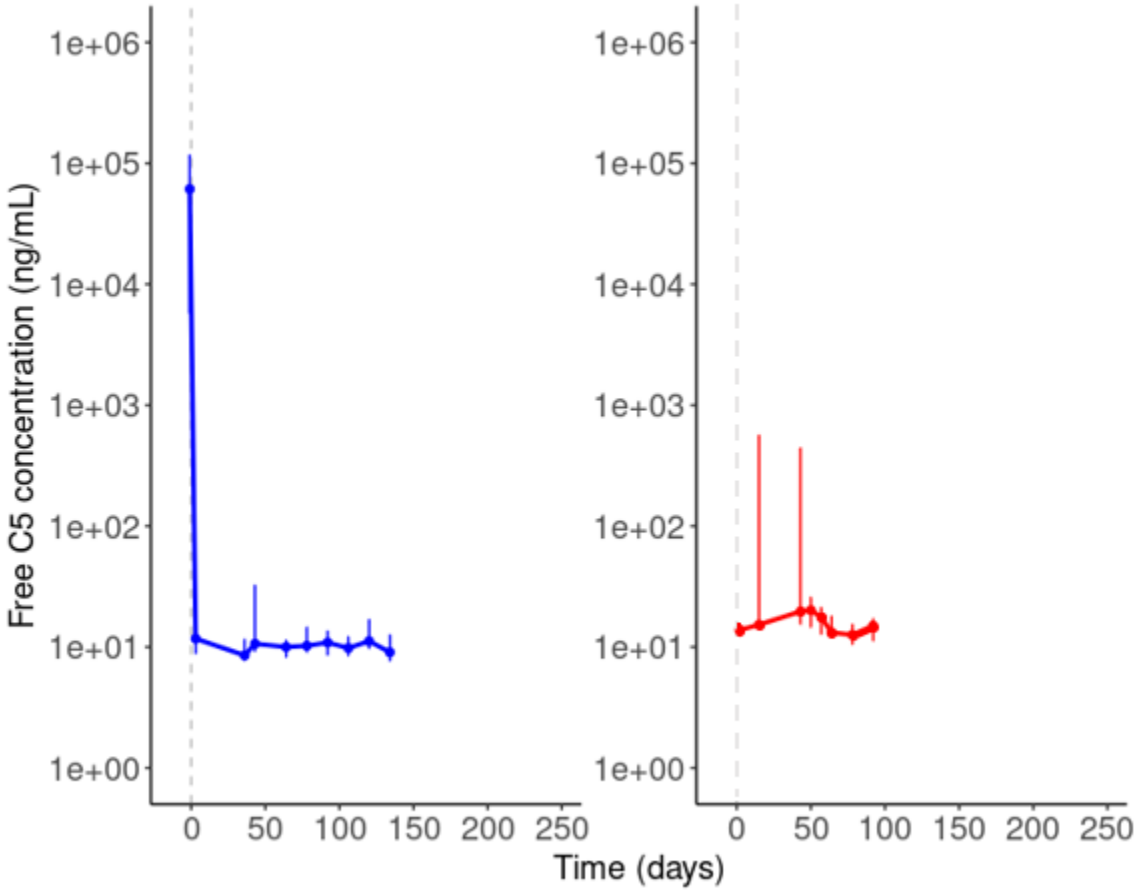


Figure S 7 Free C5 concentrations over time. Median and 95% CI is shown. Left panel: Part 2; right Panel Part 3; as measured by gyros assay

Table S 1 PNH clone size at baseline and week 12, weight, previous eculizumab dose and transfusion need;

PNH clone size [%] Granulocytes		PNH clone size [%] RBC		weight [kg]	eculizumab dose [mg Q2W]	units before crovalimab	units while on crovalimab	difference units	Follow up duration in weeks
BL	week 12	BL	week 12						
83.4	83.4	50.4	49.8	63	--	0	0	0	>52
80.8	80.2	28.7	28.3	95	--	0	0	0	>52
80.1	88.7	49.1	82.6	66	--	2	0	-2	>52
67.6	78.3	23.2	28.8	66	--	0	4	4	>52
93.9	90.1	42.3	55.6	82	--	0	0	0	>52
94.2	98.0*	71.4	99.7*	58.7	--	0	0	0	>52
88.8	88.9	78.5	76.0	69.2	--	0	0	0	>52
91.5	89.6	63.1	69.1	98	--	4	12	8	>52
34.2	33.2	18.0	13.8	96.5	--	0	0	0	47
83.4	84.9*	48.8	68.0*	59	--	2	0	-2	41
--	--	97.2	98.6	54.8	900	0	0	0	>52
--	--	63.1	46.1	66.5	900	21	16	-5	>52
--	--	99.1	99.3	63	900	0	0	0	>52
--	--	42.2	48.0	102	900	0	0	0	>52
96.8	96.8	0.1	13.6	83.4	900	0	0	0	40
99.8	99.8	89.4	89.9	131.5	1200	2	0	-2	38
--	--	20.3	19.0	123.4	1200	0	0	0	38
69.5	73.1	16.2	15.4	45	900	2	0	-2	35
99.6	99.7	93.0	--	93.2	900	8	8	0	38
99.9	99.9	67.8	87.1	51	900	8	14	6	20
85.4	85.0	53.3	51.7	93.4	900	10	6	-4	34
82.7	82.3	38.3	39.3	89	900	0	0	0	32
69.7	68.3	62.4	70.2	40.6	900	0	0	0	30
86.0	86.5	42.6	51.5	94	900	0	0	0	14
82.3	84.6	12.8	11.8	112	1200	0	0	0	14
--	--	93.9	93.5	76	1200	1	1	0	44
--	--	81.4	89.7	54.8	900	0	0	0	>52
--	--	90.0	77.9	69.2	900	2	0	-2	>52
94.8	98.0	42.1	31.7	78.2	900	0	0	0	18

(white = neutral; green = improved; red = worsened)

*sample time point week 20 as no week 12 sample was available

Table S 2 Breakthrough hemolysis rates

	Patient years	Events	Event rate / patient year	95% CI
COMPOSER Part 2	14.7	0	0.00	0.00 - 0.25
COMPOSER Part 3	15.1	4	0.28	0.07 - 0.68
COMPOSER overall	29.8	4	0.13	0.04 - 0.34
301 eculizumab (Lee et al. 2019)	60.63	15	0.25	0.14 - 0.41
301 ravulizumab (Lee et al. 2019)	60.62	5	0.08	0.03 - 0.19
302 eculizumab (Kulasekararaj et al. 2019)	49.1	7	0.14	0.06 - 0.29
302 ravulizumab (Kulasekararaj et al. 2019)	48.6	0	0.00	0.00 - 0.08
eculizumab overall	109.73	22	0.20	0.13 - 0.30
ravulizumab overall	109.22	5	0.05	0.01 - 0.10

Data used to calculate event rates for eculizumab and ravulizumab were taken from:
Lee et al 2019 for treatment naive patients
eculizumab: rate=0.25, 95%CI= 0.14 to 0.41
ravulizumab: rate= 0.08, 95%CI= 0.03 to 0.19

Kulasakararaj et al. 2019 for eculizumab pre-treated patients
eculizumab: rate=0.14, 95%CI= 0.0.6 to 0.29
ravulizumab: rate= 0.0, 95%CI= 0.0 to 0.08

The rationale is the following.
We need to work with rates because working with proportion of patients is misleading as one patient can have more than one event. The total number of events in treatment naive patients receiving eculizumab is 15 (from 13 pts) and ravulizumab is 5 (from 4 pts). The total number of events in eculizumab pre-treated patients receiving eculizumab is 7 (4 pts with 1 event and 1 pt with 3 events), and ravulizumab is 0.

The actual ratio is "number of events / patient-years at risk.
Therefore, the total patients-risk in treatment naive patients treated with eculizumab is 121patients x 183 days/ 365.25days/year = 60.62patient years and with ravulizumab is 125patients x 183days / 365.25days/year = 60.63patient years
The total patients-risk in eculizumab pre-treated patients with eculizumab is 98patients x 183days / 365.25days/year = 49.10patient years and with ravulizumab is 97patients x 183days / 365.25days/year = 48.60patient years

Note: the total time at risk in both studies is an approximation as only 119 treatment naive patients on eculizumab finish the study (2 dropped out) and among pre-treated patients 96 completed the study on ravulizumab (1 drop out) and 95 on eculizumab (3 dropped out). As we don't know from the publications the exact number of days these patients contributed to the study but almost certainly they contributed more than 0 days, we are assuming in first approximation they completed the study. This leads to a slight underestimation of the calculated rates.

To calculate the rates we divide the number of events by the total time at risk.

To calculate the 95%CI we use the formulae associated with Poisson rates (e.g. https://www.statsdirect.com/help/rates/poisson_rate_ci.htm).

LCI= X^2(0.025, 2xevents / (2 x pt_years))
UCI= X^2(0.975, 2 x (events +1) / (2 x pt_years))

where X^2 is the function that renders the quantiles of X^2 distribution.

Supplementary Details

Health-related quality of life (HRQoL)

The FACIT-Fatigue has 13 items that assess fatigue using a 7-day recall period on a 5-point Likert-type response scale. Total scores range 0-52, with higher scores indicative of less fatigue. The EORTC QLQ-C30 was originally developed for patients undergoing cancer treatment and has 30 questions that assess aspects of patient functioning, symptom severity, and global health status and quality of life (QoL), with a one-week recall period. The global health status/QoL scale uses a 7-point Likert-type response scale, whereas the other scales use a 4-point scale. Scores on each scale are summed and transformed to a 0-100 range with higher scores indicative of higher response levels (i.e., higher health-related QoL, higher symptom severity). While not specifically designed for patients with PNH, both measures have demonstrated content validity in PNH patients and been used in previous trials to characterize clinical benefit.

Inclusion Criteria:

- Male or female participants with PNH between 18 and 75 years of age
- Neisseria meningitidis vaccination in accordance with most current local guidelines or standard of care (SOC) for participants at increased risk for meningococcal disease (Part 2)
- Participant has been vaccinated with Neisseria meningitidis vaccine(s) in accordance with most current local guidelines or SOC for participants at increased risk for meningococcal disease or is being revaccinated if applicable (Part 3)
- Antibiotic prophylaxis for meningococcal infection must be initiated prior to initiation of RO7112689 therapy if the time period between initial Neisseria meningitidis vaccination and first dose of RO7112689 is less than 2 weeks (Part 2)
- Antibiotic prophylaxis of meningococcal infection may be initiated prior to initiation of RO7112689 therapy based on local guidelines or SOC for participants at increased risk for meningococcal disease (Parts 2 and 3)

- Stable dose for greater than or equal to (>/=) 28 days prior to screening of other therapies (immunosuppressant therapy, corticosteroids, iron supplements)
  Part 2 only (currently untreated PNH participants who are candidates for treatment with complement inhibitors only):
- PNH participants who have not been treated with any complement inhibitor or if previously treated stopped treatment due to lack of efficacy based on a single missense C5 heterozygous mutation
- Serum LDH levels at least 1.5-fold above the ULN at screening
- Hepatitis B participants can be enrolled if their liver function test values are less than 2 x ULN and there is no liver function impairment
  Part 3 only (PNH participants currently treated with eculizumab only):
- PNH participants who have been treated continuously with eculizumab for at least 3 months preceding enrollment in the trial
- Participants receive regular infusions of eculizumab
- Subjects with a negative hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C antibody, and HIV test result
  OLE only - PNH participants:
- PNH participants who have completed Parts 2 and 3 respectively
- PNH participants who derived, in the investigator's opinion, benefit from treatment with RO7112689
  All Parts:
- Male and female participants should use proper means of contraception

Exclusion Criteria:

- Evidence of moderate to severe concurrent renal, liver, cardiac, pulmonary or gastrointestinal disease not related to PNH as determined by the investigator
- History of an illness that, in the opinion of the study investigator, might confound the results of the study or that poses an additional risk to the participant by his or her participation in the study
- History of bone marrow transplantation
- Treatment with azathioprine or erythrocyte-stimulating agents within 14 days prior to first study drug administration
  Part 3 - PNH patients only:
- Any evidence of sero-positive auto-immune connective tissue diseases (such as systemic lupus erythematosus, or rheumatoid arthritis)
- Any evidence of active inflammatory conditions (including inflammatory bowel disease, or cryoglobulinemia)
  All Parts:
- Under active therapy with intravenous immunoglobulin (IVIG)
- Mentally incapacitated or history of a clinically significant psychiatric disorder over the previous 5 years
- Known or suspected hereditary complement deficiency
- Prior splenectomy
- History of meningococcal meningitis
- History of allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies or known hypersensitivity to any constituent of the product

- Any major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 28 days prior to screening or oral antibiotics within 2 weeks prior to screening and up to first study drug administration
- History of or currently active primary or secondary immunodeficiency, including known history of human immunodeficiency virus (HIV) infection
- Evidence of chronic active hepatitis C infection
- Evidence of malignant disease including myelodysplastic syndrome, or malignancies diagnosed within the previous 5 years