

Iptacopan in patients with PNH and residual anemia despite anti-C5 antibody therapy

Study CLNP023C12302 (APPLY-PNH)

AMNOG follow-up dossier submission

Subpopulation:

Patients without symptoms (without abdominal pain, chest pain and dyspnea and with maximally mild urine color, weakness/tiredness, dysphagia and erectile dysfunction) and with reticulocytes \leq upper limit of normal (ULN) ($123 \times 10^9/l$) at baseline

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1 Patient disposition, demographic and disease characteristics, follow-up times, PRO compliance rates and treatments

Table 1-1 Follow-up time (Full Analysis Set)

	Treatment Groups		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Total (N = 66)
Follow-up time (days)			
n	44	22	66
Mean ± SD	169.0 ± 2.35	172.9 ± 7.67	170.3 ± 5.10
Median	169.0	169.0	169.0
Range 1st to 3rd quartile	168.0 to 169.0	169.0 to 174.0	169.0 to 169.0
Range minimum to maximum	166.0 to 183.0	166.0 to 195.0	166.0 to 195.0
N: Number of patients in the analysis set Follow-up time [days] = minimum (date of completion or discontinuation from randomized treatment period, death date, cut-off date) – date of first exposure to treatment + 1 Cut-off date for analysis: 06-Mar-2023			

Table 1-2.1 FACIT Fatigue: return rates (Full Analysis Set)

	Treatment Groups		
	Iptacopan (N = 44) n (%)	Anti-C5 antibody (N = 22) n (%)	Total (N = 66) n (%)
FACIT Fatigue			
Baseline	44 (100.0)	21 (95.5)	65 (98.5)
Day 7	42 (95.5)	15 (68.2)	57 (86.4)
Day 14	39 (88.6)	17 (77.3)	56 (84.8)
Day 42	44 (100.0)	20 (90.9)	64 (97.0)
Day 84	40 (90.9)	17 (77.3)	57 (86.4)
Day 126	41 (93.2)	17 (77.3)	58 (87.9)
Day 140	42 (95.5)	16 (72.7)	58 (87.9)
Day 154	41 (93.2)	16 (72.7)	57 (86.4)
Day 168	42 (95.5)	18 (81.8)	60 (90.9)
Baseline and at least one post-baseline assessment	44 (100.0)	21 (95.5)	65 (98.5)
<p>N: Number of patients in the analysis set n: Number of returns </p> <p>The number of returns is the number of patients with non-missing data at the respective visit. N is the denominator for percentage (%) calculation.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>			

Table 1-2.2 EORTC QLQ-C30: return rates (Full Analysis Set)

	Treatment Groups		
	Iptacopan (N = 44) n (%)	Anti-C5 antibody (N = 22) n (%)	Total (N = 66) n (%)
EORTC QLQ-C30			
Baseline	44 (100.0)	21 (95.5)	65 (98.5)
Day 14	39 (88.6)	17 (77.3)	56 (84.8)
Day 42	44 (100.0)	20 (90.9)	64 (97.0)
Day 84	40 (90.9)	17 (77.3)	57 (86.4)
Day 126	41 (93.2)	17 (77.3)	58 (87.9)
Day 140	42 (95.5)	16 (72.7)	58 (87.9)
Day 154	41 (93.2)	16 (72.7)	57 (86.4)
Day 168	42 (95.5)	18 (81.8)	60 (90.9)
Baseline and at least one post-baseline assessment	44 (100.0)	21 (95.5)	65 (98.5)
<p>N: Number of patients in the analysis set n: Number of returns </p> <p>The number of returns is the number of patients with non-missing data (i.e. at least one [sub-]score present) at the respective visit. N is the denominator for percentage (%) calculation.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>			

Table 1-2.3 EQ-5D VAS: return rates (Full Analysis Set)

	Treatment Groups		
	Iptacopan (N = 44) n (%)	Anti-C5 antibody (N = 22) n (%)	Total (N = 66) n (%)
EQ-5D VAS			
Baseline	44 (100.0)	21 (95.5)	65 (98.5)
Day 14	38 (86.4)	17 (77.3)	55 (83.3)
Day 42	44 (100.0)	20 (90.9)	64 (97.0)
Day 84	40 (90.9)	17 (77.3)	57 (86.4)
Day 126	41 (93.2)	17 (77.3)	58 (87.9)
Day 140	42 (95.5)	16 (72.7)	58 (87.9)
Day 154	41 (93.2)	16 (72.7)	57 (86.4)
Day 168	42 (95.5)	18 (81.8)	60 (90.9)
Baseline and at least one post-baseline assessment	44 (100.0)	21 (95.5)	65 (98.5)
<p>N: Number of patients in the analysis set n: Number of returns </p> <p>The number of returns is the number of patients with non-missing data at the respective visit. N is the denominator for percentage (%) calculation.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>			

Table 1-2.4 PGI-S: Return rates (Full Analysis Set)

	Treatment Groups		
	Iptacopan (N = 44) n (%)	Anti-C5 antibody (N = 22) n (%)	Total (N = 66) n (%)
PGI - Symptoms of Fatigue			
Baseline	44 (100.0)	21 (95.5)	65 (98.5)
Day 7	42 (95.5)	15 (68.2)	57 (86.4)
Day 14	39 (88.6)	17 (77.3)	56 (84.8)
Day 42	44 (100.0)	20 (90.9)	64 (97.0)
Day 84	40 (90.9)	17 (77.3)	57 (86.4)
Day 126	41 (93.2)	17 (77.3)	58 (87.9)
Day 140	41 (93.2)	16 (72.7)	57 (86.4)
Day 154	41 (93.2)	16 (72.7)	57 (86.4)
Day 168	42 (95.5)	18 (81.8)	60 (90.9)
Baseline and at least one post-baseline assessment	44 (100.0)	21 (95.5)	65 (98.5)
N: Number of patients in the analysis set n: Number of returns The number of returns is the number of patients with non-missing data at the respective visit. N is the denominator for percentage (%) calculation. Cut-off date for analysis: 06-Mar-2023			

Table 1-3 Dose of study treatment for patients receiving Ravulizumab by body weight (Safety Set)

Treatment Group	
	Anti-C5 antibody (N = 22) n (%)
Patients receiving Ravulizumab by body weight category	
Ravulizumab 3000mg	2 (9.1)
≥ 40 to < 60 kg	1 (4.5)
≥ 60 to < 100 kg	1 (4.5)
≥ 100 kg	0 (0.0)
Ravulizumab 3300mg	2 (9.1)
≥ 40 to < 60 kg	0 (0.0)
≥ 60 to < 100 kg	2 (9.1)
≥ 100 kg	0 (0.0)
Ravulizumab 3600mg	1 (4.5)
≥ 40 to < 60 kg	0 (0.0)
≥ 60 to < 100 kg	0 (0.0)
≥ 100 kg	1 (4.5)
N: Number of patients in the analysis set n: Number of patients in the respective category N is the denominator for percentage (%) calculation. Cut-off date for analysis: 06-Mar-2023	

Table 1-5 Subgroups (Full Analysis Set)

	Treatment Groups		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Overall (N = 66)
Length of time since diagnosis, n (%)			
< 5 years	11 (25.0)	8 (36.4)	19 (28.8)
≥ 5 years	33 (75.0)	14 (63.6)	47 (71.2)
Age categories, n (%)			
< 45 years	16 (36.4)	10 (45.5)	26 (39.4)
≥ 45 years	28 (63.6)	12 (54.5)	40 (60.6)
Sex, n (%)			
Male	14 (31.8)	6 (27.3)	20 (30.3)
Female	30 (68.2)	16 (72.7)	46 (69.7)
Baseline hemoglobin, n (%)			
< 9 g/dL	22 (50.0)	10 (45.5)	32 (48.5)
≥ 9 g/dL	22 (50.0)	12 (54.5)	34 (51.5)
History of MAVE prior to screening, n (%)			
No	34 (77.3)	15 (68.2)	49 (74.2)
Yes	10 (22.7)	7 (31.8)	17 (25.8)
Anti-C5 medication history 6 months prior to randomization, n (%)			
Eculizumab	30 (68.2)	17 (77.3)	47 (71.2)
Ravulizumab	14 (31.8)	5 (22.7)	19 (28.8)
Transfusion in the last 6 months prior to randomization, n (%)			
No	23 (52.3)	10 (45.5)	33 (50.0)
Yes	21 (47.7)	12 (54.5)	33 (50.0)
Number of transfusions in the last 6 months prior to randomization, n (%)			
< 2	29 (65.9)	15 (68.2)	44 (66.7)
≥ 2	15 (34.1)	7 (31.8)	22 (33.3)
Duration of anti-C5 treatment, n (%)			
< 12 months	7 (15.9)	2 (9.1)	9 (13.6)
≥ 12 months	37 (84.1)	20 (90.9)	57 (86.4)
Region, n (%)			
Europe	34 (77.3)	18 (81.8)	52 (78.8)
Other	10 (22.7)	4 (18.2)	14 (21.2)
N: Number of patients in the analysis set MAVE: Major Adverse Vascular Event N is the denominator for percentage (%) calculation. Cut-off date for analysis: 06-Mar-2023			

Table 1-6 Demographic summary (Full Analysis Set)

	Treatment Groups		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Total (N = 66)
Age (years)			
n	44	22	66
Mean ± SD	54.0 ± 16.98	49.0 ± 17.62	52.4 ± 17.22
Median	54.0	45.0	53.0
Range 1st to 3rd quartile	39.0 to 68.0	34.0 to 62.0	38.0 to 68.0
Range minimum to maximum	22.0 to 84.0	20.0 to 82.0	20.0 to 84.0
Age category (years), n (%)			
< 65 years	28 (63.6)	17 (77.3)	45 (68.2)
≥ 65 years	16 (36.4)	5 (22.7)	21 (31.8)
Race, n (%)			
Asian	9 (20.5)	5 (22.7)	14 (21.2)
Black Or African American	1 (2.3)	2 (9.1)	3 (4.5)
White	34 (77.3)	15 (68.2)	49 (74.2)
Disease duration (years)^a			
n	44	22	66
Mean ± SD	12.4 ± 10.12	11.7 ± 10.21	12.2 ± 10.08
Median	9.6	8.0	9.5
Range 1st to 3rd quartile	4.5 to 17.3	3.0 to 18.5	4.0 to 17.7
Range minimum to maximum	0.7 to 40.2	1.5 to 39.6	0.7 to 40.2
Number of transfusions in the last 6 months prior to randomization among patients who had a transfusion			
n	21	12	33
Mean ± SD	3.4 ± 3.04	4.6 ± 5.40	3.8 ± 4.02
Median	3.0	2.5	3.0
Range 1st to 3rd quartile	1.0 to 4.0	1.0 to 6.5	1.0 to 4.0
Range minimum to maximum	1.0 to 13.0	1.0 to 19.0	1.0 to 19.0
Baseline Hemoglobin (g/dL)			
n	44	22	66
Mean ± SD	9.0 ± 0.68	9.0 ± 0.80	9.0 ± 0.72
Median	9.0	9.1	9.0
Range 1st to 3rd quartile	8.6 to 9.5	8.3 to 9.6	8.6 to 9.6
Range minimum to maximum	6.8 to 10.0	7.6 to 9.9	6.8 to 10.0
LDH level at baseline, n (%)			
≤ 1.5 x ULN	40 (90.9)	21 (95.5)	61 (92.4)
> 1.5 x ULN	4 (9.1)	1 (4.5)	5 (7.6)

	Treatment Groups		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Total (N = 66)
LDH levels at baseline (U/L)			
n	44	22	66
Mean ± SD	267.2 ± 75.85	252.8 ± 86.20	262.4 ± 79.08
Median	264.0	249.0	255.0
Range 1st to 3rd quartile	219.0 to 294.0	207.0 to 278.0	218.0 to 289.0
Range minimum to maximum	150.0 to 539.0	133.0 to 562.0	133.0 to 562.0
Absolute reticulocyte count (10/L), Blood			
n	44	22	66
Mean ± SD	180.9 ± 74.75	175.5 ± 70.78	179.1 ± 72.95
Median	167.3	162.9	167.3
Range 1st to 3rd quartile	118.9 to 235.4	114.7 to 231.4	118.8 to 232.0
Range minimum to maximum	51.0 to 350.0	90.3 to 374.4	51.0 to 374.4
Total PNH RBC Clone Size (%)^b			
n	44	22	66
Mean ± SD	64.2 ± 29.12	52.1 ± 28.81	60.2 ± 29.36
Median	66.0	47.9	59.1
Range 1st to 3rd quartile	38.8 to 95.5	34.5 to 83.3	36.6 to 93.4
Range minimum to maximum	10.6 to 99.9	9.8 to 98.4	9.8 to 99.9
FLAER dim-, Granulocytes (Total Granulocyte Clone Size) (%)			
n	43	22	65
Mean ± SD	93.3 ± 10.02	91.8 ± 8.96	92.8 ± 9.63
Median	97.2	95.9	96.5
Range 1st to 3rd quartile	90.9 to 99.2	87.8 to 97.9	90.7 to 99.0
Range minimum to maximum	56.5 to 100.4	65.8 to 100.0	56.5 to 100.4
FLAER- Monocytes (Monocyte Clone Size) (%)^c			
n	44	22	66
Mean ± SD	94.0 ± 9.08	93.7 ± 6.59	93.9 ± 8.28
Median	97.7	95.8	97.5
Range 1st to 3rd quartile	92.3 to 99.5	90.7 to 98.3	92.3 to 99.3
Range minimum to maximum	62.3 to 100.0	73.6 to 99.8	62.3 to 100.0
Duration of anti-C5 treatment (years)^d			
n	44	22	66
Mean ± SD	4.5 ± 3.93	4.7 ± 4.10	4.6 ± 3.96
Median	3.7	3.6	3.7
Range 1st to 3rd quartile	1.3 to 5.9	1.7 to 6.3	1.5 to 6.1
Range minimum to maximum	0.5 to 16.6	0.5 to 16.3	0.5 to 16.6
Eculizumab dose administered (mg)			
n	30	17	47
Mean ± SD	940.0 ± 103.72	1005.9 ± 181.90	963.8 ± 138.98
Median	900.0	900.0	900.0
Range 1st to 3rd quartile	900.0 to 900.0	900.0 to 1200.0	900.0 to 900.0
Range minimum to maximum	900.0 to 1200.0	900.0 to 1500.0	900.0 to 1500.0

	Treatment Groups		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Total (N = 66)
Ravulizumab dose administered (mg)			
n	14	5	19
Mean ± SD	3128.6 ± 154.07	3240.0 ± 251.00	3157.9 ± 183.53
Median	3000.0	3300.0	3000.0
Range 1st to 3rd quartile	3000.0 to 3300.0	3000.0 to 3300.0	3000.0 to 3300.0
Range minimum to maximum	3000.0 to 3300.0	3000.0 to 3600.0	3000.0 to 3600.0
N: Number of patients n: Number of patients in the respective category / with non-missing value in the summary statistics SD: Standard deviation ^a Disease duration is derived from the start date of PNH in Medical History page up to the date of screening. ^b Total PNH clone size is calculated as sum of percentages of positive Red Blood Cells of Type II and Type III. ^c Percentage of FLAER- granulocytes and monocytes is defined as a percentage of positive Granulocytes and Monocytes cells respectively. ^d Duration of anti-C5 treatment is calculated as Treatment end date - Treatment start date +1 regardless of the dose regimen.			
Cut-off date for analysis: 06-Mar-2023			

2 Efficacy

2-1 Sustained Hb \geq 8 g/dL

Table 2-1 Achievement of sustained Hb \geq 8 g/dL in patients with severe residual anemia at baseline (Full Analysis Set)

	Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
Achievement of sustained Hb \geq 8 g/dL						
n / N' (%)	4 / 4 (100.0)	0 / 4 (0.0)	OR	81.00	[1.30; >999.99]	0.037
			RR	9.00	[0.64; 126.85]	0.104
			RD	1.0000	[N.E.; N.E.]	N.E.
<p>N: Number of patients in the analysis set N': Number of patients with severe residual anemia (i.e. Hb < 8 g/dL) at baseline and with response variable defined based on non-missing data (evaluable patients) n: Number of patients with response based on non-missing data CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference </p> <p>Analysis methods: OR, RR and RD with Wald 95% CI and p-value. For calculation of OR and RR, in case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>Response is defined as having hemoglobin \geq 8 g/dL assessed at three out of four visits between Day 126 and Day 168 in the absence of packed red blood cell transfusions between Day 14 and Day 168.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>						

2-2 Reticulocyte counts

Table 2-2.1 Reticulocyte counts: descriptive statistics by timepoint (Full Analysis Set)

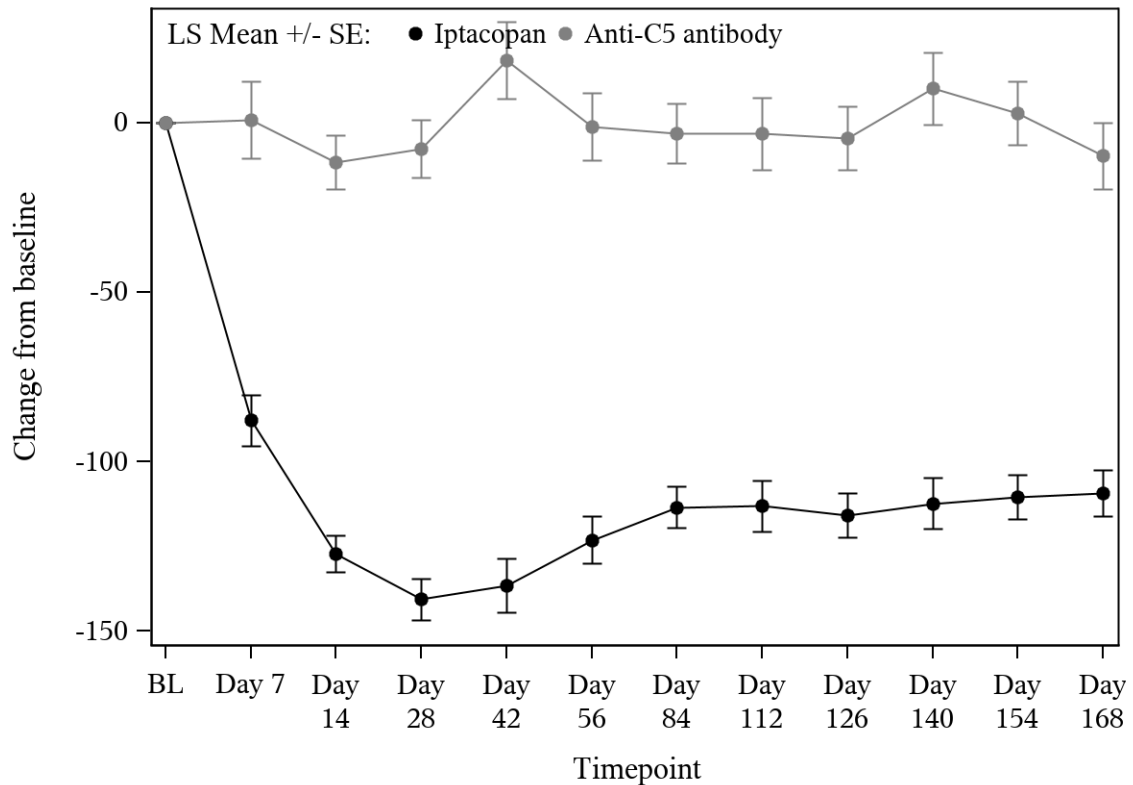
Treatment Groups		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)
Reticulocytes (10⁹/L)		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 180.94 (74.75)	22 175.48 (70.78)
Day 7	44 90.19 (39.91)	16 183.09 (81.22)
Day 14	42 50.81 (22.04)	17 146.57 (42.13)
Day 28	43 37.25 (19.26)	22 168.10 (69.87)
Day 42	41 42.74 (19.79)	18 172.91 (75.52)
Day 56	41 55.02 (35.24)	20 168.69 (75.71)
Day 84	42 65.20 (35.89)	20 175.54 (72.83)
Day 112	38 66.05 (38.47)	16 170.46 (65.93)
Day 126	44 62.41 (29.69)	21 173.70 (87.45)
Day 140	41 66.97 (36.94)	20 165.11 (66.47)
Day 154	40 68.62 (34.53)	19 167.42 (71.42)
Day 168	42 69.73 (37.00)	21 161.00 (79.96)
Day 126 - 168	44 66.19 (32.14)	22 174.55 (79.28)
N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit SD: Standard deviation Analysis methods: Descriptive means Day 126 - 168 were calculated by averaging first over the four visits for each patient and then averaging over the treatment group. Patients with non-missing value at least at baseline and at one of the four visits were included in the calculation. Cut-off date for analysis: 06-Mar-2023		

Table 2-2.2 Reticulocyte counts: MMRM analysis of change from baseline (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Reticulocytes (10⁹/L)					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 7	44 -87.83 (7.52)	16 0.72 (11.35)	-88.55	[-115.06; -62.04]	<0.001
Day 14	42 -127.15 (5.36)	17 -11.60 (7.96)	-115.55	[-133.88; -97.23]	<0.001
Day 28	43 -140.67 (6.10)	22 -7.72 (8.63)	-132.95	[-153.19; -112.71]	<0.001
Day 42	41 -136.57 (7.87)	18 18.45 (11.31)	-155.02	[-182.03; -128.01]	<0.001
Day 56	41 -123.13 (7.02)	20 -1.27 (9.97)	-121.85	[-145.46; -98.24]	<0.001
Day 84	42 -113.50 (6.19)	20 -3.13 (8.82)	-110.37	[-131.05; -89.69]	<0.001
Day 112	38 -113.16 (7.43)	16 -3.28 (10.72)	-109.88	[-135.33; -84.44]	<0.001
Day 126	44 -115.93 (6.60)	21 -4.60 (9.39)	-111.34	[-133.46; -89.22]	<0.001
Day 140	41 -112.37 (7.56)	20 10.08 (10.71)	-122.44	[-148.02; -96.87]	<0.001
Day 154	40 -110.56 (6.48)	19 2.80 (9.26)	-113.36	[-135.16; -91.55]	<0.001
Day 168	42 -109.32 (6.90)	21 -9.82 (9.79)	-99.50	[-122.66; -76.34]	<0.001
Day 126 - 168	44 -112.67 (6.45)	22 -1.01 (9.15)	-111.66	[-133.22; -90.10]	<0.001
	Hedges' G		-2.70	[-3.39; -2.02]	
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures </p> <p>Analysis methods: Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons at Day 126 - 168 were calculated as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.</p> <p>Hedges' G was calculated as model obtained adjusted mean difference / pooled SD with pooled SD = SE / sqrt (1/n1 + 1/n2) where SE is the standard error of the adjusted mean difference and n1 and n2 are the numbers of patients included in the analysis between Day 126 and 168 in treatment group 1 and 2, respectively.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Figure 2-2.2 Reticulocyte counts: line chart of least squares mean change from baseline (Full Analysis Set)

Reticulocytes ($10^9/L$)



Iptacopan	44	44	42	43	41	41	42	38	44	41	40	42
Anti-C5 antibody	22	16	17	22	18	20	20	16	21	20	19	21

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

2-3 Transfusion avoidance

Table 2-3.1 Transfusion avoidance - all definitions: logistic model analysis (Full Analysis Set)

	Treatment Groups		Parameter	Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)		Estimate	[95% CI]	p-value
Transfusion avoidance between Day 14 and Day 168						
n / N' (%)	42 / 44 (95.5)	8 / 22 (36.4)	OR	35.70	[6.28; 203.07]	<0.001
Predict. % [95% CI]	93.6 [85.7; 98.6]	37.1 [20.4; 54.9]	RR	2.52	[1.67; 4.51]	
			RD	0.5630	[0.3619; 0.7371]	
Transfusion avoidance between Day 14 and Day 168, only actual transfusions						
n / N' (%)	42 / 44 (95.5)	10 / 22 (45.5)	OR	27.15	[4.64; 158.81]	<0.001
Predict. % [95% CI]	93.5 [85.6; 98.6]	47.2 [28.9; 64.7]	RR	1.98	[1.43; 3.26]	
			RD	0.4604	[0.2691; 0.6454]	
Transfusion avoidance between Day 1 and Day 168						
n / N' (%)	39 / 44 (88.6)	8 / 22 (36.4)	OR	14.90	[3.52; 63.11]	<0.001
Predict. % [95% CI]	86.0 [75.2; 95.1]	37.2 [19.3; 56.3]	RR	2.31	[1.44; 4.43]	
			RD	0.4841	[0.2527; 0.6908]	
Transfusion avoidance between Day 14 and Day 168, only actual transfusions and/or HB ≤9 g/dl with presence of symptoms						
n / N' (%)	42 / 44 (95.5)	8 / 22 (36.4)	OR	35.70	[6.28; 203.07]	<0.001
Predict. % [95% CI]	93.6 [85.7; 98.6]	37.1 [20.4; 54.9]	RR	2.52	[1.67; 4.51]	
			RD	0.5630	[0.3619; 0.7371]	
Transfusion avoidance between Day 14 and Day 336						
n / N' (%)	40 / 44 (90.9)	8 / 22 (36.4)	OR	17.22	[4.05; 73.18]	<0.001
Predict. % [95% CI]	88.9 [78.9; 96.4]	36.5 [20.0; 54.3]	RR	2.43	[1.59; 4.44]	
			RD	0.5220	[0.3162; 0.7094]	
Transfusion avoidance between Day 1 and Day 168, only actual transfusions						
n / N' (%)	41 / 44 (93.2)	10 / 22 (45.5)	OR	19.33	[3.71; 100.86]	<0.001
Predict. % [95% CI]	91.3 [82.2; 98.3]	47.5 [29.3; 64.9]	RR	1.92	[1.37; 3.07]	
			RD	0.4356	[0.2322; 0.6238]	
Transfusion avoidance between Day 1 and Day 168, only actual transfusions with presence of symptoms						
n / N' (%)	42 / 44 (95.5)	11 / 22 (50.0)	OR	20.12	[3.70; 109.48]	<0.001
Predict. % [95% CI]	93.5 [85.6; 98.5]	51.5 [32.5; 69.7]	RR	1.81	[1.31; 2.94]	
			RD	0.4166	[0.2149; 0.6136]	
Transfusion avoidance between Day 1 and Day 336, only actual transfusions						
n / N' (%)	39 / 44 (88.6)	10 / 22 (45.5)	OR	9.95	[2.45; 40.38]	0.001
Predict. % [95% CI]	86.6 [76.1; 95.3]	46.4 [29.0; 63.9]	RR	1.86	[1.32; 3.02]	
			RD	0.3999	[0.1970; 0.5965]	

	Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Parameter	Estimate	[95% CI]	p-value
Transfusion avoidance between Day 1 and Day 336, only actual transfusions with presence of symptoms						
n / N' (%)	40 / 44 (90.9)	11 / 22 (50.0)	OR	9.77	[2.38; 40.14]	0.002
Predict. % [95% CI]	88.9 [78.9; 96.2]	50.6 [31.4; 69.0]	RR	1.75	[1.26; 2.84]	
			RD	0.3802	[0.1743; 0.5820]	
<p>N: Number of patients in the analysis set N': Number of patients included in the analysis n: Number of patients with response CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference </p> <p>Analysis methods: OR, RR and RD from logistic regression model using Firth's penalized maximum likelihood estimation: $\text{Logit}(\text{proportion}) = \text{treatment} + \text{baseline hemoglobin (indicator of hemoglobin} \geq 9 \text{ g/dL)} + \text{transfusion history} + \text{prior anti-C5-treatment}$ Anti-C5 antibody was the reference group for treatment group comparison. OR with 95% Wald CI and p-value from model linear predictor of treatment. Predicted proportions, RR and RD were calculated by marginal standardization from predicted values. First, predicted proportions were calculated by marginal standardization for each treatment group. Then RR and RD were calculated from predicted proportions. Estimates and 95% CI were constructed by median and 2.5% and 97.5% percentiles from 1000 bootstrap samples.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>						

Table 2-3.2 Transfusion avoidance - all definitions: unadjusted analysis with Wald CI and p-value (Full Analysis Set)

	Treatment Groups		Parameter	Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)		Estimate	[95% CI]	p-value
Transfusion avoidance between Day 14 and Day 168						
n / N' (%)	42 / 44 (95.5)	8 / 22 (36.4)	OR	36.75	[6.96; 193.93]	<0.001
			RR	2.63	[1.50; 4.58]	<0.001
			RD	0.5909	[0.3807; 0.8011]	<0.001
Transfusion avoidance between Day 14 and Day 168, only actual transfusions						
n / N' (%)	42 / 44 (95.5)	10 / 22 (45.5)	OR	25.20	[4.85; 130.98]	<0.001
			RR	2.10	[1.32; 3.33]	0.002
			RD	0.5000	[0.2830; 0.7170]	<0.001
Transfusion avoidance between Day 1 and Day 168						
n / N' (%)	39 / 44 (88.6)	8 / 22 (36.4)	OR	13.65	[3.82; 48.77]	<0.001
			RR	2.44	[1.39; 4.28]	0.002
			RD	0.5227	[0.3009; 0.7445]	<0.001
Transfusion avoidance between Day 14 and Day 168, only actual transfusions and/or HB ≤9 g/dl with presence of symptoms						
n / N' (%)	42 / 44 (95.5)	8 / 22 (36.4)	OR	36.75	[6.96; 193.93]	<0.001
			RR	2.63	[1.50; 4.58]	<0.001
			RD	0.5909	[0.3807; 0.8011]	<0.001
Transfusion avoidance between Day 14 and Day 336						
n / N' (%)	40 / 44 (90.9)	8 / 22 (36.4)	OR	17.50	[4.56; 67.22]	<0.001
			RR	2.50	[1.43; 4.38]	0.001
			RD	0.5455	[0.3272; 0.7637]	<0.001
Transfusion avoidance between Day 1 and Day 168, only actual transfusions						
n / N' (%)	41 / 44 (93.2)	10 / 22 (45.5)	OR	16.40	[3.88; 69.34]	<0.001
			RR	2.05	[1.29; 3.26]	0.002
			RD	0.4773	[0.2563; 0.6983]	<0.001
Transfusion avoidance between Day 1 and Day 168, only actual transfusions with presence of symptoms						
n / N' (%)	42 / 44 (95.5)	11 / 22 (50.0)	OR	21.00	[4.05; 108.95]	<0.001
			RR	1.91	[1.25; 2.91]	0.003
			RD	0.4545	[0.2367; 0.6724]	<0.001
Transfusion avoidance between Day 1 and Day 336, only actual transfusions						
n / N' (%)	39 / 44 (88.6)	10 / 22 (45.5)	OR	9.36	[2.67; 32.78]	<0.001
			RR	1.95	[1.22; 3.12]	0.005
			RD	0.4318	[0.2036; 0.6600]	<0.001
Transfusion avoidance between Day 1 and Day 336, only actual transfusions with presence of symptoms						
n / N' (%)	40 / 44 (90.9)	11 / 22 (50.0)	OR	10.00	[2.66; 37.61]	<0.001
			RR	1.82	[1.18; 2.79]	0.006
			RD	0.4091	[0.1836; 0.6346]	<0.001

Treatment Groups		Comparison		
Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Parameter	Estimate	[95% CI] p-value
<p>N: Number of patients in the analysis set N': Number of patients included in the analysis n: Number of patients with CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference </p> <p>Analysis methods: OR, RR and RD were calculated without adjustment with Wald 95% CI and p-value. For calculation of OR and RR, in case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>				

2-4 Transfusions

Table 2-4.1 Transfusions - all definitions: logistic model analysis (Full Analysis Set)

	Treatment Groups		Parameter	Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)		Estimate	[95% CI]	p-value
Transfusion between Day 14 and Day 168						
n / N' (%)	2 / 44 (4.5)	14 / 22 (63.6)	OR	0.03	[<0.01; 0.16]	<0.001
Predict. % [95% CI]	6.4 [1.4; 14.3]	62.9 [45.1; 79.6]	RR	0.10	[0.02; 0.25]	
			RD	-0.5630	[-.7371; -.3619]	
Transfusion between Day 14 and Day 168, only actual transfusions						
n / N' (%)	2 / 44 (4.5)	12 / 22 (54.5)	OR	0.04	[<0.01; 0.22]	<0.001
Predict. % [95% CI]	6.5 [1.4; 14.4]	52.8 [35.3; 71.1]	RR	0.12	[0.03; 0.31]	
			RD	-0.4604	[-.6454; -.2691]	
Transfusion between Day 1 and Day 168						
n / N' (%)	5 / 44 (11.4)	14 / 22 (63.6)	OR	0.07	[0.02; 0.28]	<0.001
Predict. % [95% CI]	14.0 [4.9; 24.8]	62.8 [43.7; 80.7]	RR	0.23	[0.08; 0.46]	
			RD	-0.4841	[-.6908; -.2527]	
Transfusion between Day 14 and Day 168, only actual transfusions and/or HB ≤9 g/dl with presence of symptoms						
n / N' (%)	2 / 44 (4.5)	14 / 22 (63.6)	OR	0.03	[<0.01; 0.16]	<0.001
Predict. % [95% CI]	6.4 [1.4; 14.3]	62.9 [45.1; 79.6]	RR	0.10	[0.02; 0.25]	
			RD	-0.5630	[-.7371; -.3619]	
Transfusion between Day 14 and Day 336						
n / N' (%)	4 / 44 (9.1)	14 / 22 (63.6)	OR	0.06	[0.01; 0.25]	<0.001
Predict. % [95% CI]	11.1 [3.6; 21.1]	63.5 [45.7; 80.0]	RR	0.17	[0.05; 0.35]	
			RD	-0.5220	[-.7094; -.3162]	
Transfusion between Day 1 and Day 168, only actual transfusions						
n / N' (%)	3 / 44 (6.8)	12 / 22 (54.5)	OR	0.05	[<0.01; 0.27]	<0.001
Predict. % [95% CI]	8.7 [1.7; 17.8]	52.5 [35.1; 70.7]	RR	0.17	[0.03; 0.39]	
			RD	-0.4356	[-.6238; -.2322]	
Transfusion between Day 1 and Day 168, only actual transfusions with presence of symptoms						
n / N' (%)	2 / 44 (4.5)	11 / 22 (50.0)	OR	0.05	[<0.01; 0.27]	<0.001
Predict. % [95% CI]	6.5 [1.5; 14.4]	48.5 [30.3; 67.5]	RR	0.13	[0.03; 0.35]	
			RD	-0.4166	[-.6136; -.2149]	
Transfusion between Day 1 and Day 336, only actual transfusions						
n / N' (%)	5 / 44 (11.4)	12 / 22 (54.5)	OR	0.10	[0.02; 0.41]	0.001
Predict. % [95% CI]	13.4 [4.7; 23.9]	53.6 [36.1; 71.0]	RR	0.25	[0.09; 0.49]	
			RD	-0.3999	[-.5965; -.1970]	
Transfusion between Day 1 and Day 336, only actual transfusions with presence of symptoms						
n / N' (%)	4 / 44 (9.1)	11 / 22 (50.0)	OR	0.10	[0.02; 0.42]	0.002
Predict. % [95% CI]	11.1 [3.8; 21.1]	49.4 [31.0; 68.6]	RR	0.23	[0.06; 0.49]	
			RD	-0.3802	[-.5820; -.1743]	

Treatment Groups		Comparison				
Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Parameter	Estimate	[95% CI]	p-value	
<p>N: Number of patients in the analysis set N': Number of patients included in the analysis n: Number of patients with response CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference </p> <p>Analysis methods: OR, RR and RD from logistic regression model using Firth's penalized maximum likelihood estimation: $\text{Logit}(\text{proportion}) = \text{treatment} + \text{baseline hemoglobin (indicator of hemoglobin} \geq 9 \text{ g/dL)} + \text{transfusion history} + \text{prior anti-C5-treatment}$ Anti-C5 antibody was the reference group for treatment group comparison. OR with 95% Wald CI and p-value from model linear predictor of treatment. Predicted proportions, RR and RD were calculated by marginal standardization from predicted values. First, predicted proportions were calculated by marginal standardization for each treatment group. Then RR and RD were calculated from predicted proportions. Estimates and 95% CI were constructed by median and 2.5% and 97.5% percentiles from 1000 bootstrap samples.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>						

Table 2-4.2 Transfusions - all definitions: unadjusted analysis with Wald CI and p-value (Full Analysis Set)

	Treatment Groups		Parameter	Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)		Estimate	[95% CI]	p-value
Transfusion between Day 14 and Day 168						
n / N' (%)	2 / 44 (4.5)	14 / 22 (63.6)	OR	0.03	[<0.01; 0.14]	<0.001
			RR	0.07	[0.02; 0.29]	<0.001
			RD	-0.5909	[-0.8011; -0.3807]	<0.001
Transfusion between Day 14 and Day 168, only actual transfusions						
n / N' (%)	2 / 44 (4.5)	12 / 22 (54.5)	OR	0.04	[<0.01; 0.21]	<0.001
			RR	0.08	[0.02; 0.34]	<0.001
			RD	-0.5000	[-0.7170; -0.2830]	<0.001
Transfusion between Day 1 and Day 168						
n / N' (%)	5 / 44 (11.4)	14 / 22 (63.6)	OR	0.07	[0.02; 0.26]	<0.001
			RR	0.18	[0.07; 0.43]	<0.001
			RD	-0.5227	[-0.7445; -0.3009]	<0.001
Transfusion between Day 14 and Day 168, only actual transfusions and/or HB ≤9 g/dl with presence of symptoms						
n / N' (%)	2 / 44 (4.5)	14 / 22 (63.6)	OR	0.03	[<0.01; 0.14]	<0.001
			RR	0.07	[0.02; 0.29]	<0.001
			RD	-0.5909	[-0.8011; -0.3807]	<0.001
Transfusion between Day 14 and Day 336						
n / N' (%)	4 / 44 (9.1)	14 / 22 (63.6)	OR	0.06	[0.01; 0.22]	<0.001
			RR	0.14	[0.05; 0.38]	<0.001
			RD	-0.5455	[-0.7637; -0.3272]	<0.001
Transfusion between Day 1 and Day 168, only actual transfusions						
n / N' (%)	3 / 44 (6.8)	12 / 22 (54.5)	OR	0.06	[0.01; 0.26]	<0.001
			RR	0.13	[0.04; 0.40]	<0.001
			RD	-0.4773	[-0.6983; -0.2563]	<0.001
Transfusion between Day 1 and Day 168, only actual transfusions with presence of symptoms						
n / N' (%)	2 / 44 (4.5)	11 / 22 (50.0)	OR	0.05	[<0.01; 0.25]	<0.001
			RR	0.09	[0.02; 0.37]	<0.001
			RD	-0.4545	[-0.6724; -0.2367]	<0.001

Treatment Groups			Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
Transfusion between Day 1 and Day 336, only actual transfusions						
n / N' (%)	5 / 44 (11.4)	12 / 22 (54.5)	OR	0.11	[0.03; 0.37]	<0.001
			RR	0.21	[0.08; 0.52]	<0.001
			RD	-0.4318	[-0.6600; - 0.2036]	<0.001
Transfusion between Day 1 and Day 336, only actual transfusions with presence of symptoms						
n / N' (%)	4 / 44 (9.1)	11 / 22 (50.0)	OR	0.10	[0.03; 0.38]	<0.001
			RR	0.18	[0.07; 0.51]	0.001
			RD	-0.4091	[-0.6346; - 0.1836]	<0.001
<p>N: Number of patients in the analysis set N': Number of patients included in the analysis n: Number of patients with CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference </p> <p>Analysis methods: OR, RR and RD were calculated without adjustment with Wald 95% CI and p-value. For calculation of OR and RR, in case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>						

Table 2-4.3 Number of transfusions: negative binomial model analysis (Full Analysis Set)

	Treatment Groups		Comparison
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Rate ratio [95% CI] p-value
Number of transfusion between Day 1 and Day 168, only actual transfusions			
Number of patients with event	3	12	
Number of events	5	57	
Annualized event rate [95% CI]	0.078 [0.018; 0.341]	1.317 [0.389; 4.457]	0.06 [0.02; 0.20] <.001
<p>N: Number of patients in the analysis set CI: Confidence interval </p> <p>Analysis methods: Annualized event rate and rate ratio from negative binomial model: $\log(\text{events}) = \text{treatment} + \text{baseline hemoglobin (indicator of hemoglobin} \geq 9 \text{ g/dL)} + \text{transfusion history} + \text{prior anti-C5-treatment}$ Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>			

2-5 Hemoglobin levels

Table 2-5 Hemoglobin levels: logistic model analysis (Full Analysis Set)

	Treatment Groups		Para- meter	Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)		Esti- mate	[95% CI]	p-value
Increase in hemoglobin levels \geq 2 g/dL from baseline^a without requiring pRBC transfusions^b						
n / N' (%)	37 / 44 (84.1)	0 / 22 (0.0)	OR	203.14	[12.40; >999.99]	<0.001
Predict. % [95% CI]	82.7 [71.6; 92.0]	2.5 [1.7; 4.2]	RR	32.19	[19.71; 49.30]	
			RD	0.7999	[0.6878; 0.8895]	
Hemoglobin levels \geq 12 g/dL^a without requiring pRBC transfusions^b						
n / N' (%)	31 / 44 (70.5)	0 / 22 (0.0)	OR	410.62	[14.09; >999.99]	<0.001
Predict. % [95% CI]	68.4 [55.7; 79.7]	1.9 [1.0; 3.7]	RR	36.15	[17.63; 67.08]	
			RD	0.6644	[0.5316; 0.7772]	
<p>N: Number of patients in the analysis set N': Number of patients included in the analysis n: Number of patients with response CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference </p> <p>Analysis methods: OR, RR and RD from logistic regression model using Firth's penalized maximum likelihood estimation: $\text{Logit}(\text{proportion}) = \text{treatment} + \text{baseline hemoglobin (indicator of hemoglobin} \geq 9 \text{ g/dL)} + \text{transfusion history} + \text{prior anti-C5-treatment}$ Anti-C5 antibody was the reference group for treatment group comparison. OR with 95% Wald CI and p-value from model linear predictor of treatment. Predicted proportions, RR and RD were calculated by marginal standardization from predicted values. First, predicted proportions were calculated by marginal standardization for each treatment group. Then RR and RD were calculated from predicted proportions. Estimates and 95% CI were constructed by median and 2.5% and 97.5% percentiles from 1000 bootstrap samples.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>a: between Day 126 and Day 168 (at least 3 out of 4 scheduled assessments) b: between Day 14 and Day 168</p> <p>Cut-off date for analysis: 06-Mar-2023</p>						

2-6 Breakthrough hemolysis

Table 2-6 Breakthrough hemolysis: negative binomial model analysis (Full Analysis Set)

	Treatment Groups		Comparison
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Rate ratio [95% CI] p-value
Number of clinical breakthrough haemolysis events with presence of symptoms during randomized treatment period			
Number of patients with event	0	5	
Number of events	0	6	
Annualized event rate [95% CI]	N.E.	N.E.	N.E.
<p>N: Number of patients in the analysis set CI: Confidence interval N.E.: Not estimable </p> <p>Analysis methods: Annualized event rate and rate ratio from negative binomial model: $\log(\text{events}) = \text{treatment}$ Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>			

2-7 Major adverse vascular events (MAVE)

Table 2-7 Major adverse vascular events (MAVE): negative binomial model analysis (Full Analysis Set)

	Treatment Groups		Comparison
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Rate ratio [95% CI] p-value
Number of major adverse vascular events (MAVE)			
Number of patients with event	1	0	
Number of events	1	0	
Annualized event rate [95% CI]	N.E.	N.E.	N.E.
<p>N: Number of patients in the analysis set CI: Confidence interval N.E.: Not estimable </p> <p>Analysis methods: Annualized event rate and rate ratio from negative binomial model: $\log(\text{events}) = \text{treatment} + \text{baseline hemoglobin (indicator of hemoglobin} \geq 9 \text{ g/dL)} + \text{transfusion history} + \text{prior anti-C5-treatment}$ Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>			

3 PRO

3-1 FACIT Fatigue

Table 3-1.1 FACIT Fatigue: descriptive statistics by timepoint (Full Analysis Set)

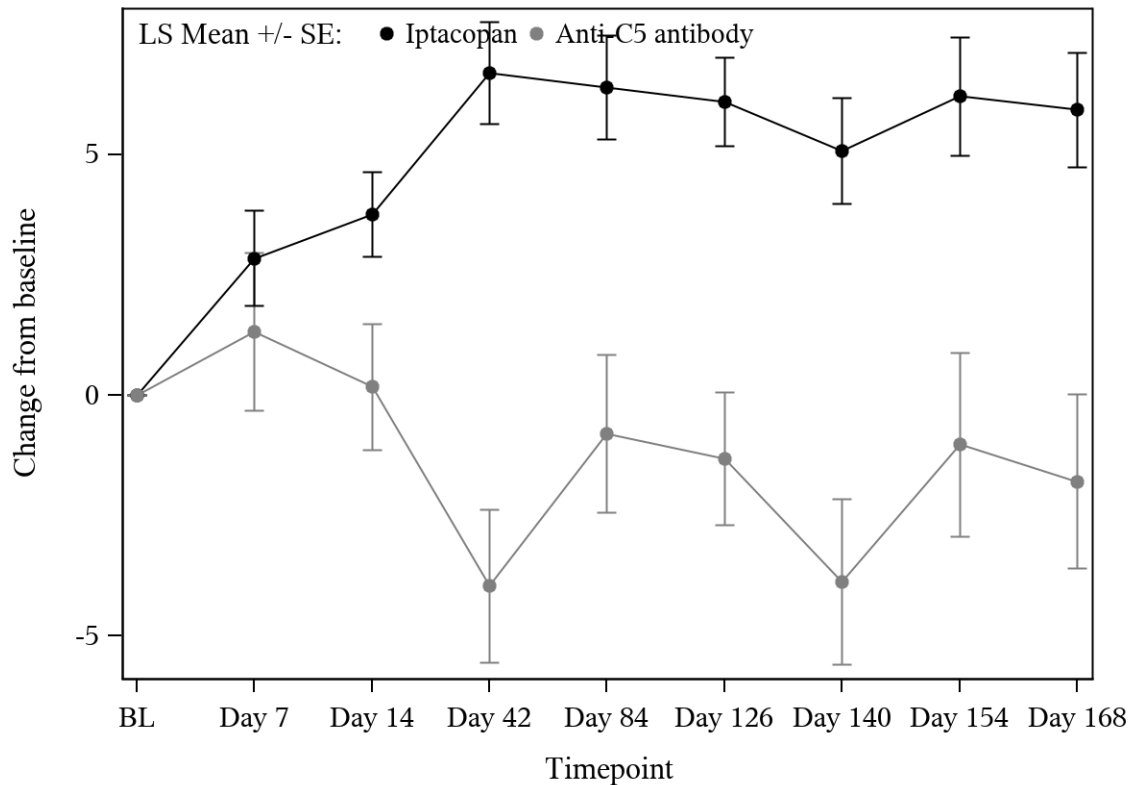
Treatment Groups		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)
FACIT Fatigue		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 37.66 (8.39)	21 33.81 (12.13)
Day 7	42 40.17 (7.67)	15 35.00 (12.08)
Day 14	39 41.18 (7.57)	17 36.18 (10.67)
Day 42	44 43.66 (7.29)	20 29.80 (12.50)
Day 84	40 43.83 (7.67)	17 31.71 (13.33)
Day 126	41 43.27 (7.05)	17 34.94 (12.41)
Day 140	42 42.12 (7.28)	16 31.06 (15.23)
Day 154	41 42.83 (8.73)	16 33.00 (13.40)
Day 168	42 43.24 (8.01)	18 31.06 (14.83)
Day 126 - 168	44 42.84 (7.22)	19 31.92 (13.90)
N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit SD: Standard deviation Analysis methods: Descriptive means Day 126 - 168 were calculated by averaging first over the four visits for each patient and then averaging over the treatment group. Patients with non-missing value at least at baseline and at one of the four visits were included in the calculation. Cut-off date for analysis: 06-Mar-2023		

Table 3-1.2 FACIT Fatigue: MMRM analysis of change from baseline (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
FACIT Fatigue					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 7	42 2.85 (0.99)	15 1.31 (1.64)	1.53	[-2.28; 5.34]	0.424
Day 14	39 3.75 (0.88)	17 0.17 (1.31)	3.58	[0.51; 6.64]	0.023
Day 42	44 6.70 (1.06)	20 -3.96 (1.58)	10.65	[6.89; 14.41]	<0.001
Day 84	40 6.40 (1.08)	17 -0.79 (1.63)	7.20	[3.31; 11.08]	<0.001
Day 126	41 6.10 (0.92)	17 -1.32 (1.38)	7.43	[4.18; 10.67]	<0.001
Day 140	42 5.08 (1.10)	16 -3.88 (1.72)	8.96	[4.94; 12.98]	<0.001
Day 154	41 6.22 (1.23)	16 -1.02 (1.91)	7.23	[2.73; 11.74]	0.002
Day 168	42 5.93 (1.19)	18 -1.79 (1.81)	7.72	[3.43; 12.01]	<0.001
Day 126 - 168	44 5.95 (0.94)	19 -1.89 (1.41)	7.83	[4.51; 11.16]	<0.001
Hedges' G			1.29	[0.71; 1.88]	
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures </p> <p>Analysis methods: Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons at Day 126 - 168 were calculated as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.</p> <p>Hedges' G was calculated as model obtained adjusted mean difference / pooled SD with pooled SD = SE / sqrt (1/n1 + 1/n2) where SE is the standard error of the adjusted mean difference and n1 and n2 are the numbers of patients included in the analysis between Day 126 and 168 in treatment group 1 and 2, respectively.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Figure 3-1.2 FACIT Fatigue: line chart of least squares mean change from baseline (Full Analysis Set)

FACIT Fatigue



Iptacopan	44	42	39	44	40	41	42	41	42
Anti-C5 antibody	21	15	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

Table 3-1.3 FACIT Fatigue responder analysis (improvement defined as ≥ 8 point increase from baseline): GLMM analysis (Full Analysis Set)

	Treatment Groups		Parameter	Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)		Estimate	[95% CI]	p-value
FACIT Fatigue						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 7	8 / 42 (19.0) 22.0 [12.4; 33.4]	1 / 15 (6.7) 6.8 [1.0; 16.9]	OR RR RD	6.26 3.20 0.1493	[0.70; 56.31] [1.11; 20.88] [0.0176; 0.2726]	0.101
Day 14	6 / 39 (15.4) 20.7 [11.8; 31.3]	2 / 17 (11.8) 4.3 [0.6; 10.7]	OR RR RD	12.16 4.76 0.1609	[1.65; 89.85] [1.80; 35.45] [0.0666; 0.2652]	0.015
Day 42	15 / 44 (34.1) 34.3 [21.5; 45.7]	1 / 20 (5.0) 2.6 [0.3; 7.0]	OR RR RD	96.89 13.29 0.3167	[11.11; 845.20] [4.89; 89.63] [0.1952; 0.4286]	<0.001
Day 84	15 / 40 (37.5) 38.8 [24.4; 52.4]	0 / 17 (0.0) 1.4 [0.1; 5.3]	OR RR RD	384.50 28.58 0.3725	[25.20; >999.99] [7.25; 394.31] [0.2292; 0.5072]	<0.001
Day 126	17 / 41 (41.5) 40.6 [28.7; 53.1]	1 / 17 (5.9) 1.9 [0.2; 7.0]	OR RR RD	190.23 21.83 0.3850	[20.87; >999.99] [5.54; 241.03] [0.2625; 0.5138]	<0.001
Day 140	13 / 42 (31.0) 41.6 [29.2; 53.8]	0 / 16 (0.0) 2.9 [0.2; 8.8]	OR RR RD	94.72 13.96 0.3826	[14.13; 634.89] [4.61; 181.32] [0.2628; 0.5038]	<0.001
Day 154	17 / 41 (41.5) 40.6 [28.6; 52.3]	2 / 16 (12.5) 5.2 [0.8; 12.3]	OR RR RD	37.43 7.56 0.3483	[6.42; 218.16] [3.18; 54.28] [0.2223; 0.4805]	<0.001
Day 168	18 / 42 (42.9) 39.6 [25.5; 53.6]	2 / 18 (11.1) 12.0 [1.8; 27.7]	OR RR RD	11.73 3.26 0.2731	[1.50; 91.91] [1.26; 23.33] [0.0573; 0.4522]	0.019
Day 126 - 168	44 40.9 [28.6; 52.2]	19 5.8 [0.9; 12.1]	OR RR RD	53.04 7.01 0.3460	[9.10; 309.06] [3.26; 44.50] [0.2229; 0.4638]	<0.001

Treatment Groups		Comparison			
Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit n: Number of patients with response CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference GLMM: Generalized linear mixed model </p> <p>Analysis methods: OR, RR and RD from logistic GLMM with random intercept and week as continuous covariate: $\text{Logit}(\text{proportion}) = \text{treatment} + \text{baseline value} + \text{treatment} * \text{week} + \text{baseline value} * \text{week} + \text{treatment} * \text{week} * \text{week} + \text{baseline value} * \text{week} * \text{week}$ Anti-C5 antibody was the reference group for treatment group comparison. OR with 95% Wald CI and p-value were calculated from model linear predictors, at Day 126 - 168 from a linear function of linear predictors. Predicted proportions, RR and RD were calculated by marginal standardization from predicted values. First, predicted proportions were calculated by marginal standardization for each treatment group at each visit. Then predicted proportions were averaged over the four visits Day 126 - 168. Then RR and RD were calculated for each visit and for Day 126 - 168. Estimates and 95% CI were constructed by median and 2.5% and 97.5% percentiles from 1000 bootstrap samples.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Response (improvement) is defined as ≥ 8 point increase from baseline.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

3-2 EORTC QLQ-C30 Symptoms

Table 3-2.1 EORTC QLQ-C30 Symptoms: descriptive statistics by timepoint (Full Analysis Set)

Treatment Groups		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)
QLQ-C30 - Fatigue		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 35.61 (18.96)	21 45.24 (29.73)
Day 14	39 27.92 (19.72)	17 38.56 (28.09)
Day 42	44 22.98 (18.78)	20 52.78 (25.46)
Day 84	40 22.22 (18.49)	17 49.02 (30.19)
Day 126	41 21.68 (17.02)	17 41.83 (28.74)
Day 140	42 24.07 (18.19)	16 48.61 (35.11)
Day 154	41 23.58 (21.11)	16 47.22 (33.33)
Day 168	42 24.07 (19.77)	18 46.91 (29.41)
Day 126 - 168	44 23.70 (16.74)	19 47.12 (31.13)
QLQ-C30 - Nausea and vomiting		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 4.36 (8.89)	21 7.94 (11.63)
Day 14	39 5.13 (14.38)	17 5.88 (10.11)
Day 42	44 3.79 (9.42)	20 14.17 (18.95)
Day 84	40 5.00 (11.45)	17 10.78 (16.61)
Day 126	41 2.44 (7.03)	17 5.88 (14.36)
Day 140	42 4.76 (9.94)	16 11.46 (18.97)
Day 154	41 5.28 (16.43)	16 8.33 (14.91)
Day 168	42 5.16 (12.48)	18 8.33 (11.79)
Day 126 - 168	44 4.70 (9.52)	19 8.92 (14.09)
QLQ-C30 - Pain		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 9.28 (17.07)	21 23.02 (30.38)
Day 14	39 9.40 (19.42)	17 13.73 (21.44)
Day 42	44 8.33 (15.04)	20 26.67 (35.62)
Day 84	40 8.33 (14.62)	17 23.53 (27.68)
Day 126	41 6.91 (14.90)	17 14.71 (22.73)
Day 140	42 9.92 (20.18)	16 22.92 (30.96)
Day 154	41 10.57 (16.56)	16 14.58 (23.47)
Day 168	42 9.13 (14.82)	18 22.22 (30.78)
Day 126 - 168	44 9.15 (14.67)	19 20.91 (26.00)

Treatment Groups		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)
QLQ-C30 - Dyspnoea		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 31.06 (22.90)	21 39.68 (31.39)
Day 14	39 17.09 (22.78)	17 41.18 (32.34)
Day 42	44 14.39 (22.04)	20 45.00 (32.94)
Day 84	40 12.50 (20.93)	17 49.02 (31.44)
Day 126	41 13.82 (24.69)	17 41.18 (34.42)
Day 140	42 15.87 (23.56)	16 45.83 (40.14)
Day 154	41 14.63 (18.33)	16 39.58 (27.81)
Day 168	42 13.49 (20.90)	18 42.59 (33.93)
Day 126 - 168	44 14.77 (20.38)	19 43.13 (31.35)
QLQ-C30 - Insomnia		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 29.55 (26.87)	21 28.57 (32.12)
Day 14	39 23.93 (26.43)	17 19.61 (23.74)
Day 42	44 23.48 (26.49)	20 25.00 (30.35)
Day 84	40 20.83 (22.25)	17 27.45 (33.82)
Day 126	41 19.51 (23.54)	17 21.57 (23.40)
Day 140	42 22.22 (29.14)	16 16.67 (24.34)
Day 154	41 21.95 (28.49)	16 27.08 (30.35)
Day 168	42 20.63 (23.23)	18 29.63 (34.09)
Day 126 - 168	44 21.28 (21.25)	19 25.88 (26.40)
QLQ-C30 - Appetite loss		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 7.95 (14.60)	21 11.11 (17.74)
Day 14	39 4.27 (13.64)	17 7.84 (14.57)
Day 42	44 2.27 (8.50)	20 15.00 (25.31)
Day 84	40 5.83 (14.88)	17 15.69 (26.66)
Day 126	41 3.25 (10.01)	17 7.84 (14.57)
Day 140	42 4.76 (15.74)	16 18.75 (29.74)
Day 154	41 4.07 (13.32)	16 10.42 (15.96)
Day 168	42 3.17 (9.90)	18 18.52 (30.73)
Day 126 - 168	44 3.79 (8.52)	19 14.62 (20.13)

Treatment Groups		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)
QLQ-C30 - Constipation		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 7.20 (16.23)	21 9.52 (19.42)
Day 14	39 7.69 (16.15)	17 3.92 (16.17)
Day 42	44 5.30 (14.28)	20 10.00 (21.90)
Day 84	40 5.00 (14.22)	17 11.76 (20.21)
Day 126	41 5.69 (14.72)	17 11.76 (23.40)
Day 140	42 7.14 (13.84)	16 10.42 (20.07)
Day 154	41 7.32 (15.83)	16 14.58 (20.97)
Day 168	42 7.14 (15.68)	18 7.41 (14.26)
Day 126 - 168	44 6.50 (11.37)	19 11.26 (17.85)
QLQ-C30 - Diarrhoea		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 7.58 (15.44)	21 11.11 (18.51)
Day 14	39 10.26 (18.97)	17 9.80 (19.60)
Day 42	44 9.85 (19.79)	20 26.67 (35.21)
Day 84	40 10.83 (20.52)	17 19.61 (33.46)
Day 126	41 7.32 (13.97)	17 11.76 (20.21)
Day 140	42 10.32 (21.45)	16 12.50 (26.87)
Day 154	41 11.38 (20.56)	16 12.50 (16.67)
Day 168	42 7.94 (17.74)	18 12.96 (16.72)
Day 126 - 168	44 9.66 (16.66)	19 13.45 (16.95)
N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit SD: Standard deviation Analysis methods: Descriptive means Day 126 - 168 were calculated by averaging first over the four visits for each patient and then averaging over the treatment group. Patients with non-missing value at least at baseline and at one of the four visits were included in the calculation. Cut-off date for analysis: 06-Mar-2023		

Table 3-2.2 EORTC QLQ-C30 Symptoms: MMRM analysis of change from baseline (Full Analysis Set)

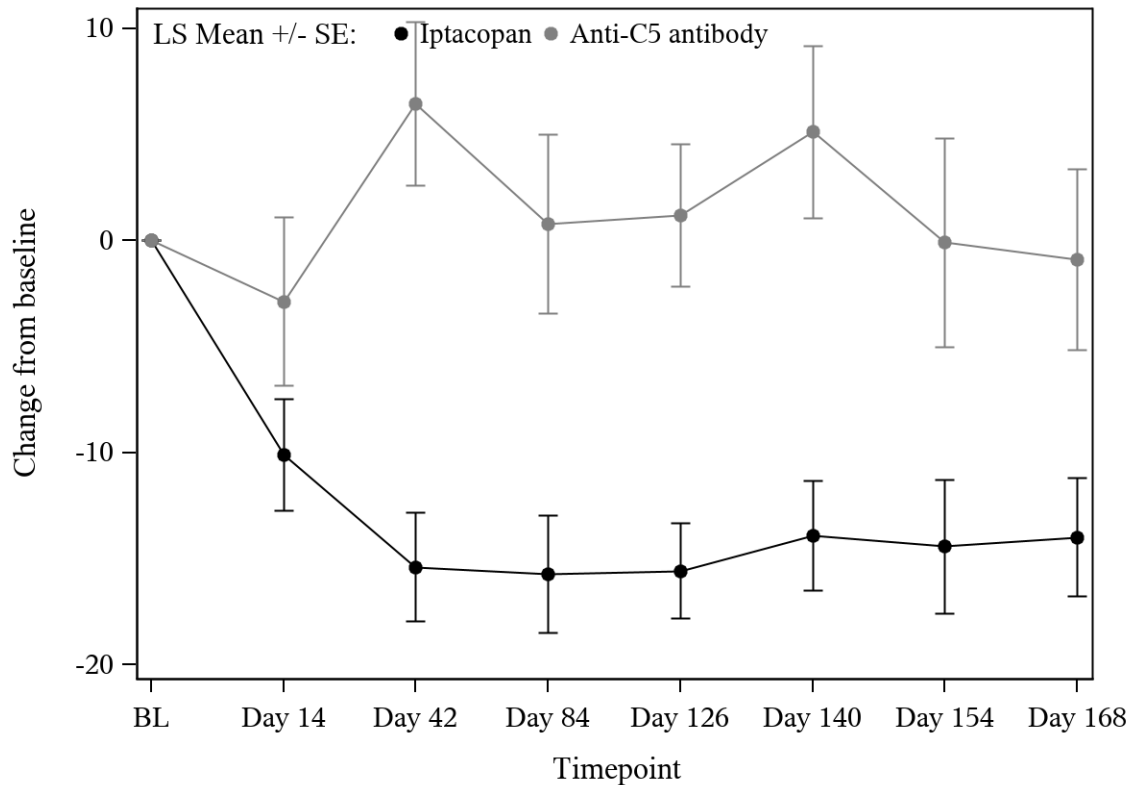
	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Fatigue					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	39 -10.11 (2.64)	17 -2.88 (3.97)	-7.24	[-16.60; 2.12]	0.127
Day 42	44 -15.41 (2.56)	20 6.45 (3.85)	-21.86	[-30.96; -12.76]	<0.001
Day 84	40 -15.72 (2.76)	17 0.79 (4.22)	-16.51	[-26.49; -6.54]	0.002
Day 126	41 -15.58 (2.24)	17 1.17 (3.35)	-16.74	[-24.59; -8.90]	<0.001
Day 140	42 -13.92 (2.60)	16 5.12 (4.07)	-19.04	[-28.54; -9.55]	<0.001
Day 154	41 -14.43 (3.14)	16 -0.10 (4.93)	-14.34	[-25.93; -2.74]	0.016
Day 168	42 -13.99 (2.80)	18 -0.90 (4.27)	-13.09	[-23.18; -3.00]	0.012
Day 126 - 168	44 -14.70 (2.25)	19 1.11 (3.39)	-15.80	[-23.73; -7.87]	<0.001
Hedges' G			-1.09	[-1.66; -0.52]	
QLQ-C30 - Nausea and vomiting					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	39 0.07 (1.54)	17 -0.41 (2.32)	0.48	[-5.02; 5.98]	0.863
Day 42	44 -1.03 (1.82)	20 6.97 (2.74)	-7.99	[-14.53; -1.45]	0.017
Day 84	40 0.45 (1.57)	17 1.83 (2.42)	-1.38	[-7.12; 4.37]	0.634
Day 126	41 -1.58 (1.10)	17 0.23 (1.65)	-1.82	[-5.69; 2.05]	0.351
Day 140	42 0.16 (1.53)	16 4.64 (2.38)	-4.48	[-10.07; 1.11]	0.114
Day 154	41 0.61 (1.88)	16 0.95 (2.92)	-0.35	[-7.24; 6.55]	0.921
Day 168	42 0.13 (1.72)	18 0.89 (2.60)	-0.76	[-6.98; 5.46]	0.808
Day 126 - 168	44 -0.24 (1.16)	19 1.61 (1.75)	-1.85	[-5.97; 2.26]	0.372
Hedges' G			-0.25	[-0.79; 0.29]	
QLQ-C30 - Pain					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	39 0.01 (2.74)	17 -0.98 (4.14)	0.99	[-8.88; 10.85]	0.841
Day 42	44 -1.44 (3.00)	20 8.38 (4.51)	-9.82	[-20.61; 0.97]	0.074
Day 84	40 -1.98 (2.48)	17 5.37 (3.84)	-7.35	[-16.38; 1.68]	0.109
Day 126	41 -2.15 (2.16)	17 1.91 (3.22)	-4.06	[-11.69; 3.57]	0.290
Day 140	42 0.48 (2.92)	16 7.85 (4.47)	-7.37	[-17.99; 3.26]	0.170
Day 154	41 -0.19 (2.60)	16 -0.98 (3.99)	0.78	[-8.62; 10.19]	0.868
Day 168	42 -0.50 (2.68)	18 4.64 (4.03)	-5.14	[-14.73; 4.45]	0.287
Day 126 - 168	44 -1.17 (2.19)	19 2.77 (3.21)	-3.94	[-11.57; 3.68]	0.304
Hedges' G			-0.29	[-0.83; 0.26]	

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Dyspnoea					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	39 -15.47 (3.25)	17 4.87 (4.85)	-20.34	[-31.74; -8.93]	<0.001
Day 42	44 -18.41 (3.39)	20 5.40 (5.06)	-23.81	[-35.75; -11.87]	<0.001
Day 84	40 -19.71 (3.38)	17 6.70 (5.16)	-26.41	[-38.60; -14.22]	<0.001
Day 126	41 -18.34 (3.33)	17 5.13 (5.06)	-23.47	[-35.34; -11.61]	<0.001
Day 140	42 -16.46 (3.39)	16 4.88 (5.33)	-21.34	[-33.75; -8.93]	0.001
Day 154	41 -17.53 (2.81)	16 1.72 (4.35)	-19.26	[-29.35; -9.16]	<0.001
Day 168	42 -19.18 (3.01)	18 0.71 (4.58)	-19.89	[-30.57; -9.20]	<0.001
Day 126 - 168	44 -18.05 (2.54)	19 2.94 (3.82)	-20.99	[-29.81; -12.16]	<0.001
Hedges' G			-1.31	[-1.89; -0.72]	
QLQ-C30 - Insomnia					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	39 -6.47 (2.99)	17 -6.80 (4.52)	0.33	[-10.23; 10.90]	0.950
Day 42	44 -7.06 (3.10)	20 -6.27 (4.56)	-0.78	[-11.51; 9.95]	0.884
Day 84	40 -8.86 (2.94)	17 -3.90 (4.45)	-4.96	[-15.32; 5.40]	0.342
Day 126	41 -11.38 (3.15)	17 -4.40 (4.82)	-6.97	[-18.26; 4.32]	0.221
Day 140	42 -7.92 (3.75)	16 -7.58 (5.98)	-0.34	[-14.30; 13.62]	0.961
Day 154	41 -8.75 (4.03)	16 -3.09 (6.36)	-5.67	[-20.52; 9.19]	0.448
Day 168	42 -10.25 (3.49)	18 -0.92 (5.29)	-9.33	[-21.78; 3.12]	0.139
Day 126 - 168	44 -9.65 (2.67)	19 -4.07 (4.04)	-5.58	[-14.96; 3.80]	0.239
Hedges' G			-0.33	[-0.87; 0.21]	
QLQ-C30 - Appetite loss					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	39 -3.75 (2.16)	17 2.28 (3.26)	-6.03	[-13.78; 1.73]	0.125
Day 42	44 -5.52 (2.31)	20 5.91 (3.41)	-11.43	[-19.58; -3.29]	0.007
Day 84	40 -1.30 (2.57)	17 5.12 (3.93)	-6.43	[-15.78; 2.93]	0.174
Day 126	41 -4.53 (1.44)	17 0.01 (2.15)	-4.54	[-9.58; 0.51]	0.077
Day 140	42 -2.92 (2.49)	16 10.72 (4.02)	-13.64	[-23.05; -4.24]	0.005
Day 154	41 -3.82 (2.13)	16 1.66 (3.35)	-5.48	[-13.33; 2.38]	0.168
Day 168	42 -4.44 (2.66)	18 9.70 (4.01)	-14.14	[-23.70; -4.59]	0.004
Day 126 - 168	44 -4.26 (1.49)	19 5.19 (2.25)	-9.45	[-14.71; -4.19]	<0.001
Hedges' G			-0.99	[-1.55; -0.42]	

Treatment Groups			Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Constipation					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	39 0.14 (1.41)	17 -3.78 (2.12)	3.92	[-1.03; 8.87]	0.118
Day 42	44 -1.80 (1.69)	20 0.76 (2.47)	-2.56	[-8.42; 3.29]	0.385
Day 84	40 -1.64 (1.70)	17 4.06 (2.58)	-5.70	[-11.76; 0.35]	0.064
Day 126	41 -1.54 (1.66)	17 1.72 (2.52)	-3.26	[-9.19; 2.66]	0.275
Day 140	42 -0.11 (2.02)	16 0.79 (3.17)	-0.91	[-8.34; 6.53]	0.808
Day 154	41 -0.23 (2.14)	16 6.51 (3.34)	-6.75	[-14.62; 1.13]	0.091
Day 168	42 -0.54 (2.21)	18 -1.58 (3.34)	1.05	[-6.87; 8.97]	0.792
Day 126 - 168	44 -0.52 (1.47)	19 1.95 (2.20)	-2.47	[-7.62; 2.68]	0.341
Hedges' G			-0.26	[-0.80; 0.28]	
QLQ-C30 - Diarrhoea					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	39 2.52 (2.63)	17 1.07 (3.99)	1.45	[-7.94; 10.85]	0.758
Day 42	44 2.56 (3.29)	20 15.69 (4.84)	-13.13	[-24.70; -1.56]	0.027
Day 84	40 3.25 (2.91)	17 6.96 (4.33)	-3.71	[-13.98; 6.56]	0.473
Day 126	41 0.78 (2.35)	17 5.71 (3.52)	-4.93	[-13.19; 3.34]	0.237
Day 140	42 2.40 (3.17)	16 4.53 (4.84)	-2.13	[-13.53; 9.27]	0.710
Day 154	41 3.39 (2.90)	16 5.68 (4.43)	-2.29	[-12.75; 8.17]	0.662
Day 168	42 0.86 (2.77)	18 4.34 (4.17)	-3.48	[-13.35; 6.39]	0.483
Day 126 - 168	44 1.72 (2.24)	19 4.93 (3.30)	-3.21	[-10.97; 4.55]	0.412
Hedges' G			-0.23	[-0.77; 0.31]	
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures </p> <p>Analysis methods: Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons at Day 126 - 168 were calculated as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.</p> <p>Hedges' G was calculated as model obtained adjusted mean difference / pooled SD with pooled SD = SE / sqrt (1/n1 + 1/n2) where SE is the standard error of the adjusted mean difference and n1 and n2 are the numbers of patients included in the analysis between Day 126 and 168 in treatment group 1 and 2, respectively.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Figure 3-2.2 EORTC QLQ-C30 Symptoms: line chart of least squares mean change from baseline (Full Analysis Set)

QLQ-C30 - Fatigue



Iptacopan	44	39	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

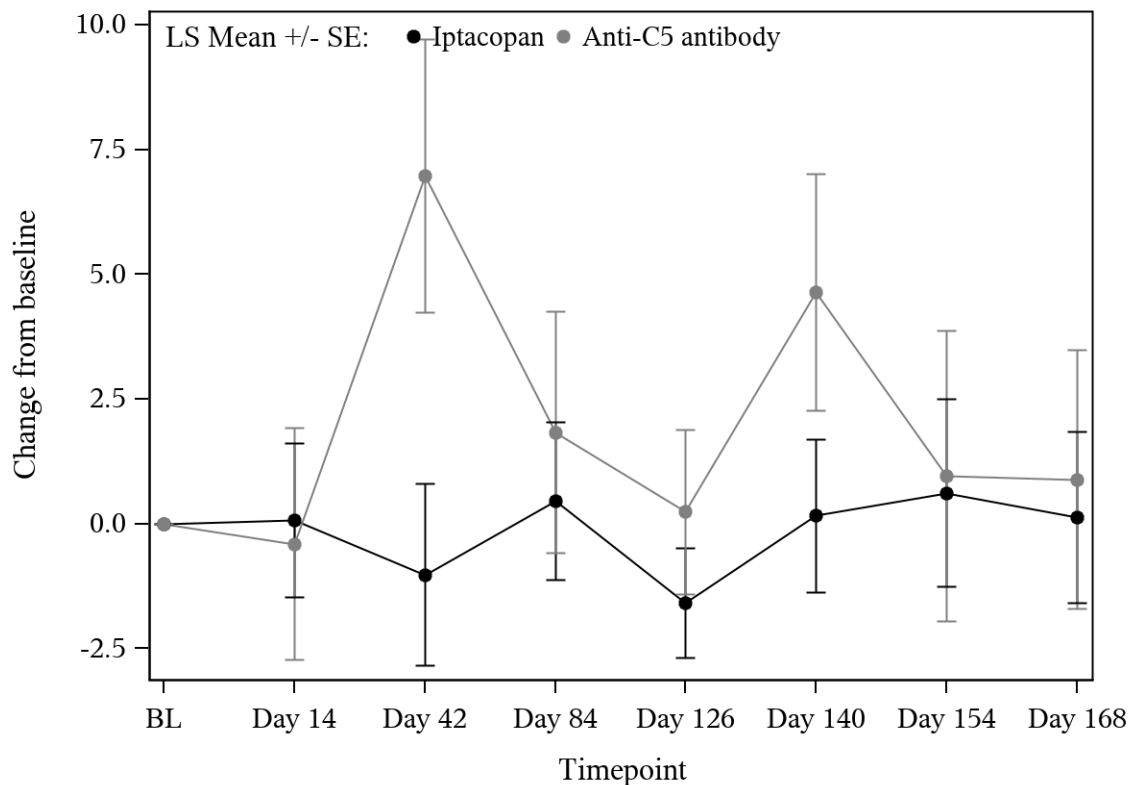
Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Nausea and vomiting



Iptacopan	44	39	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

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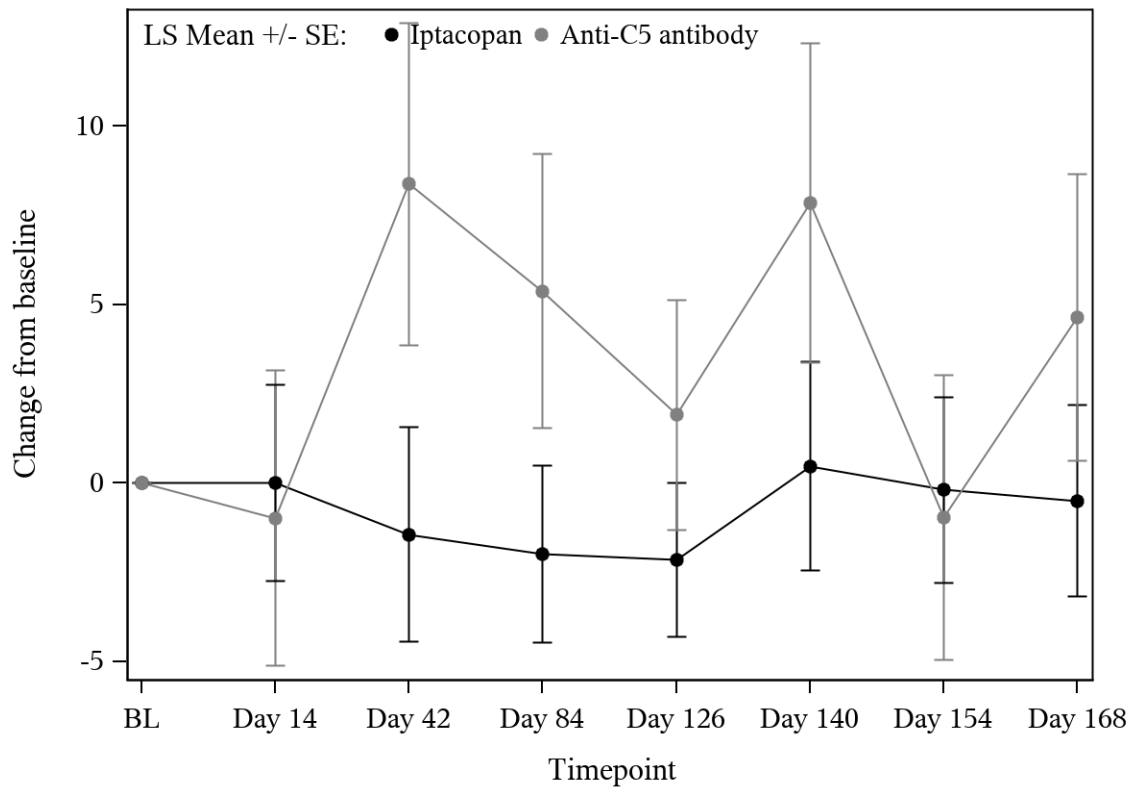
Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Pain



Iptacopan	44	39	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

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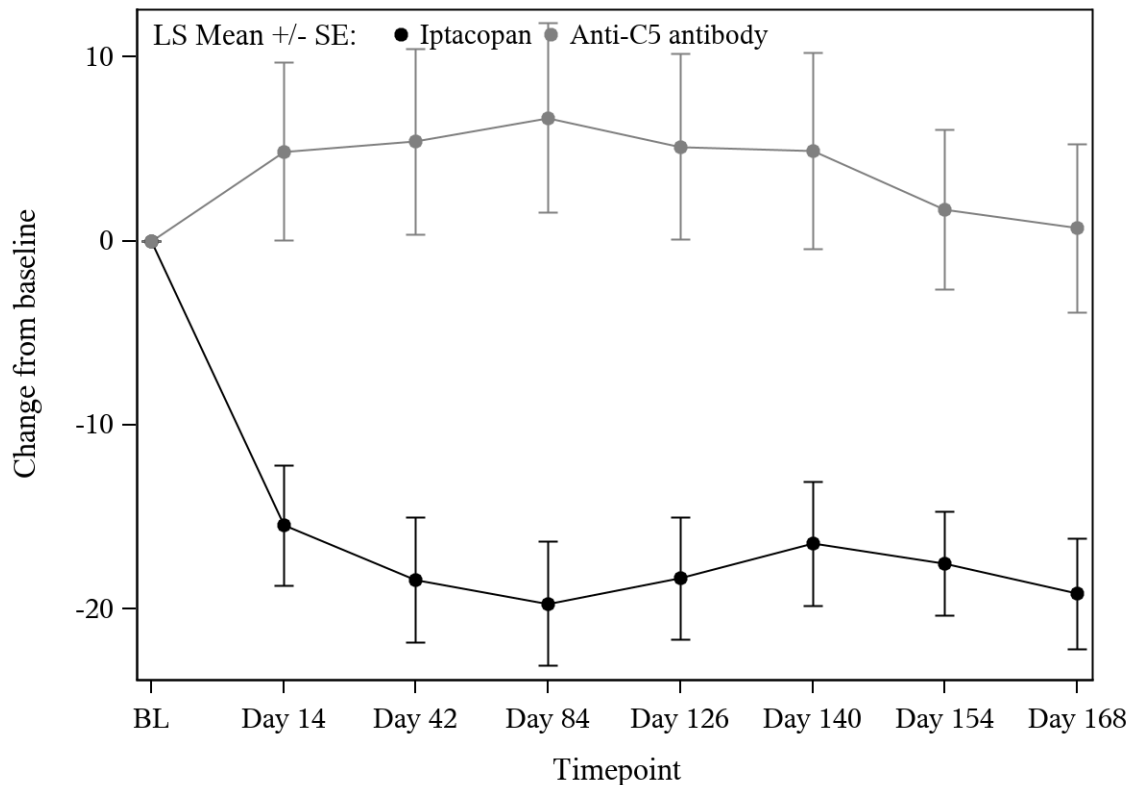
Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Dyspnoea



Iptacopan	44	39	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

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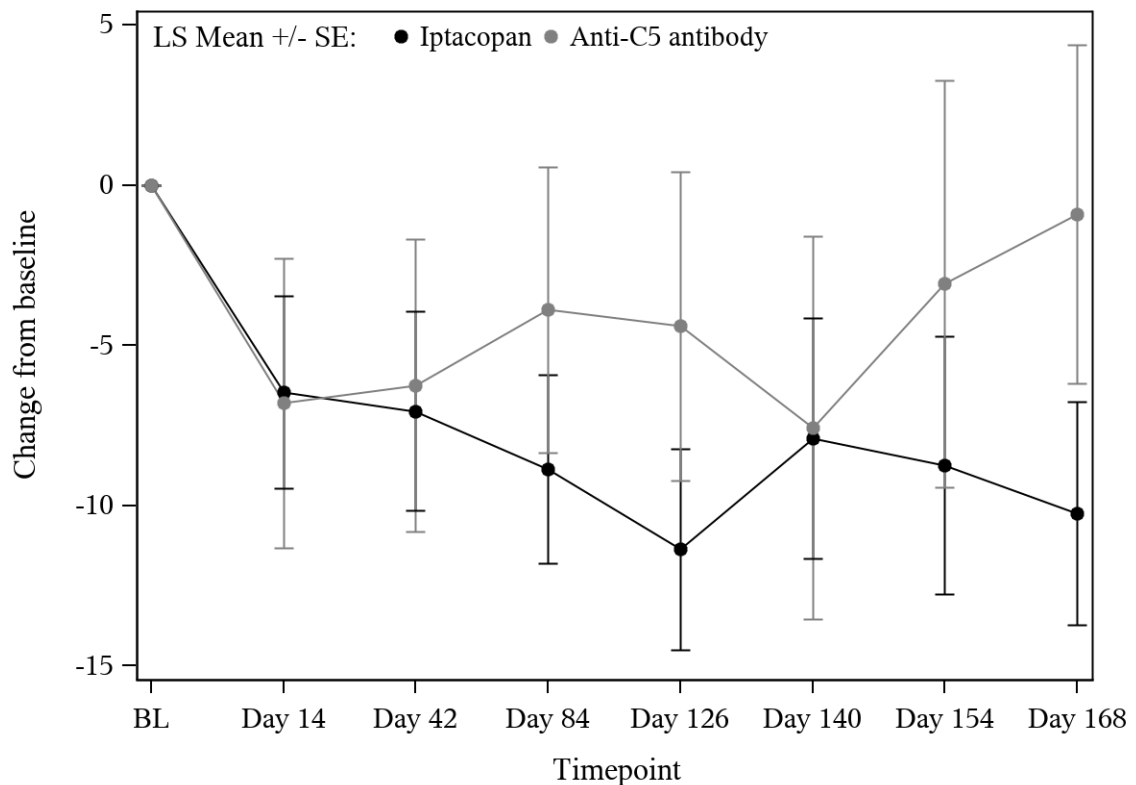
Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Insomnia



Iptacopan	44	39	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

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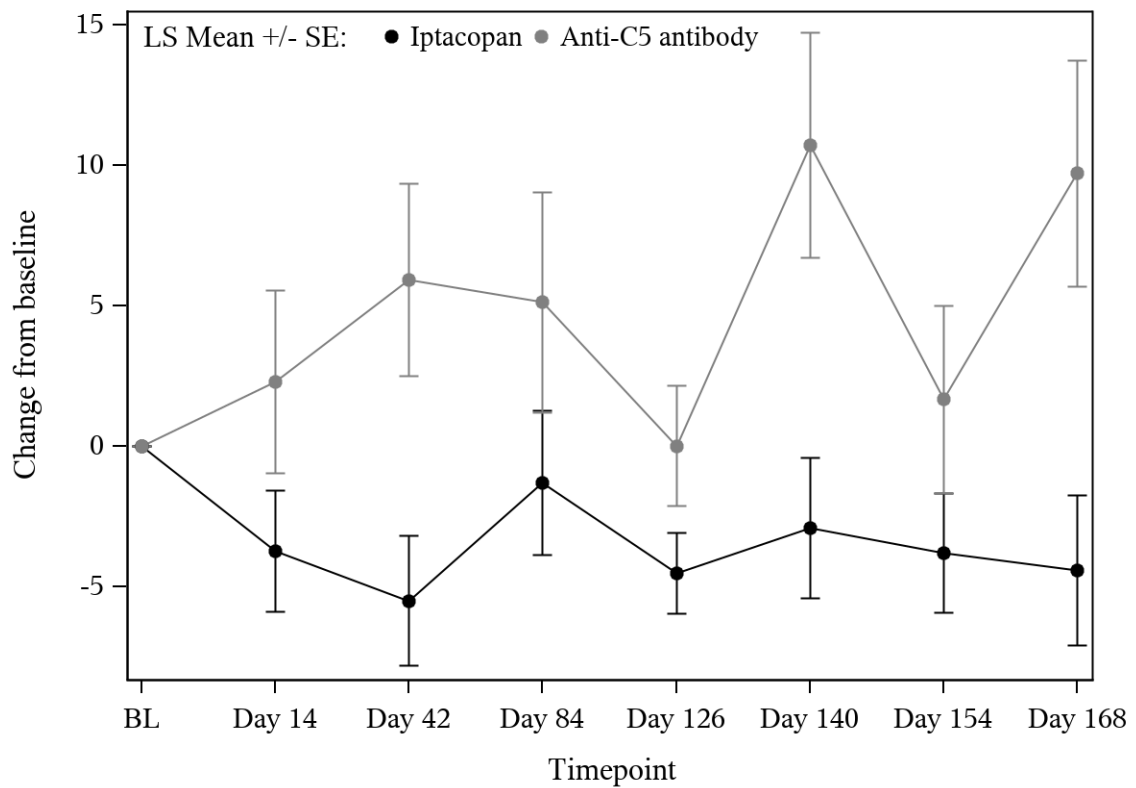
Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Appetite loss



Iptacopan	44	39	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

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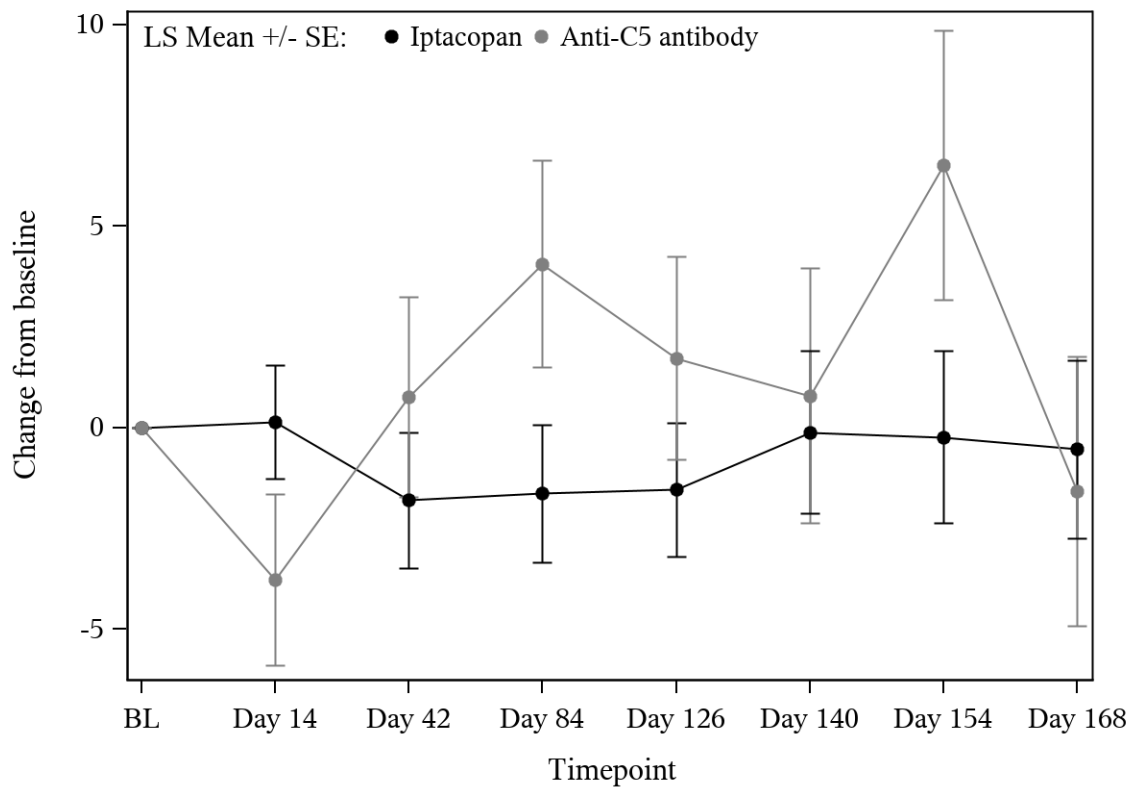
Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Constipation



Iptacopan	44	39	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

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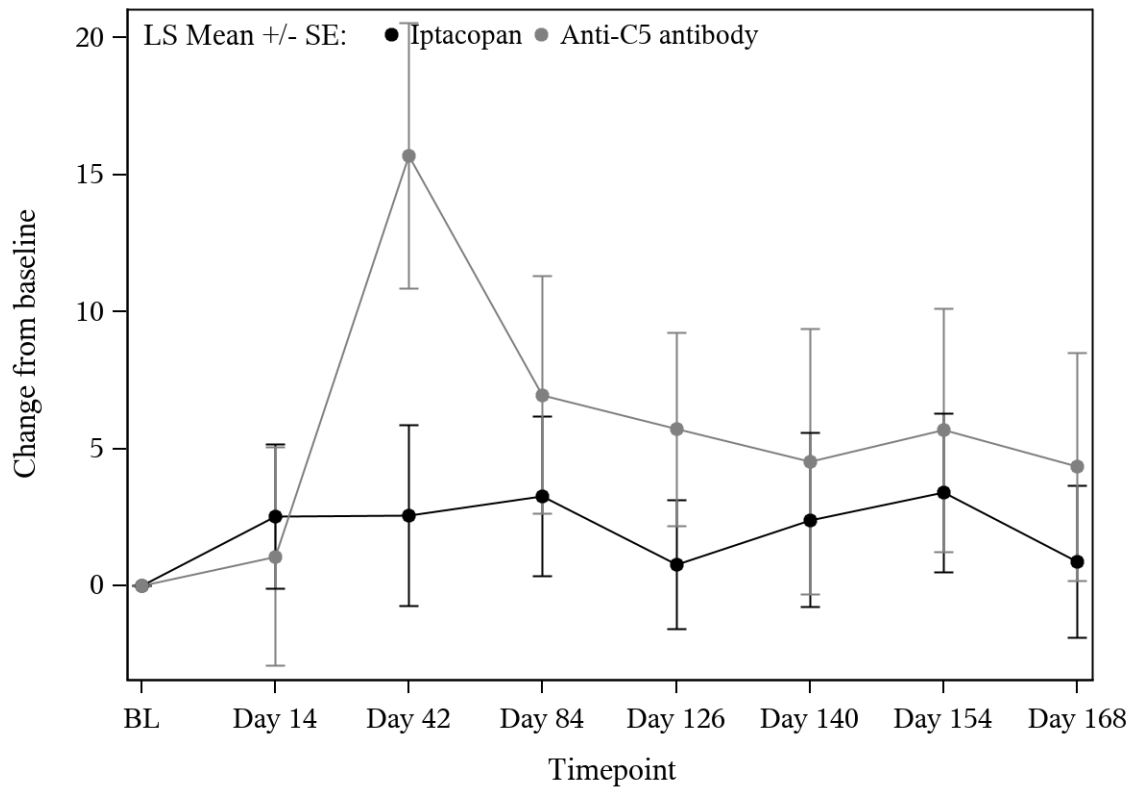
Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Diarrhoea



Iptacopan	44	39	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

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Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

Table 3-2.3 EORTC QLQ-C30 Symptoms responder analysis (improvement defined as ≥ 10 point decrease from baseline): GLMM analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Fatigue						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 14	18 / 39 (46.2) 46.8 [34.2; 59.8]	5 / 17 (29.4) 24.6 [8.3; 40.9]	OR	6.84	[0.97; 48.02]	0.053
			RR	1.92	[1.14; 5.61]	
			RD	0.2209	[0.0517; 0.4155]	
Day 42	23 / 44 (52.3) 56.4 [44.5; 68.0]	6 / 20 (30.0) 23.9 [9.0; 38.1]	OR	10.64	[2.39; 47.34]	0.002
			RR	2.31	[1.50; 6.22]	
			RD	0.3221	[0.1705; 0.5058]	
Day 84	24 / 40 (60.0) 60.9 [47.6; 73.2]	5 / 17 (29.4) 22.8 [8.8; 36.3]	OR	14.38	[2.95; 70.18]	0.001
			RR	2.61	[1.68; 7.01]	
			RD	0.3760	[0.2201; 0.5549]	
Day 126	26 / 41 (63.4) 63.1 [50.8; 74.1]	6 / 17 (35.3) 27.1 [10.6; 41.2]	OR	12.61	[3.08; 51.65]	<0.001
			RR	2.31	[1.58; 5.94]	
			RD	0.3559	[0.2098; 0.5477]	
Day 140	25 / 42 (59.5) 63.4 [51.9; 74.1]	4 / 16 (25.0) 28.6 [11.4; 44.0]	OR	10.97	[2.88; 41.78]	<0.001
			RR	2.18	[1.49; 5.35]	
			RD	0.3402	[0.1965; 0.5421]	
Day 154	26 / 41 (63.4) 62.1 [50.7; 74.2]	4 / 16 (25.0) 30.0 [11.2; 45.4]	OR	9.09	[2.26; 36.46]	0.002
			RR	2.06	[1.35; 5.61]	
			RD	0.3177	[0.1551; 0.5345]	
Day 168	26 / 42 (61.9) 63.4 [50.5; 76.6]	8 / 18 (44.4) 35.6 [14.4; 54.3]	OR	7.18	[1.37; 37.73]	0.020
			RR	1.77	[1.17; 4.29]	
			RD	0.2727	[0.0839; 0.5192]	
Day 126 - 168	44 63.0 [52.2; 74.3]	19 30.4 [12.9; 45.6]	OR	9.75	[2.55; 37.26]	<0.001
			RR	2.05	[1.40; 4.67]	
			RD	0.3230	[0.1692; 0.5282]	

Treatment Groups			Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Nausea and vomiting						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 14	2 / 39 (5.1) 7.0 [0.5; 16.1]	2 / 17 (11.8) 8.1 [1.8; 18.4]	OR	0.92	[0.03; 24.91]	0.958
			RR	0.88	[0.07; 4.25]	
			RD	-0.0088	[-.1229; 0.0895]	
Day 42	4 / 44 (9.1) 7.2 [1.8; 12.9]	1 / 20 (5.0) 8.9 [3.2; 16.5]	OR	1.06	[0.08; 14.40]	0.966
			RR	0.80	[0.22; 2.24]	
			RD	-0.0181	[-.0964; 0.0556]	
Day 84	2 / 40 (5.0) 7.1 [0.8; 15.7]	2 / 17 (11.8) 7.4 [2.3; 15.2]	OR	1.56	[0.09; 27.15]	0.759
			RR	0.96	[0.17; 3.15]	
			RD	-0.0027	[-.0862; 0.0806]	
Day 126	2 / 41 (4.9) 4.4 [0.6; 10.0]	0 / 17 (0.0) 2.8 [0.1; 8.0]	OR	2.84	[0.21; 39.08]	0.434
			RR	1.47	[0.25; 30.52]	
			RD	0.0125	[-.0297; 0.0737]	
Day 140	3 / 42 (7.1) 8.3 [2.3; 15.8]	1 / 16 (6.3) 5.2 [0.1; 11.3]	OR	3.63	[0.27; 48.41]	0.329
			RR	1.61	[0.46; 76.79]	
			RD	0.0315	[-.0399; 0.1134]	
Day 154	4 / 41 (9.8) 8.7 [2.4; 17.5]	1 / 16 (6.3) 4.5 [0.0; 10.8]	OR	4.74	[0.28; 79.80]	0.279
			RR	1.90	[0.55; 241.14]	
			RD	0.0424	[-.0255; 0.1413]	
Day 168	3 / 42 (7.1) 7.6 [1.1; 17.9]	0 / 18 (0.0) 2.9 [0.0; 8.2]	OR	6.35	[0.20; 198.51]	0.292
			RR	2.60	[0.43; >999.99]	
			RD	0.0449	[-.0225; 0.1558]	
Day 126 - 168	44 7.4 [2.2; 14.3]	19 4.1 [0.1; 9.4]	OR	4.20	[0.29; 61.10]	0.293
			RR	1.84	[0.59; 96.18]	
			RD	0.0329	[-.0208; 0.1100]	

Treatment Groups			Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Pain						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 14	5 / 39 (12.8) 15.0 [6.8; 25.1]	6 / 17 (35.3) 21.8 [9.9; 35.9]	OR	0.35	[0.04; 3.24]	0.351
			RR	0.68	[0.33; 1.28]	
			RD	-0.675	[-.1967; 0.0341]	
Day 42	3 / 44 (6.8) 15.2 [7.3; 24.5]	6 / 20 (30.0) 20.3 [10.1; 30.6]	OR	0.48	[0.08; 2.67]	0.398
			RR	0.74	[0.38; 1.41]	
			RD	-0.525	[-.1597; 0.0527]	
Day 84	5 / 40 (12.5) 14.5 [6.6; 23.6]	4 / 17 (23.5) 15.7 [6.3; 25.2]	OR	0.80	[0.11; 5.79]	0.821
			RR	0.93	[0.45; 2.06]	
			RD	-0.121	[-.1110; 0.0906]	
Day 126	6 / 41 (14.6) 14.1 [7.1; 22.7]	5 / 17 (29.4) 11.7 [4.2; 19.0]	OR	1.38	[0.23; 8.38]	0.724
			RR	1.21	[0.66; 2.73]	
			RD	0.0241	[-.0503; 0.0989]	
Day 140	4 / 42 (9.5) 13.7 [6.3; 21.8]	0 / 16 (0.0) 10.1 [3.5; 17.0]	OR	1.68	[0.30; 9.45]	0.558
			RR	1.31	[0.70; 3.13]	
			RD	0.0322	[-.0375; 0.1104]	
Day 154	4 / 41 (9.8) 15.8 [7.3; 26.4]	5 / 16 (31.3) 11.3 [3.2; 20.9]	OR	2.04	[0.33; 12.73]	0.444
			RR	1.36	[0.69; 4.08]	
			RD	0.0434	[-.0411; 0.1445]	
Day 168	7 / 42 (16.7) 17.4 [6.9; 29.7]	2 / 18 (11.1) 11.8 [3.2; 23.6]	OR	2.49	[0.27; 23.02]	0.419
			RR	1.45	[0.57; 4.95]	
			RD	0.0539	[-.0625; 0.1858]	
Day 126 - 168	44 15.1 [7.5; 24.4]	19 11.2 [3.7; 19.4]	OR	1.85	[0.32; 10.66]	0.489
			RR	1.32	[0.70; 3.30]	
			RD	0.0369	[-.0378; 0.1229]	

Treatment Groups			Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Dyspnoea						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 14	24 / 39 (61.5) 60.8 [46.4; 74.6]	3 / 17 (17.6) 18.6 [3.6; 33.8]	OR	27.69	[3.64; 210.77]	0.001
			RR	3.24	[1.72; 15.84]	
			RD	0.4241	[0.2253; 0.6048]	
Day 42	28 / 44 (63.6) 64.3 [53.2; 75.4]	4 / 20 (20.0) 15.9 [4.8; 27.5]	OR	41.90	[8.36; 209.96]	<0.001
			RR	4.04	[2.29; 13.30]	
			RD	0.4863	[0.3427; 0.6224]	
Day 84	26 / 40 (65.0) 63.8 [51.6; 75.8]	3 / 17 (17.6) 12.1 [4.3; 21.4]	OR	47.75	[8.34; 273.34]	<0.001
			RR	5.30	[2.95; 14.43]	
			RD	0.5137	[0.3787; 0.6527]	
Day 126	28 / 41 (68.3) 65.8 [53.2; 77.7]	3 / 17 (17.6) 19.2 [7.1; 30.8]	OR	30.20	[6.59; 138.49]	<0.001
			RR	3.42	[2.17; 8.86]	
			RD	0.4649	[0.3207; 0.6247]	
Day 140	27 / 42 (64.3) 67.7 [55.0; 79.2]	3 / 16 (18.8) 23.8 [10.2; 35.4]	OR	22.74	[5.50; 94.02]	<0.001
			RR	2.84	[1.91; 6.42]	
			RD	0.4381	[0.2973; 0.6000]	
Day 154	27 / 41 (65.9) 69.0 [56.0; 80.9]	5 / 16 (31.3) 30.8 [14.9; 44.7]	OR	16.04	[3.78; 67.97]	<0.001
			RR	2.20	[1.57; 4.52]	
			RD	0.3734	[0.2363; 0.5464]	
Day 168	31 / 42 (73.8) 70.1 [56.7; 82.9]	7 / 18 (38.9) 37.0 [19.6; 52.8]	OR	10.60	[1.91; 58.65]	0.007
			RR	1.88	[1.33; 3.56]	
			RD	0.3227	[0.1511; 0.5253]	
Day 126 - 168	44 68.0 [55.7; 79.7]	19 27.8 [13.5; 40.2]	OR	18.48	[4.54; 75.23]	<0.001
			RR	2.42	[1.71; 5.00]	
			RD	0.3979	[0.2654; 0.5630]	

Treatment Groups			Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Insomnia						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 14	12 / 39 (30.8) 31.3 [19.0; 43.7]	5 / 17 (29.4) 36.4 [19.7; 53.9]	OR	0.61	[0.06; 6.01]	0.675
			RR	0.86	[0.54; 1.42]	
			RD	-0.530	[-.2011; 0.1042]	
Day 42	17 / 44 (38.6) 36.7 [25.5; 47.9]	9 / 20 (45.0) 43.8 [25.9; 60.9]	OR	0.56	[0.10; 3.02]	0.500
			RR	0.85	[0.59; 1.31]	
			RD	-0.692	[-.2262; 0.0910]	
Day 84	16 / 40 (40.0) 39.4 [27.4; 51.7]	7 / 17 (41.2) 44.1 [27.0; 62.2]	OR	0.65	[0.10; 4.01]	0.640
			RR	0.89	[0.63; 1.38]	
			RD	-0.481	[-.2088; 0.1151]	
Day 126	19 / 41 (46.3) 42.1 [30.0; 54.2]	6 / 17 (35.3) 42.0 [24.9; 58.2]	OR	1.05	[0.20; 5.58]	0.952
			RR	1.00	[0.74; 1.54]	
			RD	0.0012	[-.1244; 0.1561]	
Day 140	16 / 42 (38.1) 44.9 [32.4; 56.6]	7 / 16 (43.8) 42.1 [24.1; 57.3]	OR	1.33	[0.27; 6.66]	0.726
			RR	1.06	[0.79; 1.73]	
			RD	0.0265	[-.0978; 0.1879]	
Day 154	19 / 41 (46.3) 41.0 [28.5; 53.3]	5 / 16 (31.3) 35.4 [16.4; 52.6]	OR	1.75	[0.32; 9.60]	0.516
			RR	1.16	[0.80; 2.33]	
			RD	0.0563	[-.0943; 0.2404]	
Day 168	18 / 42 (42.9) 42.5 [29.4; 54.8]	7 / 18 (38.9) 34.2 [14.1; 52.7]	OR	2.39	[0.31; 18.52]	0.402
			RR	1.24	[0.83; 3.02]	
			RD	0.0829	[-.0812; 0.3002]	
Day 126 - 168	44 42.7 [30.3; 54.3]	19 38.4 [20.6; 54.1]	OR	1.56	[0.31; 7.95]	0.593
			RR	1.11	[0.81; 1.91]	
			RD	0.0420	[-.0918; 0.2097]	

Treatment Groups			Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Appetite loss						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 14	9 / 39 (23.1) 20.4 [10.4; 31.4]	2 / 17 (11.8) 17.6 [4.5; 29.3]	OR	2.47	[0.07; 87.40]	0.618
			RR	1.09	[0.80; 4.26]	
			RD	0.0176	[-.0395; 0.1650]	
Day 42	10 / 44 (22.7) 22.6 [12.7; 32.6]	4 / 20 (20.0) 16.3 [5.3; 27.4]	OR	4.10	[0.29; 58.59]	0.298
			RR	1.33	[0.86; 4.13]	
			RD	0.0550	[-.0294; 0.1991]	
Day 84	5 / 40 (12.5) 16.2 [8.0; 25.9]	2 / 17 (11.8) 8.5 [0.7; 17.3]	OR	7.12	[0.36; 139.62]	0.195
			RR	1.87	[0.97; 17.38]	
			RD	0.0721	[-.0040; 0.1857]	
Day 126	9 / 41 (22.0) 21.0 [10.8; 31.8]	3 / 17 (17.6) 11.1 [2.8; 19.7]	OR	9.69	[0.59; 158.65]	0.111
			RR	1.83	[1.10; 6.60]	
			RD	0.0954	[0.0126; 0.2118]	
Day 140	9 / 42 (21.4) 20.5 [11.4; 31.7]	0 / 16 (0.0) 11.3 [3.6; 19.8]	OR	10.17	[0.69; 149.60]	0.091
			RR	1.77	[1.12; 5.13]	
			RD	0.0902	[0.0164; 0.1910]	
Day 154	10 / 41 (24.4) 22.7 [11.8; 34.0]	3 / 16 (18.8) 13.0 [2.5; 23.2]	OR	10.39	[0.65; 166.98]	0.098
			RR	1.68	[1.03; 8.83]	
			RD	0.0891	[0.0057; 0.2257]	
Day 168	9 / 42 (21.4) 23.0 [12.4; 34.1]	3 / 18 (16.7) 15.0 [2.5; 27.4]	OR	10.34	[0.41; 262.13]	0.156
			RR	1.47	[0.91; 8.45]	
			RD	0.0729	[-.0169; 0.2181]	
Day 126 - 168	44 21.9 [11.7; 32.6]	19 12.6 [3.7; 21.3]	OR	10.15	[0.69; 149.26]	0.091
			RR	1.67	[1.08; 6.01]	
			RD	0.0861	[0.0124; 0.2015]	

Treatment Groups			Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Constipation						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 14	2 / 39 (5.1) 9.2 [3.6; 16.4]	2 / 17 (11.8) 8.3 [1.8; 20.1]	OR	1.46	[0.01; 176.34]	0.877
			RR	1.10	[0.48; 4.48]	
			RD	0.0072	[-.0943; 0.0745]	
Day 42	6 / 44 (13.6) 10.8 [4.8; 17.8]	2 / 20 (10.0) 9.1 [1.8; 17.4]	OR	1.62	[0.07; 38.12]	0.764
			RR	1.14	[0.65; 4.77]	
			RD	0.0134	[-.0474; 0.0971]	
Day 84	4 / 40 (10.0) 13.1 [6.1; 21.2]	3 / 17 (17.6) 10.6 [2.2; 20.4]	OR	2.48	[0.10; 61.52]	0.579
			RR	1.21	[0.62; 4.85]	
			RD	0.0223	[-.0621; 0.1163]	
Day 126	6 / 41 (14.6) 14.4 [7.0; 22.6]	1 / 17 (5.9) 9.4 [2.2; 17.6]	OR	5.20	[0.24; 110.24]	0.289
			RR	1.49	[0.82; 6.18]	
			RD	0.0461	[-.0274; 0.1469]	
Day 140	5 / 42 (11.9) 14.8 [7.7; 23.1]	2 / 16 (12.5) 9.1 [2.2; 17.0]	OR	7.14	[0.33; 153.93]	0.209
			RR	1.62	[0.92; 6.07]	
			RD	0.0563	[-.0100; 0.1469]	
Day 154	6 / 41 (14.6) 14.8 [7.0; 23.4]	1 / 16 (6.3) 7.5 [0.8; 15.3]	OR	10.16	[0.33; 314.91]	0.185
			RR	1.89	[1.06; 13.87]	
			RD	0.0697	[0.0053; 0.1568]	
Day 168	6 / 42 (14.3) 15.6 [8.4; 24.9]	3 / 18 (16.7) 8.5 [2.3; 16.9]	OR	14.98	[0.20; >999.99]	0.216
			RR	1.76	[1.08; 5.84]	
			RD	0.0666	[0.0088; 0.1516]	
Day 126 - 168	44 15.0 [7.7; 23.3]	19 8.6 [2.2; 15.8]	OR	8.67	[0.34; 218.07]	0.189
			RR	1.67	[1.00; 5.37]	
			RD	0.0603	[-.0003; 0.1468]	

	Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Diarrhoea						
	n / N' (%)	n / N' (%)				
	Predict. % [95% CI]	Predict. % [95% CI]				
Day 14	4 / 39 (10.3)	2 / 17 (11.8)	OR	1.78	[0.13; 24.52]	0.665
	11.4 [3.1; 22.7]	8.9 [0.0; 21.6]	RR	1.27	[0.30; 461.86]	
			RD	0.0231	[-.1012; 0.1644]	
Day 42	8 / 44 (18.2)	0 / 20 (0.0)	OR	5.19	[0.62; 43.62]	0.129
	15.2 [6.8; 25.0]	5.9 [0.4; 13.4]	RR	2.48	[1.04; 37.58]	
			RD	0.0911	[0.0038; 0.1927]	
Day 84	5 / 40 (12.5)	1 / 17 (5.9)	OR	10.15	[0.89; 115.29]	0.062
	18.0 [8.1; 30.3]	5.1 [0.2; 13.9]	RR	3.39	[1.15; 89.23]	
			RD	0.1251	[0.0143; 0.2456]	
Day 126	8 / 41 (19.5)	1 / 17 (5.9)	OR	6.47	[0.76; 55.01]	0.087
	16.3 [7.9; 26.9]	7.5 [0.3; 16.9]	RR	2.12	[0.97; 63.55]	
			RD	0.0855	[-.0029; 0.1928]	
Day 140	8 / 42 (19.0)	1 / 16 (6.3)	OR	4.34	[0.59; 31.88]	0.148
	17.0 [8.8; 28.2]	9.2 [0.6; 19.2]	RR	1.79	[0.93; 24.76]	
			RD	0.0759	[-.0077; 0.1930]	
Day 154	6 / 41 (14.6)	3 / 16 (18.8)	OR	2.57	[0.34; 19.54]	0.360
	17.2 [8.8; 27.8]	12.4 [2.9; 21.5]	RR	1.38	[0.80; 4.96]	
			RD	0.0494	[-.0264; 0.1555]	
Day 168	7 / 42 (16.7)	2 / 18 (11.1)	OR	1.35	[0.12; 14.91]	0.808
	16.2 [7.4; 27.0]	14.5 [4.8; 23.8]	RR	1.11	[0.59; 3.09]	
			RD	0.0174	[-.0700; 0.1287]	
Day 126 - 168	44	19	OR	3.14	[0.44; 22.49]	0.253
	16.7 [9.0; 27.0]	11.0 [2.9; 19.8]	RR	1.50	[0.88; 5.14]	
			RD	0.0567	[-.0146; 0.1585]	

Treatment Groups		Comparison			
Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit n: Number of patients with response CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference GLMM: Generalized linear mixed model </p> <p>Analysis methods: OR, RR and RD from logistic GLMM with random intercept and week as continuous covariate: $\text{Logit}(\text{proportion}) = \text{treatment} + \text{baseline value} + \text{treatment} * \text{week} + \text{baseline value} * \text{week} + \text{treatment} * \text{week} * \text{week} + \text{baseline value} * \text{week} * \text{week}$ Anti-C5 antibody was the reference group for treatment group comparison. OR with 95% Wald CI and p-value were calculated from model linear predictors, at Day 126 - 168 from a linear function of linear predictors. Predicted proportions, RR and RD were calculated by marginal standardization from predicted values. First, predicted proportions were calculated by marginal standardization for each treatment group at each visit. Then predicted proportions were averaged over the four visits Day 126 - 168. Then RR and RD were calculated for each visit and for Day 126 - 168. Estimates and 95% CI were constructed by median and 2.5% and 97.5% percentiles from 1000 bootstrap samples.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Response (improvement) is defined as ≥ 10 point decrease from baseline.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

3-3 EORTC QLQ-C30 QoL

Table 3-3.1 EORTC QLQ-C30 QoL: descriptive statistics by timepoint (Full Analysis Set)

Treatment Groups		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)
QLQ-C30 - Global health status		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 62.69 (17.88)	21 62.50 (19.98)
Day 14	39 68.80 (17.60)	17 60.29 (20.10)
Day 42	44 75.38 (17.33)	20 53.75 (24.10)
Day 84	40 76.67 (18.80)	17 55.88 (24.25)
Day 126	41 76.42 (14.90)	17 64.22 (17.86)
Day 140	42 71.03 (16.99)	16 59.38 (24.32)
Day 154	41 74.19 (17.16)	15 60.56 (25.29)
Day 168	42 73.21 (16.62)	18 57.87 (26.27)
Day 126 - 168	44 73.44 (14.49)	19 59.36 (22.37)
QLQ-C30 - Physical functioning		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 77.12 (18.02)	21 71.27 (21.69)
Day 14	39 85.13 (17.20)	17 73.73 (21.27)
Day 42	44 85.61 (14.87)	20 68.33 (22.67)
Day 84	40 86.83 (14.12)	17 69.41 (22.98)
Day 126	41 87.80 (15.05)	17 74.51 (20.31)
Day 140	42 88.41 (13.50)	16 68.75 (29.49)
Day 154	41 84.55 (21.21)	16 71.25 (23.06)
Day 168	42 86.35 (17.36)	18 69.26 (23.67)
Day 126 - 168	44 86.55 (15.00)	19 69.82 (23.56)
QLQ-C30 - Role functioning		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 73.30 (24.22)	21 70.24 (30.00)
Day 14	39 76.92 (24.67)	17 67.65 (27.30)
Day 42	44 85.61 (20.20)	20 61.67 (31.58)
Day 84	40 85.00 (22.58)	17 64.71 (32.75)
Day 126	41 84.55 (18.41)	17 68.63 (27.56)
Day 140	42 82.94 (23.71)	16 60.42 (33.26)
Day 154	41 82.11 (28.48)	16 58.33 (32.20)
Day 168	42 82.54 (23.84)	18 62.04 (31.73)
Day 126 - 168	44 82.83 (20.92)	19 61.18 (29.00)

Treatment Groups		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)
QLQ-C30 - Emotional functioning		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 71.21 (23.53)	21 75.20 (24.24)
Day 14	39 75.85 (21.44)	17 69.61 (23.00)
Day 42	44 81.06 (18.00)	20 70.83 (27.64)
Day 84	40 83.33 (16.01)	17 67.65 (27.30)
Day 126	41 78.25 (22.27)	17 77.94 (17.91)
Day 140	42 75.40 (22.01)	16 72.92 (25.18)
Day 154	41 79.07 (18.27)	16 71.87 (24.88)
Day 168	42 79.76 (21.00)	18 73.15 (29.78)
Day 126 - 168	44 77.84 (18.83)	19 72.70 (25.15)
QLQ-C30 - Cognitive functioning		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 79.36 (20.05)	21 73.41 (30.58)
Day 14	39 87.18 (15.03)	17 75.49 (27.71)
Day 42	44 84.09 (16.06)	20 66.67 (27.57)
Day 84	40 86.25 (19.93)	17 64.71 (33.79)
Day 126	41 88.62 (15.11)	17 71.57 (32.68)
Day 140	42 85.71 (18.61)	16 66.67 (34.43)
Day 154	41 86.18 (18.97)	16 64.58 (30.35)
Day 168	42 84.52 (18.55)	18 63.89 (34.42)
Day 126 - 168	44 85.89 (16.63)	19 67.03 (31.20)
QLQ-C30 - Social functioning		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 76.14 (25.26)	21 68.65 (30.27)
Day 14	39 78.63 (26.20)	17 70.59 (27.34)
Day 42	44 84.09 (24.10)	20 63.33 (33.16)
Day 84	40 87.92 (19.97)	17 60.78 (33.82)
Day 126	41 85.77 (19.21)	17 67.65 (29.15)
Day 140	42 84.52 (21.27)	16 62.50 (34.16)
Day 154	41 84.96 (24.67)	16 65.63 (30.10)
Day 168	42 85.71 (21.64)	18 58.33 (35.81)
Day 126 - 168	44 84.94 (19.68)	19 62.72 (30.23)
N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit SD: Standard deviation Analysis methods: Descriptive means Day 126 - 168 were calculated by averaging first over the four visits for each patient and then averaging over the treatment group. Patients with non-missing value at least at baseline and at one of the four visits were included in the calculation. Cut-off date for analysis: 06-Mar-2023		

Table 3-3.2 EORTC QLQ-C30 QoL: MMRM analysis of change from baseline (Full Analysis Set)

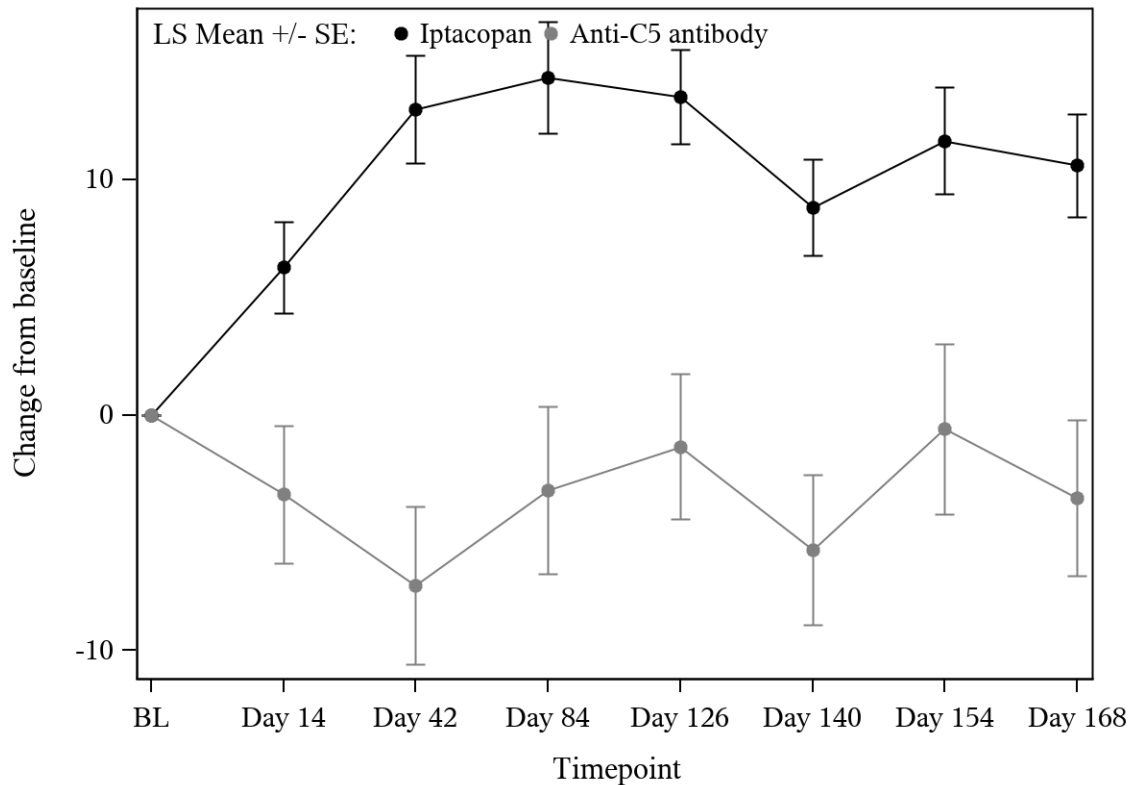
	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Global health status					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	39 6.26 (1.93)	17 -3.38 (2.91)	9.64	[2.86; 16.42]	0.006
Day 42	44 12.98 (2.27)	20 -7.25 (3.36)	20.23	[12.29; 28.17]	<0.001
Day 84	40 14.34 (2.36)	17 -3.20 (3.57)	17.54	[9.14; 25.94]	<0.001
Day 126	41 13.51 (2.00)	17 -1.35 (3.07)	14.86	[7.71; 22.02]	<0.001
Day 140	42 8.83 (2.04)	16 -5.73 (3.19)	14.55	[7.15; 21.96]	<0.001
Day 154	41 11.65 (2.28)	15 -0.60 (3.62)	12.25	[3.85; 20.65]	0.005
Day 168	42 10.59 (2.19)	18 -3.52 (3.30)	14.11	[6.36; 21.87]	<0.001
Day 126 - 168	44 11.26 (1.70)	19 -2.69 (2.56)	13.95	[8.02; 19.87]	<0.001
Hedges' G			1.29	[0.71; 1.88]	
QLQ-C30 - Physical functioning					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	39 8.23 (1.67)	17 -2.00 (2.49)	10.23	[4.46; 16.01]	<0.001
Day 42	44 9.38 (1.91)	20 -3.50 (2.83)	12.88	[6.22; 19.54]	<0.001
Day 84	40 10.54 (1.81)	17 -0.91 (2.71)	11.45	[5.12; 17.79]	<0.001
Day 126	41 11.60 (1.78)	17 -1.12 (2.68)	12.72	[6.47; 18.97]	<0.001
Day 140	42 12.01 (1.97)	16 -5.48 (3.03)	17.49	[10.44; 24.54]	<0.001
Day 154	41 8.10 (2.84)	16 -0.79 (4.50)	8.89	[-1.66; 19.45]	0.097
Day 168	42 9.87 (1.96)	18 -1.87 (2.97)	11.74	[4.78; 18.71]	0.001
Day 126 - 168	44 10.63 (1.71)	19 -2.08 (2.57)	12.71	[6.73; 18.69]	<0.001
Hedges' G			1.17	[0.59; 1.74]	
QLQ-C30 - Role functioning					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	39 5.17 (2.69)	17 -6.94 (4.05)	12.11	[2.67; 21.55]	0.013
Day 42	44 13.72 (2.91)	20 -6.78 (4.30)	20.50	[10.38; 30.62]	<0.001
Day 84	40 12.92 (3.08)	17 -2.49 (4.62)	15.42	[4.55; 26.29]	0.006
Day 126	41 12.33 (2.63)	17 -5.11 (3.98)	17.44	[8.19; 26.69]	<0.001
Day 140	42 10.69 (3.38)	16 -11.81 (5.25)	22.50	[10.22; 34.77]	<0.001
Day 154	41 10.51 (4.10)	16 -8.78 (6.39)	19.29	[4.28; 34.29]	0.013
Day 168	42 10.46 (3.09)	18 -6.61 (4.66)	17.07	[6.12; 28.02]	0.003
Day 126 - 168	44 11.27 (2.69)	19 -7.80 (4.03)	19.07	[9.66; 28.48]	<0.001
Hedges' G			1.11	[0.54; 1.68]	

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Emotional functioning					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	39 5.08 (2.49)	17 -2.77 (3.72)	7.86	[-0.85; 16.57]	0.076
Day 42	44 10.31 (2.51)	20 -1.60 (3.69)	11.92	[3.26; 20.58]	0.008
Day 84	40 12.28 (2.65)	17 -1.24 (4.01)	13.52	[4.15; 22.89]	0.005
Day 126	41 6.52 (2.88)	17 2.46 (4.40)	4.05	[-6.25; 14.36]	0.434
Day 140	42 5.45 (2.85)	16 -1.56 (4.43)	7.01	[-3.33; 17.34]	0.180
Day 154	41 8.22 (2.60)	16 -0.27 (3.98)	8.49	[-0.79; 17.77]	0.072
Day 168	42 9.02 (2.68)	18 2.02 (4.03)	7.00	[-2.44; 16.45]	0.143
Day 126 - 168	44 7.16 (2.39)	19 0.52 (3.59)	6.64	[-1.71; 14.99]	0.117
Hedges' G			0.44	[-0.11; 0.98]	
QLQ-C30 - Cognitive functioning					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	39 8.32 (2.40)	17 -0.44 (3.58)	8.76	[0.41; 17.11]	0.040
Day 42	44 5.74 (2.59)	20 -7.28 (3.82)	13.02	[4.01; 22.02]	0.005
Day 84	40 5.77 (2.75)	17 -3.79 (4.16)	9.56	[-0.24; 19.36]	0.056
Day 126	41 9.44 (2.32)	17 -5.51 (3.47)	14.94	[6.86; 23.02]	<0.001
Day 140	42 7.35 (2.60)	16 -5.69 (3.99)	13.04	[3.76; 22.32]	0.007
Day 154	41 7.81 (2.52)	16 -7.10 (3.85)	14.91	[5.93; 23.89]	0.002
Day 168	42 5.51 (2.37)	18 -7.65 (3.57)	13.16	[4.83; 21.50]	0.002
Day 126 - 168	44 7.61 (2.08)	19 -6.40 (3.08)	14.01	[6.88; 21.15]	<0.001
Hedges' G			1.08	[0.51; 1.65]	
QLQ-C30 - Social functioning					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	39 2.99 (2.62)	17 -3.52 (3.91)	6.51	[-2.70; 15.72]	0.162
Day 42	44 8.70 (3.26)	20 -5.12 (4.80)	13.83	[2.40; 25.25]	0.019
Day 84	40 11.52 (3.20)	17 -6.62 (4.85)	18.14	[6.61; 29.67]	0.003
Day 126	41 9.94 (2.42)	17 -4.94 (3.62)	14.88	[6.39; 23.37]	<0.001
Day 140	42 9.18 (2.73)	16 -9.15 (4.19)	18.33	[8.54; 28.12]	<0.001
Day 154	41 9.59 (3.20)	16 -1.97 (4.97)	11.56	[-0.12; 23.24]	0.052
Day 168	42 10.00 (3.03)	18 -7.71 (4.54)	17.71	[6.98; 28.44]	0.002
Day 126 - 168	44 9.84 (2.32)	19 -5.78 (3.43)	15.62	[7.59; 23.65]	<0.001
Hedges' G			1.07	[0.50; 1.64]	

Treatment Groups		Comparison		
Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures </p> <p>Analysis methods: Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons at Day 126 - 168 were calculated as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.</p> <p>Hedges' G was calculated as model obtained adjusted mean difference / pooled SD with pooled SD = SE / sqrt (1/n1 + 1/n2) where SE is the standard error of the adjusted mean difference and n1 and n2 are the numbers of patients included in the analysis between Day 126 and 168 in treatment group 1 and 2, respectively.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>				

Figure 3-3.2 EORTC QLQ-C30 QoL: line chart of least squares mean change from baseline (Full Analysis Set)

QLQ-C30 - Global health status



Iptacopan	44	39	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	15	18

LS Mean: Least square mean
 SE: Standard error

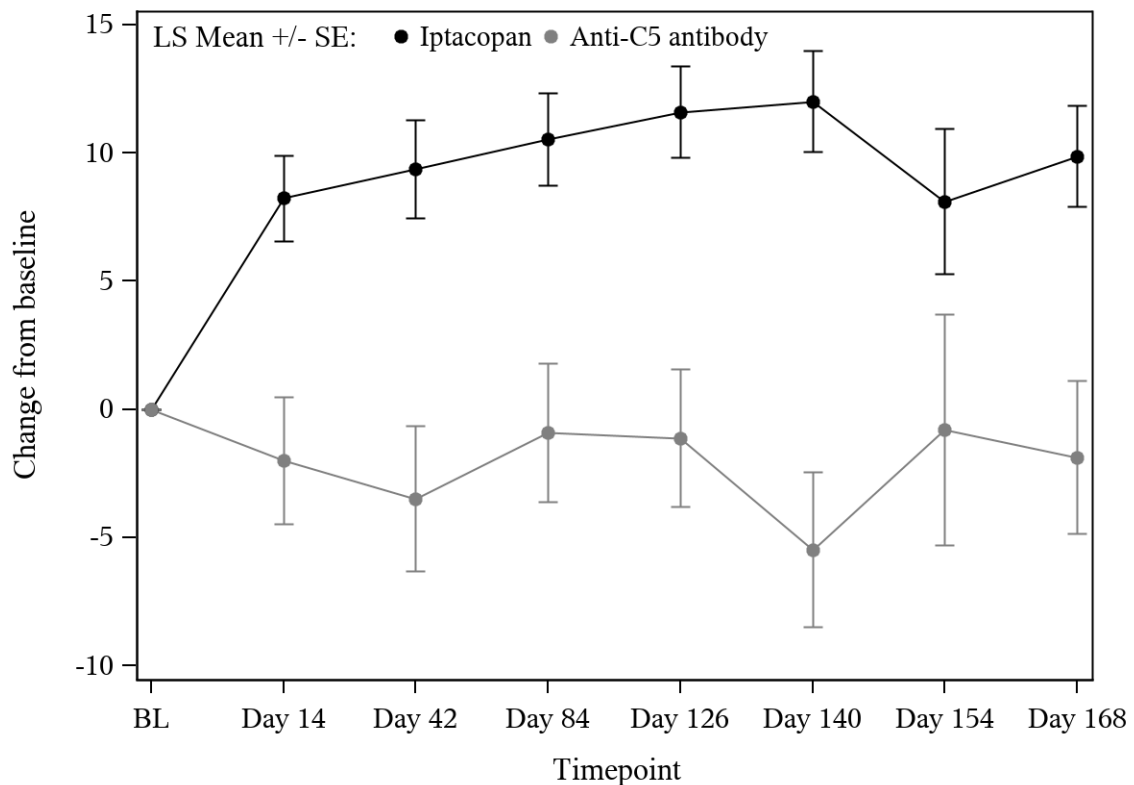
Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Physical functioning



Iptacopan	44	39	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

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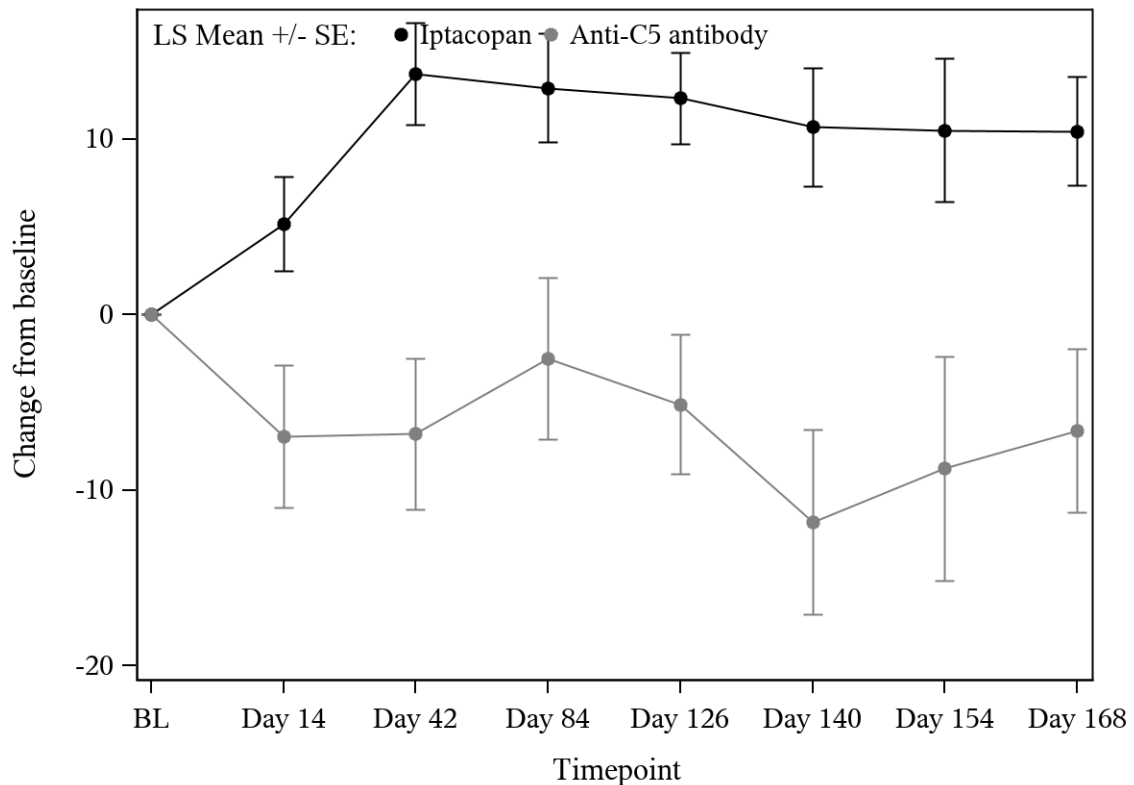
Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Role functioning



Iptacopan	44	39	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

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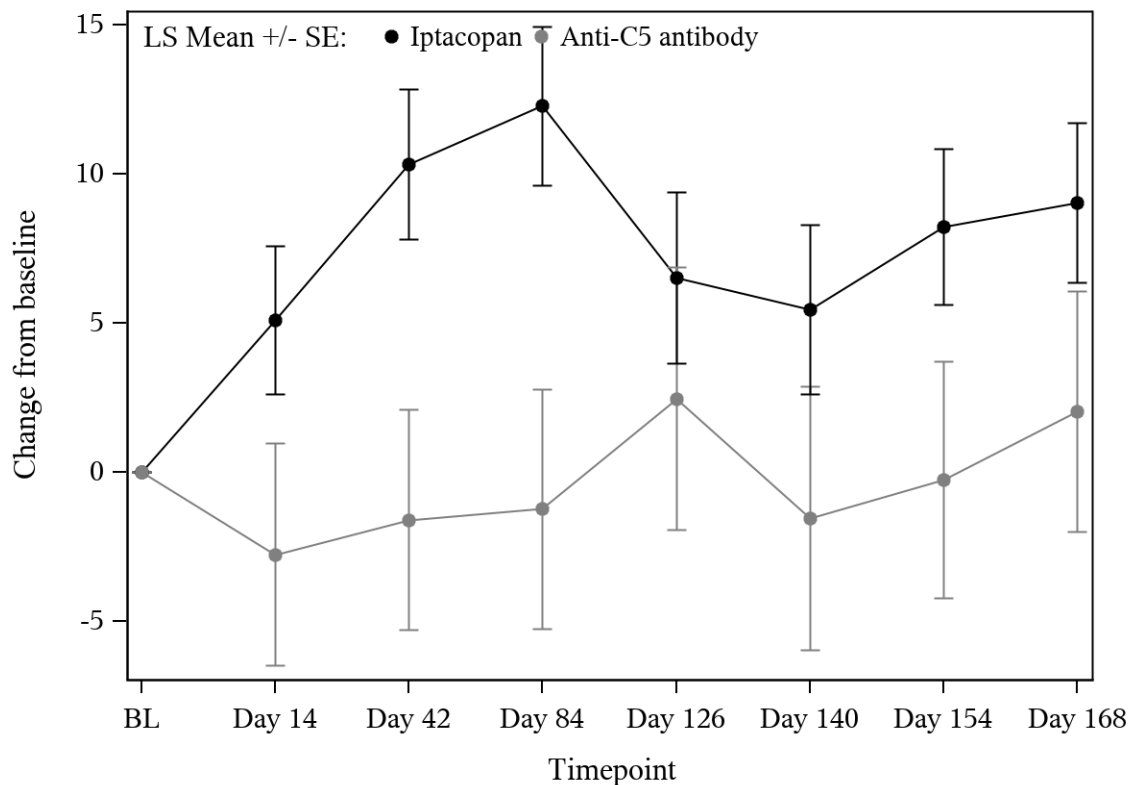
Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 $\text{Change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{baseline value} + \text{baseline value} * \text{visit} + \text{transfusion history} + \text{prior anti-C5-treatment}$

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Emotional functioning



Iptacopan	44	39	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

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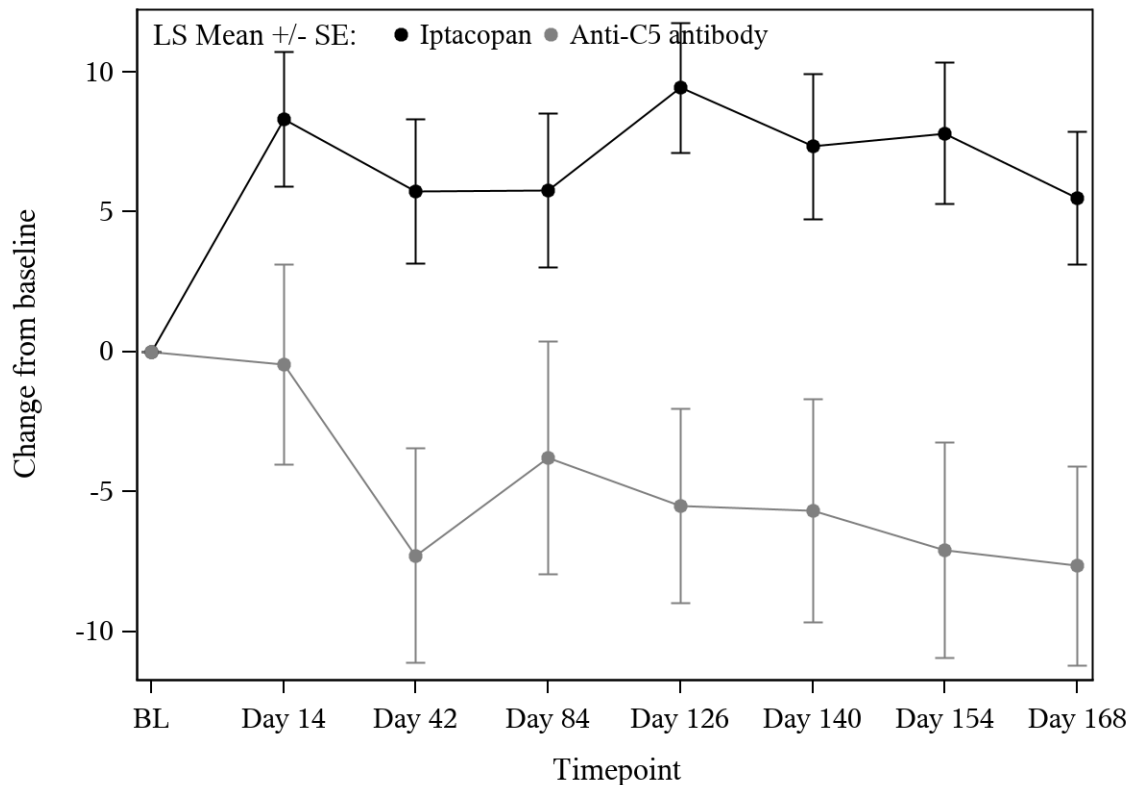
Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Cognitive functioning



Iptacopan	44	39	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

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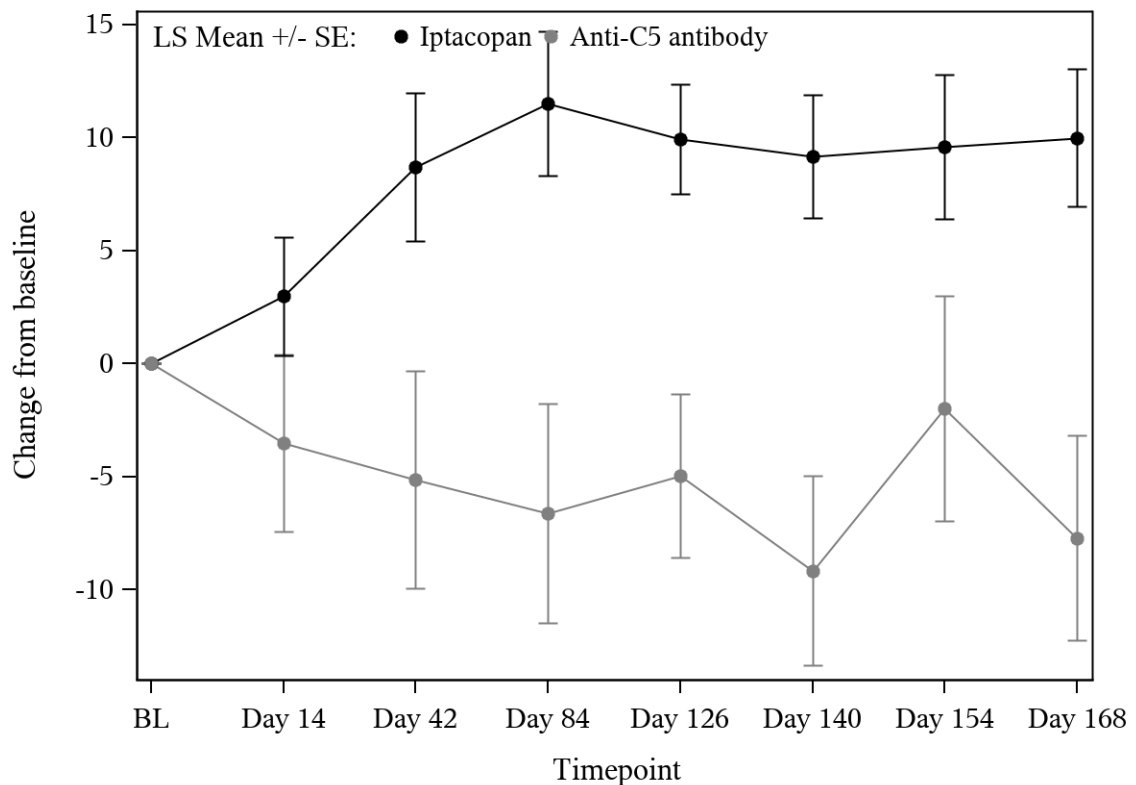
Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Social functioning



Iptacopan	44	39	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

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Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

Table 3-3.3 EORTC QLQ-C30 QoL responder analysis (improvement defined as ≥ 10 point increase from baseline): GLMM analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Global health status						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 14	12 / 39 (30.8) 30.0 [18.5; 42.5]	0 / 17 (0.0) 0.0 [0.0; 1.0]	OR RR RD	>999.9 686.14 0.2982	[1.25; >999.99] [30.83; >999.99] [0.1830; 0.4234]	0.043
Day 42	20 / 44 (45.5) 44.5 [32.9; 55.8]	0 / 20 (0.0) 0.7 [0.0; 3.5]	OR RR RD	237.61 61.47 0.4361	[4.62; >999.99] [12.91; >999.99] [0.3205; 0.5476]	0.007
Day 84	24 / 40 (60.0) 55.3 [43.7; 68.7]	2 / 17 (11.8) 8.3 [0.5; 17.4]	OR RR RD	36.49 6.68 0.4685	[5.83; 228.17] [3.06; 106.89] [0.3363; 0.6206]	<0.001
Day 126	23 / 41 (56.1) 55.6 [44.1; 68.3]	3 / 17 (17.6) 19.6 [7.3; 33.5]	OR RR RD	11.68 2.77 0.3578	[2.73; 49.93] [1.65; 7.76] [0.2045; 0.5355]	<0.001
Day 140	20 / 42 (47.6) 55.3 [43.5; 67.5]	2 / 16 (12.5) 21.3 [8.0; 36.0]	OR RR RD	9.41 2.57 0.3364	[2.54; 34.87] [1.53; 6.90] [0.1719; 0.5126]	<0.001
Day 154	24 / 41 (58.5) 51.0 [38.8; 64.1]	3 / 15 (20.0) 18.8 [5.4; 34.0]	OR RR RD	8.22 2.69 0.3166	[2.22; 30.41] [1.44; 9.37] [0.1416; 0.5027]	0.002
Day 168	21 / 42 (50.0) 47.4 [33.8; 61.3]	3 / 18 (16.7) 18.4 [4.2; 37.2]	OR RR RD	7.80 2.55 0.2850	[1.43; 42.49] [1.18; 10.80] [0.0641; 0.4900]	0.018
Day 126 - 168	44 52.4 [40.9; 64.2]	19 19.5 [7.1; 33.6]	OR RR RD	9.16 2.66 0.3221	[2.61; 32.16] [1.49; 7.29] [0.1563; 0.4911]	<0.001

Treatment Groups			Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Physical functioning						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 14	15 / 39 (38.5) 35.0 [22.4; 48.8]	2 / 17 (11.8) 16.7 [2.9; 34.1]	OR	5.48	[0.60; 49.93]	0.131
			RR	2.08	[0.95; 12.59]	
			RD	0.1795	[-.0159; 0.3694]	
Day 42	19 / 44 (43.2) 45.5 [33.4; 58.5]	5 / 20 (25.0) 16.5 [5.4; 30.4]	OR	14.89	[2.43; 91.35]	0.004
			RR	2.73	[1.51; 8.16]	
			RD	0.2851	[0.1310; 0.4411]	
Day 84	17 / 40 (42.5) 46.5 [33.2; 61.5]	3 / 17 (17.6) 13.0 [2.3; 27.8]	OR	34.29	[4.19; 280.80]	0.001
			RR	3.58	[1.65; 21.80]	
			RD	0.3336	[0.1571; 0.4980]	
Day 126	21 / 41 (51.2) 47.5 [35.3; 62.1]	4 / 17 (23.5) 15.0 [3.9; 29.5]	OR	35.58	[5.44; 232.69]	<0.001
			RR	3.14	[1.73; 12.35]	
			RD	0.3232	[0.1806; 0.4801]	
Day 140	21 / 42 (50.0) 48.6 [36.0; 61.7]	1 / 16 (6.3) 14.9 [4.1; 27.8]	OR	30.17	[5.13; 177.46]	<0.001
			RR	3.23	[1.82; 11.07]	
			RD	0.3316	[0.1977; 0.4898]	
Day 154	21 / 41 (51.2) 48.0 [34.8; 60.8]	2 / 16 (12.5) 13.6 [3.9; 26.7]	OR	23.41	[3.77; 145.51]	<0.001
			RR	3.41	[1.80; 11.80]	
			RD	0.3316	[0.1904; 0.4933]	
Day 168	19 / 42 (45.2) 47.3 [32.1; 61.8]	4 / 18 (22.2) 16.8 [5.6; 32.9]	OR	16.63	[1.89; 146.13]	0.011
			RR	2.74	[1.35; 8.39]	
			RD	0.2963	[0.1006; 0.4858]	
Day 126 - 168	44 47.7 [35.2; 60.8]	19 15.2 [5.3; 26.6]	OR	25.43	[4.35; 148.49]	<0.001
			RR	3.08	[1.79; 8.21]	
			RD	0.3206	[0.1874; 0.4672]	

Treatment Groups			Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Role functioning						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 14	9 / 39 (23.1) 24.0 [12.2; 36.6]	1 / 17 (5.9) 8.2 [0.2; 24.1]	OR	6.30	[0.65; 61.18]	0.112
			RR	2.87	[0.83; 155.08]	
			RD	0.1519	[-.0366; 0.3061]	
Day 42	18 / 44 (40.9) 36.4 [25.3; 49.6]	3 / 20 (15.0) 16.1 [2.7; 29.1]	OR	6.55	[1.30; 32.85]	0.023
			RR	2.25	[1.21; 11.98]	
			RD	0.2057	[0.0533; 0.3735]	
Day 84	15 / 40 (37.5) 40.7 [28.3; 55.2]	4 / 17 (23.5) 22.6 [7.3; 37.4]	OR	7.12	[1.29; 39.41]	0.025
			RR	1.81	[1.10; 5.55]	
			RD	0.1811	[0.0358; 0.3683]	
Day 126	17 / 41 (41.5) 42.1 [29.6; 56.6]	4 / 17 (23.5) 21.5 [6.9; 36.8]	OR	8.01	[1.77; 36.28]	0.007
			RR	1.98	[1.15; 5.80]	
			RD	0.2071	[0.0559; 0.3756]	
Day 140	18 / 42 (42.9) 41.8 [30.3; 56.0]	2 / 16 (12.5) 19.5 [7.6; 31.9]	OR	8.39	[2.01; 34.99]	0.004
			RR	2.15	[1.32; 5.21]	
			RD	0.2218	[0.0893; 0.3787]	
Day 154	17 / 41 (41.5) 39.8 [27.7; 54.0]	2 / 16 (12.5) 15.9 [6.6; 25.7]	OR	8.82	[1.95; 39.91]	0.005
			RR	2.49	[1.55; 5.90]	
			RD	0.2348	[0.1158; 0.3776]	
Day 168	15 / 42 (35.7) 36.7 [22.3; 50.4]	2 / 18 (11.1) 12.3 [3.6; 24.9]	OR	9.31	[1.44; 60.28]	0.019
			RR	2.90	[1.37; 10.91]	
			RD	0.2423	[0.0764; 0.4001]	
Day 126 - 168	44 40.2 [28.5; 53.7]	19 17.3 [7.4; 27.7]	OR	8.62	[2.04; 36.43]	0.004
			RR	2.30	[1.50; 5.14]	
			RD	0.2245	[0.1141; 0.3650]	

Treatment Groups			Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Emotional functioning						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 14	14 / 39 (35.9) 37.6 [23.1; 52.4]	0 / 17 (0.0) 9.8 [1.2; 23.9]	OR	17.62	[1.93; 160.58]	0.011
			RR	3.85	[1.43; 31.13]	
			RD	0.2729	[0.0845; 0.4411]	
Day 42	19 / 44 (43.2) 36.1 [25.4; 46.8]	4 / 20 (20.0) 14.7 [4.0; 27.1]	OR	7.90	[1.71; 36.55]	0.008
			RR	2.42	[1.28; 8.28]	
			RD	0.2107	[0.0654; 0.3510]	
Day 84	15 / 40 (37.5) 34.7 [22.3; 46.2]	3 / 17 (17.6) 21.8 [8.3; 35.3]	OR	3.32	[0.73; 15.21]	0.121
			RR	1.58	[0.92; 4.01]	
			RD	0.1259	[-.0229; 0.2769]	
Day 126	12 / 41 (29.3) 31.7 [19.9; 42.6]	3 / 17 (17.6) 22.4 [8.9; 36.8]	OR	2.09	[0.56; 7.78]	0.269
			RR	1.39	[0.83; 3.12]	
			RD	0.0886	[-.0483; 0.2348]	
Day 140	14 / 42 (33.3) 34.8 [23.2; 46.2]	2 / 16 (12.5) 25.9 [12.2; 39.7]	OR	1.96	[0.59; 6.56]	0.273
			RR	1.33	[0.85; 2.55]	
			RD	0.0876	[-.0511; 0.2289]	
Day 154	16 / 41 (39.0) 34.9 [21.8; 47.6]	4 / 16 (25.0) 25.8 [12.9; 39.6]	OR	1.92	[0.56; 6.57]	0.296
			RR	1.35	[0.82; 2.83]	
			RD	0.0884	[-.0619; 0.2593]	
Day 168	16 / 42 (38.1) 36.1 [21.1; 49.8]	5 / 18 (27.8) 25.7 [9.6; 44.6]	OR	1.97	[0.44; 8.82]	0.373
			RR	1.39	[0.70; 3.97]	
			RD	0.1011	[-.1138; 0.3020]	
Day 126 - 168	44 34.4 [22.5; 46.3]	19 25.0 [12.8; 38.6]	OR	1.99	[0.61; 6.52]	0.257
			RR	1.36	[0.85; 2.69]	
			RD	0.0899	[-.0490; 0.2465]	

Treatment Groups			Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Cognitive functioning						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 14	14 / 39 (35.9) 34.9 [23.7; 46.9]	4 / 17 (23.5) 14.5 [4.2; 26.1]	OR	13.26	[0.96; 182.46]	0.053
			RR	2.37	[1.38; 7.40]	
			RD	0.2005	[0.0812; 0.3227]	
Day 42	14 / 44 (31.8) 35.6 [25.2; 45.9]	3 / 20 (15.0) 14.7 [4.6; 24.7]	OR	17.68	[2.16; 144.55]	0.008
			RR	2.32	[1.54; 6.74]	
			RD	0.2061	[0.1114; 0.3303]	
Day 84	11 / 40 (27.5) 35.2 [23.2; 46.8]	4 / 17 (23.5) 13.9 [2.6; 25.9]	OR	19.95	[1.97; 201.69]	0.011
			RR	2.51	[1.41; 12.47]	
			RD	0.2097	[0.0863; 0.3657]	
Day 126	13 / 41 (31.7) 30.8 [19.7; 42.3]	2 / 17 (11.8) 10.9 [1.3; 22.3]	OR	15.48	[2.08; 114.97]	0.008
			RR	2.75	[1.47; 20.99]	
			RD	0.1956	[0.0785; 0.3387]	
Day 140	16 / 42 (38.1) 33.0 [21.9; 43.6]	3 / 16 (18.8) 11.7 [1.6; 22.7]	OR	13.09	[2.02; 84.95]	0.007
			RR	2.71	[1.52; 17.45]	
			RD	0.2036	[0.0928; 0.3426]	
Day 154	13 / 41 (31.7) 32.2 [21.2; 43.1]	4 / 16 (25.0) 13.3 [3.0; 24.9]	OR	10.62	[1.55; 72.80]	0.016
			RR	2.35	[1.38; 9.77]	
			RD	0.1804	[0.0763; 0.3139]	
Day 168	11 / 42 (26.2) 31.5 [20.1; 43.9]	2 / 18 (11.1) 14.3 [2.8; 27.8]	OR	8.26	[0.81; 84.15]	0.074
			RR	2.20	[1.08; 10.45]	
			RD	0.1685	[0.0192; 0.3207]	
Day 126 - 168	44 31.9 [21.3; 42.4]	19 12.5 [2.6; 23.4]	OR	11.55	[1.80; 74.07]	0.010
			RR	2.48	[1.44; 10.84]	
			RD	0.1862	[0.0842; 0.3146]	

Treatment Groups			Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Social functioning						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 14	8 / 39 (20.5) 23.2 [12.8; 36.2]	3 / 17 (17.6) 20.2 [5.8; 35.1]	OR	1.26	[0.18; 8.70]	0.813
			RR	1.14	[0.56; 4.16]	
			RD	0.0278	[-.1291; 0.2108]	
Day 42	14 / 44 (31.8) 30.1 [18.3; 41.6]	7 / 20 (35.0) 26.1 [12.3; 38.9]	OR	1.45	[0.32; 6.50]	0.629
			RR	1.14	[0.71; 2.42]	
			RD	0.0374	[-.0947; 0.2010]	
Day 84	14 / 40 (35.0) 34.3 [21.9; 46.8]	4 / 17 (23.5) 24.2 [10.5; 38.1]	OR	3.00	[0.53; 16.97]	0.213
			RR	1.40	[0.92; 3.06]	
			RD	0.0974	[-.0265; 0.2344]	
Day 126	12 / 41 (29.3) 36.1 [24.3; 48.5]	3 / 17 (17.6) 14.3 [3.0; 28.3]	OR	11.69	[2.22; 61.62]	0.004
			RR	2.49	[1.32; 11.73]	
			RD	0.2152	[0.0809; 0.3592]	
Day 140	17 / 42 (40.5) 38.2 [25.5; 50.9]	1 / 16 (6.3) 10.8 [1.2; 25.6]	OR	21.15	[3.66; 122.20]	<0.001
			RR	3.48	[1.52; 28.28]	
			RD	0.2655	[0.1124; 0.4137]	
Day 154	15 / 41 (36.6) 36.6 [23.3; 49.8]	1 / 16 (6.3) 6.6 [0.3; 19.4]	OR	41.04	[5.19; 324.49]	<0.001
			RR	5.46	[1.91; 115.40]	
			RD	0.2969	[0.1406; 0.4537]	
Day 168	17 / 42 (40.5) 37.7 [24.6; 51.9]	1 / 18 (5.6) 4.4 [0.0; 17.7]	OR	85.38	[6.07; >999.99]	0.001
			RR	8.56	[2.14; 643.69]	
			RD	0.3255	[0.1687; 0.4826]	
Day 126 - 168	44 37.3 [24.5; 50.0]	19 9.1 [1.2; 22.2]	OR	30.51	[4.54; 205.08]	<0.001
			RR	4.06	[1.72; 24.88]	
			RD	0.2770	[0.1313; 0.4202]	

Treatment Groups		Comparison			
Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit n: Number of patients with response CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference GLMM: Generalized linear mixed model </p> <p>Analysis methods: OR, RR and RD from logistic GLMM with random intercept and week as continuous covariate: $\text{Logit}(\text{proportion}) = \text{treatment} + \text{baseline value} + \text{treatment} * \text{week} + \text{baseline value} * \text{week} + \text{treatment} * \text{week} * \text{week} + \text{baseline value} * \text{week} * \text{week}$ Anti-C5 antibody was the reference group for treatment group comparison. OR with 95% Wald CI and p-value were calculated from model linear predictors, at Day 126 - 168 from a linear function of linear predictors. Predicted proportions, RR and RD were calculated by marginal standardization from predicted values. First, predicted proportions were calculated by marginal standardization for each treatment group at each visit. Then predicted proportions were averaged over the four visits Day 126 - 168. Then RR and RD were calculated for each visit and for Day 126 - 168. Estimates and 95% CI were constructed by median and 2.5% and 97.5% percentiles from 1000 bootstrap samples.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Response (improvement) is defined as ≥ 10 point increase from baseline.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

3-4 EQ-5D VAS

Table 3-4.1 EQ-5D VAS: descriptive statistics by timepoint (Full Analysis Set)

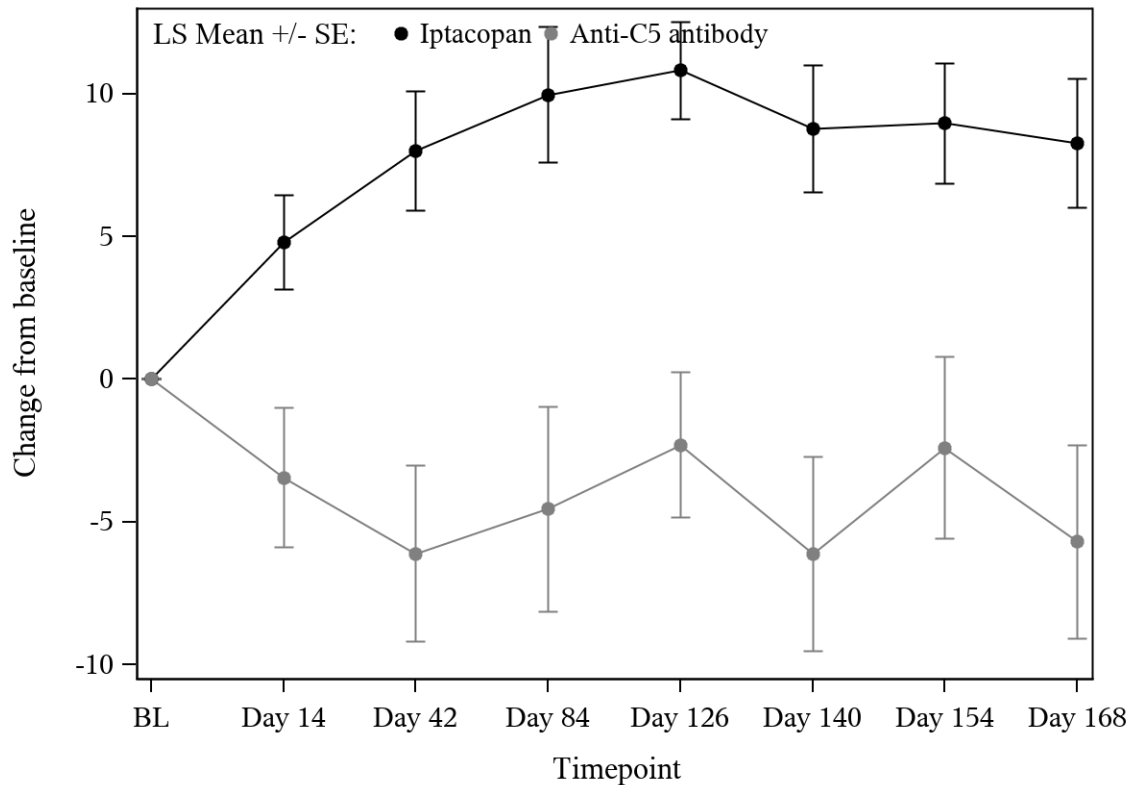
Treatment Groups		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)
EQ-5D VAS		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 66.23 (16.02)	21 63.24 (19.87)
Day 14	38 70.84 (14.67)	17 60.76 (22.12)
Day 42	44 73.39 (15.97)	20 55.65 (21.20)
Day 84	40 75.08 (16.60)	17 55.71 (23.63)
Day 126	41 76.85 (13.23)	17 63.24 (20.19)
Day 140	42 73.79 (14.27)	16 58.06 (26.37)
Day 154	41 74.05 (15.92)	16 59.44 (24.09)
Day 168	42 73.81 (16.08)	18 55.78 (24.42)
Day 126 - 168	44 74.53 (13.35)	19 58.19 (22.98)
N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit SD: Standard deviation Analysis methods: Descriptive means Day 126 - 168 were calculated by averaging first over the four visits for each patient and then averaging over the treatment group. Patients with non-missing value at least at baseline and at one of the four visits were included in the calculation. Cut-off date for analysis: 06-Mar-2023		

Table 3-4.2 EQ-5D VAS: MMRM analysis of change from baseline (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
EQ-5D VAS					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 14	38 4.81 (1.65)	17 -3.44 (2.45)	8.25	[2.55; 13.94]	0.005
Day 42	44 8.00 (2.10)	20 -6.11 (3.09)	14.11	[6.81; 21.40]	<0.001
Day 84	40 9.97 (2.39)	17 -4.54 (3.59)	14.52	[6.01; 23.03]	0.001
Day 126	41 10.82 (1.70)	17 -2.29 (2.56)	13.12	[7.17; 19.06]	<0.001
Day 140	42 8.78 (2.21)	16 -6.13 (3.40)	14.91	[6.96; 22.85]	<0.001
Day 154	41 8.96 (2.09)	16 -2.40 (3.18)	11.37	[3.91; 18.82]	0.003
Day 168	42 8.27 (2.25)	18 -5.69 (3.39)	13.96	[5.97; 21.95]	<0.001
Day 126 - 168	44 9.29 (1.75)	19 -4.04 (2.59)	13.34	[7.29; 19.39]	<0.001
Hedges' G			1.21	[0.63; 1.79]	
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures </p> <p>Analysis methods: Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons at Day 126 - 168 were calculated as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.</p> <p>Hedges' G was calculated as model obtained adjusted mean difference / pooled SD with pooled SD = SE / sqrt (1/n1 + 1/n2) where SE is the standard error of the adjusted mean difference and n1 and n2 are the numbers of patients included in the analysis between Day 126 and 168 in treatment group 1 and 2, respectively.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Figure 3-4.2 EQ-5D VAS: line chart of least squares mean change from baseline (Full Analysis Set)

EQ-5D VAS



Iptacopan	44	38	44	40	41	42	41	42
Anti-C5 antibody	21	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

Table 3-4.3 EQ-5D VAS responder analysis (improvement defined as ≥ 15 point increase from baseline): GLMM analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
EQ-5D VAS						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 14	5 / 38 (13.2) 12.3 [4.2; 21.9]	0 / 17 (0.0) 3.0 [0.4; 13.2]	OR	51.02	[0.27; >999.99]	0.142
			RR	3.86	[0.71; 37.83]	
			RD	0.0827	[-.0360; 0.1869]	
Day 42	11 / 44 (25.0) 24.5 [13.3; 35.9]	1 / 20 (5.0) 5.6 [1.2; 15.0]	OR	36.97	[1.75; 782.69]	0.021
			RR	4.32	[1.40; 20.94]	
			RD	0.1853	[0.0532; 0.3055]	
Day 84	14 / 40 (35.0) 35.1 [21.5; 51.3]	0 / 17 (0.0) 6.9 [2.2; 14.9]	OR	36.31	[2.62; 502.18]	0.008
			RR	5.08	[2.37; 16.47]	
			RD	0.2760	[0.1392; 0.4365]	
Day 126	15 / 41 (36.6) 38.8 [26.5; 53.1]	1 / 17 (5.9) 6.7 [1.8; 15.0]	OR	62.32	[6.00; 646.71]	<0.001
			RR	5.77	[2.65; 21.75]	
			RD	0.3104	[0.1942; 0.4547]	
Day 140	18 / 42 (42.9) 40.4 [28.6; 53.6]	0 / 16 (0.0) 5.7 [1.3; 13.5]	OR	84.47	[8.62; 827.32]	<0.001
			RR	7.05	[3.01; 29.94]	
			RD	0.3433	[0.2183; 0.4763]	
Day 154	17 / 41 (41.5) 39.9 [27.5; 52.1]	1 / 16 (6.3) 4.2 [0.6; 11.6]	OR	121.82	[8.93; >999.99]	<0.001
			RR	9.45	[3.44; 63.30]	
			RD	0.3556	[0.2202; 0.4813]	
Day 168	15 / 42 (35.7) 38.4 [24.1; 51.7]	0 / 18 (0.0) 3.9 [0.3; 12.3]	OR	186.93	[5.67; >999.99]	0.003
			RR	9.76	[2.80; 128.61]	
			RD	0.3473	[0.1804; 0.4748]	
Day 126 - 168	44 39.4 [27.8; 51.9]	19 5.2 [1.3; 12.8]	OR	104.63	[9.39; >999.99]	<0.001
			RR	7.50	[3.21; 32.21]	
			RD	0.3385	[0.2116; 0.4639]	

Treatment Groups		Comparison			
Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit n: Number of patients with response CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference GLMM: Generalized linear mixed model </p> <p>Analysis methods: OR, RR and RD from logistic GLMM with random intercept and week as continuous covariate: $\text{Logit}(\text{proportion}) = \text{treatment} + \text{baseline value} + \text{treatment} * \text{week} + \text{baseline value} * \text{week} + \text{treatment} * \text{week} * \text{week} + \text{baseline value} * \text{week} * \text{week}$ Anti-C5 antibody was the reference group for treatment group comparison. OR with 95% Wald CI and p-value were calculated from model linear predictors, at Day 126 - 168 from a linear function of linear predictors. Predicted proportions, RR and RD were calculated by marginal standardization from predicted values. First, predicted proportions were calculated by marginal standardization for each treatment group at each visit. Then predicted proportions were averaged over the four visits Day 126 - 168. Then RR and RD were calculated for each visit and for Day 126 - 168. Estimates and 95% CI were constructed by median and 2.5% and 97.5% percentiles from 1000 bootstrap samples.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Response (improvement) is defined as ≥ 15 point increase from baseline.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

3-5 PGIS

Table 3-5.1 PGIS: descriptive statistics by timepoint (Full Analysis Set)

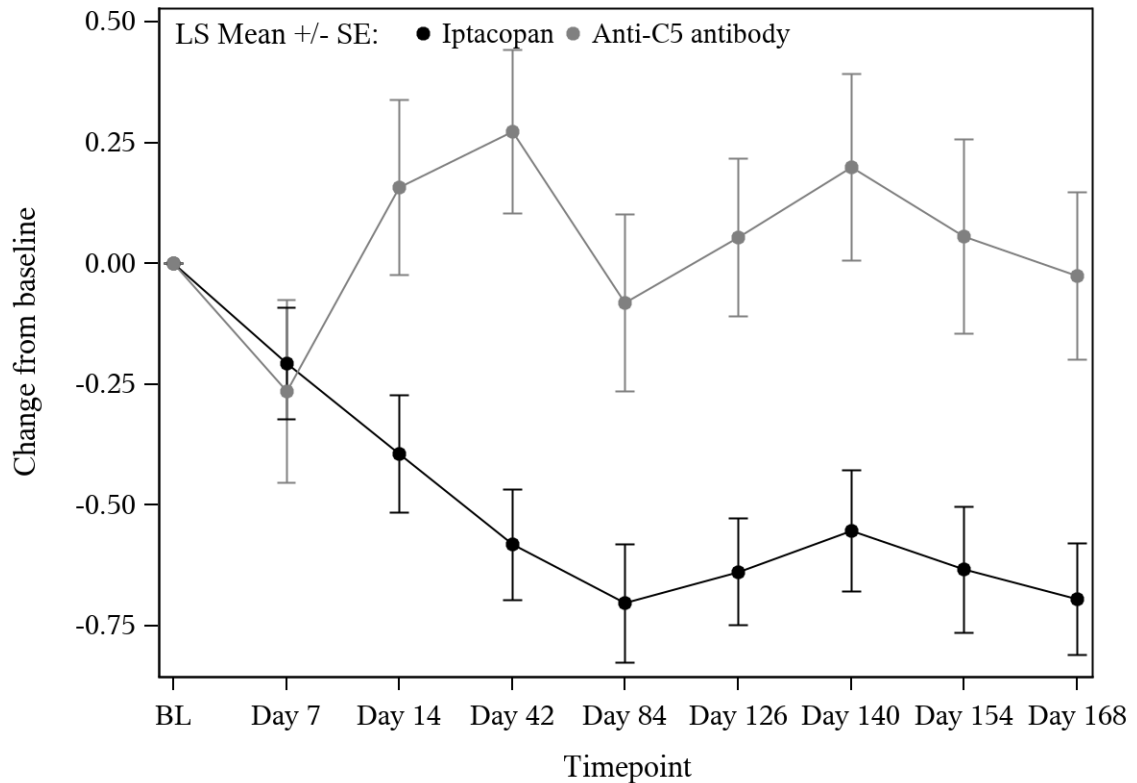
Treatment Groups		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)
PGIS		
	N' Mean (SD)	N' Mean (SD)
Baseline	44 1.39 (0.81)	21 1.62 (1.16)
Day 7	42 1.21 (0.90)	15 1.40 (0.83)
Day 14	39 1.03 (0.84)	17 1.59 (1.06)
Day 42	44 0.86 (0.73)	20 1.90 (1.07)
Day 84	40 0.78 (0.70)	17 1.53 (1.01)
Day 126	41 0.78 (0.69)	17 1.53 (1.07)
Day 140	41 0.88 (0.78)	16 1.75 (1.24)
Day 154	41 0.83 (0.80)	16 1.63 (1.15)
Day 168	42 0.74 (0.77)	18 1.67 (1.08)
Day 126 - 168	44 0.83 (0.69)	19 1.71 (1.05)
N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit SD: Standard deviation Analysis methods: Descriptive means Day 126 - 168 were calculated by averaging first over the four visits for each patient and then averaging over the treatment group. Patients with non-missing value at least at baseline and at one of the four visits were included in the calculation. The ordinal scale was used for the nominal categories of the PGIS (No symptoms = 0, mild = 1, moderate = 2, severe = 3, very severe = 4). Cut-off date for analysis: 06-Mar-2023		

Table 3-5.2 PGIS: MMRM analysis of change from baseline (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
PGIS					
	N' LS Mean (SE)	N' LS Mean (SE)			
Day 7	42 -0.21 (0.12)	15 -0.26 (0.19)	0.06	[-0.38; 0.49]	0.794
Day 14	39 -0.39 (0.12)	17 0.16 (0.18)	-0.55	[-0.98; -0.12]	0.012
Day 42	44 -0.58 (0.11)	20 0.27 (0.17)	-0.85	[-1.25; -0.46]	<0.001
Day 84	40 -0.70 (0.12)	17 -0.08 (0.18)	-0.62	[-1.06; -0.19]	0.006
Day 126	41 -0.64 (0.11)	17 0.05 (0.16)	-0.69	[-1.08; -0.31]	<0.001
Day 140	41 -0.55 (0.13)	16 0.20 (0.19)	-0.75	[-1.20; -0.30]	0.001
Day 154	41 -0.63 (0.13)	16 0.06 (0.20)	-0.69	[-1.16; -0.22]	0.005
Day 168	42 -0.69 (0.12)	18 -0.03 (0.17)	-0.67	[-1.08; -0.26]	0.002
Day 126 - 168	44 -0.64 (0.10)	19 0.06 (0.15)	-0.70	[-1.05; -0.35]	<0.001
Hedges' G			-1.09	[-1.66; -0.52]	
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures </p> <p>Analysis methods: Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons at Day 126 - 168 were calculated as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.</p> <p>Hedges' G was calculated as model obtained adjusted mean difference / pooled SD with pooled SD = SE / sqrt (1/n1 + 1/n2) where SE is the standard error of the adjusted mean difference and n1 and n2 are the numbers of patients included in the analysis between Day 126 and 168 in treatment group 1 and 2, respectively.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>The ordinal scale was used for the nominal categories of the PGIS (No symptoms = 0, mild = 1, moderate = 2, severe = 3, very severe = 4).</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Figure 3-5.2 PGIS: line chart of least squares mean change from baseline (Full Analysis Set)

PGIS



Iptacopan	44	42	39	44	40	41	41	41	42
Anti-C5 antibody	21	15	17	20	17	17	16	16	18

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.

The ordinal scale was used for the nominal categories of the PGIS (No symptoms = 0, mild = 1, moderate = 2, severe = 3, very severe = 4).

Cut-off date for analysis: 06-Mar-2023

Table 3-5.3 PGIS responder analysis (improvement defined as ≥ 1 step decrease in severity level from baseline): GLMM analysis (Full Analysis Set)

	Treatment Groups		Parameter	Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)		Estimate	[95% CI]	p-value
PGIS						
	n / N' (%) Predict. % [95% CI]	n / N' (%) Predict. % [95% CI]				
Day 7	14 / 42 (33.3) 40.3 [27.6; 55.1]	6 / 15 (40.0) 25.1 [5.6; 43.7]	OR RR RD	3.30 1.59 0.1525	[0.62; 17.43] [0.92; 6.48] [-.0314; 0.3585]	0.160
Day 14	17 / 39 (43.6) 38.6 [26.7; 51.5]	2 / 17 (11.8) 20.2 [6.1; 34.3]	OR RR RD	4.73 1.89 0.1802	[1.01; 22.05] [1.14; 5.78] [0.0493; 0.3379]	0.048
Day 42	23 / 44 (52.3) 51.0 [40.3; 61.7]	4 / 20 (20.0) 19.2 [8.7; 30.2]	OR RR RD	14.92 2.63 0.3155	[3.19; 69.79] [1.69; 5.46] [0.1936; 0.4512]	<0.001
Day 84	22 / 40 (55.0) 53.9 [42.0; 65.8]	6 / 17 (35.3) 15.7 [5.2; 27.5]	OR RR RD	34.61 3.42 0.3777	[5.68; 210.98] [2.01; 9.98] [0.2308; 0.5266]	<0.001
Day 126	21 / 41 (51.2) 54.4 [42.4; 67.2]	3 / 17 (17.6) 19.3 [7.1; 32.4]	OR RR RD	27.85 2.84 0.3539	[5.77; 134.33] [1.69; 7.32] [0.2022; 0.5045]	<0.001
Day 140	20 / 41 (48.8) 55.8 [43.5; 68.4]	3 / 16 (18.8) 22.1 [8.5; 35.9]	OR RR RD	20.47 2.55 0.3386	[4.67; 89.70] [1.56; 6.19] [0.1820; 0.4986]	<0.001
Day 154	23 / 41 (56.1) 55.8 [43.0; 68.3]	6 / 16 (37.5) 24.5 [10.6; 38.4]	OR RR RD	13.38 2.25 0.3126	[2.96; 60.46] [1.45; 5.25] [0.1543; 0.4744]	<0.001
Day 168	24 / 42 (57.1) 53.3 [39.5; 66.3]	5 / 18 (27.8) 27.2 [11.1; 42.7]	OR RR RD	7.77 1.94 0.2580	[1.33; 45.44] [1.21; 4.73] [0.0811; 0.4465]	0.023
Day 126 - 168	44 54.7 [42.7; 67.0]	19 23.2 [10.0; 36.6]	OR RR RD	15.61 2.35 0.3182	[3.60; 67.58] [1.49; 5.36] [0.1653; 0.4699]	<0.001

Treatment Groups		Comparison			
Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit n: Number of patients with response CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference GLMM: Generalized linear mixed model </p> <p>Analysis methods: OR, RR and RD from logistic GLMM with random intercept and week as continuous covariate: $\text{Logit}(\text{proportion}) = \text{treatment} + \text{baseline value} + \text{treatment} * \text{week} + \text{baseline value} * \text{week} + \text{treatment} * \text{week} * \text{week} + \text{baseline value} * \text{week} * \text{week}$ Anti-C5 antibody was the reference group for treatment group comparison. OR with 95% Wald CI and p-value were calculated from model linear predictors, at Day 126 - 168 from a linear function of linear predictors. Predicted proportions, RR and RD were calculated by marginal standardization from predicted values. First, predicted proportions were calculated by marginal standardization for each treatment group at each visit. Then predicted proportions were averaged over the four visits Day 126 - 168. Then RR and RD were calculated for each visit and for Day 126 - 168. Estimates and 95% CI were constructed by median and 2.5% and 97.5% percentiles from 1000 bootstrap samples.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>Response (improvement) is defined as ≥ 1 step decrease in severity level from baseline.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

4 Safety analyses

Table 4-1 Adverse events overview: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
Any adverse event, n (%)	34 (77.3)	20 (90.9)	OR	0.34	[0.07; 1.71]	0.191
			RR	0.85	[0.69; 1.05]	0.125
			RD	-0.1364	[-0.3089; 0.0362]	0.121
Any severe adverse event, n (%)	3 (6.8)	2 (9.1)	OR	0.73	[0.11; 4.73]	0.743
			RR	0.75	[0.14; 4.17]	0.742
			RD	-0.0227	[-0.1641; 0.1186]	0.753
Any serious adverse event, n (%)	6 (13.6)	4 (18.2)	OR	0.71	[0.18; 2.84]	0.628
			RR	0.75	[0.24; 2.39]	0.626
			RD	-0.0455	[-0.2359; 0.1450]	0.640
<p>N: Number of patients in the analysis set n: Number of patients with event CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference TEAE: Treatment Emergent Adverse Event </p> <p>Analysis methods: OR, RR and RD with Wald 95% CI and p-value. For calculation of OR and RR, in case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>The table displays TEAE, defined as events that started during the on-treatment period. The on-treatment period for Iptacopan is from first dose date until 7 days after the date of last dose administered or the date of the day 168 visit, whichever is earlier. The on-treatment period for Anti-C5 is from first dose date until one day before the next planned dose or the date of the day 168 visit, whichever is earlier.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>						

Table 4-2 Adverse events by SOC and PT: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
Infections and infestations, n (%)	15 (34.1)	11 (50.0)	OR	0.52	[0.18; 1.47]	0.215
			RR	0.68	[0.38; 1.23]	0.200
			RD	-0.1591	[-0.4106; 0.0924]	0.215
COVID-19, n (%)	2 (4.5)	8 (36.4)	OR	0.08	[0.02; 0.44]	0.003
			RR	0.13	[0.03; 0.54]	0.005
			RD	-0.3182	[-0.5284; -0.1080]	0.003
Gastrointestinal disorders, n (%)	10 (22.7)	4 (18.2)	OR	1.32	[0.36; 4.82]	0.671
			RR	1.25	[0.44; 3.54]	0.674
			RD	0.0455	[-0.1578; 0.2487]	0.661
Nervous system disorders, n (%)	10 (22.7)	0 (0.0)	OR	13.70	[0.76; >99.99]	0.076
			RR	10.73	[0.66; >99.99]	0.096
			RD	0.2273	[0.1034; 0.3511]	<0.001
Headache, n (%)	7 (15.9)	0 (0.0)	OR	9.00	[0.49; >99.99]	0.139
			RR	7.67	[0.46; >99.99]	0.157
			RD	0.1591	[0.0510; 0.2672]	0.004
Investigations, n (%)	8 (18.2)	2 (9.1)	OR	2.22	[0.43; 11.49]	0.341
			RR	2.00	[0.46; 8.63]	0.353
			RD	0.0909	[-0.0747; 0.2565]	0.282
General disorders and administration site conditions, n (%)	7 (15.9)	2 (9.1)	OR	1.89	[0.36; 9.98]	0.452
			RR	1.75	[0.40; 7.73]	0.460
			RD	0.0682	[-0.0934; 0.2298]	0.408
Musculoskeletal and connective tissue disorders, n (%)	6 (13.6)	1 (4.5)	OR	3.32	[0.37; 29.42]	0.282
			RR	3.00	[0.38; 23.40]	0.295
			RD	0.0909	[-0.0427; 0.2245]	0.182
Blood and lymphatic system disorders, n (%)	5 (11.4)	6 (27.3)	OR	0.34	[0.09; 1.28]	0.111
			RR	0.42	[0.14; 1.22]	0.109
			RD	-0.1591	[-0.3675; 0.0493]	0.135
Breakthrough haemolysis, n (%)	1 (2.3)	5 (22.7)	OR	0.08	[<0.01; 0.73]	0.025
			RR	0.10	[0.01; 0.80]	0.030
			RD	-0.2045	[-0.3851; -0.0240]	0.026
Renal and urinary disorders, n (%)	5 (11.4)	1 (4.5)	OR	2.69	[0.29; 24.58]	0.380
			RR	2.50	[0.31; 20.11]	0.389
			RD	0.0682	[-0.0598; 0.1961]	0.296

Treatment Groups		Comparison			
Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
<p>N: Number of patients in the analysis set n: Number of patients with event CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference TEAE: Treatment Emergent Adverse Event </p> <p>Analysis methods: OR, RR and RD with Wald 95% CI and p-value. For calculation of OR and RR, in case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>The table displays TEAE that occurred in at least one treatment arm in $\geq 10\%$ of patients. TEAE are defined as events that started during the on-treatment period. The on-treatment period for Iptacopan is from first dose date until 7 days after the date of last dose administered or the date of the day 168 visit, whichever is earlier. The on-treatment period for Anti-C5 is from first dose date until one day before the next planned dose or the date of the day 168 visit, whichever is earlier.</p> <p>MedDRA Version: 25.0 Cut-off date for analysis: 06-Mar-2023</p>					

Table 4-3 Severe adverse events by SOC and PT: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
Infections and infestations, n (%)	1 (2.3)	2 (9.1)	OR	0.23	[0.02; 2.72]	0.245
			RR	0.25	[0.02; 2.61]	0.247
			RD	-0.0682	[-0.1961; 0.0598]	0.296
<p>N: Number of patients in the analysis set n: Number of patients with event CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference TEAE: Treatment Emergent Adverse Event </p> <p>Analysis methods: OR, RR and RD with Wald 95% CI and p-value. For calculation of OR and RR, in case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>The table displays TEAE that occurred in at least one treatment arm in $\geq 5\%$ of patients. TEAE are defined as events that started during the on-treatment period. The on-treatment period for Iptacopan is from first dose date until 7 days after the date of last dose administered or the date of the day 168 visit, whichever is earlier. The on-treatment period for Anti-C5 is from first dose date until one day before the next planned dose or the date of the day 168 visit, whichever is earlier.</p> <p>MedDRA Version: 25.0 Cut-off date for analysis: 06-Mar-2023</p>						

Table 4-4 Serious adverse events by SOC and PT: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
Infections and infestations, n (%)	2 (4.5)	3 (13.6)	OR	0.30	[0.05; 1.96]	0.209
			RR	0.33	[0.06; 1.85]	0.209
			RD	-0.0909	[-0.2470; 0.0651]	0.254
COVID-19, n (%)	1 (2.3)	2 (9.1)	OR	0.23	[0.02; 2.72]	0.245
			RR	0.25	[0.02; 2.61]	0.247
			RD	-0.0682	[-0.1961; 0.0598]	0.296
<p>N: Number of patients in the analysis set n: Number of patients with event CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference TEAE: Treatment Emergent Adverse Event </p> <p>Analysis methods: OR, RR and RD with Wald 95% CI and p-value. For calculation of OR and RR, in case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>The table displays TEAE that occurred in at least one treatment arm in $\geq 5\%$ of patients. TEAE are defined as events that started during the on-treatment period. The on-treatment period for Iptacopan is from first dose date until 7 days after the date of last dose administered or the date of the day 168 visit, whichever is earlier. The on-treatment period for Anti-C5 is from first dose date until one day before the next planned dose or the date of the day 168 visit, whichever is earlier.</p> <p>MedDRA Version: 25.0 Cut-off date for analysis: 06-Mar-2023</p>						

Table 4-5 Adverse events of special interest: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
Decreased platelets, n (%)	2 (4.5)	0 (0.0)	OR	2.65	[0.12; 57.54]	0.535
			RR	2.56	[0.13; 51.05]	0.539
			RD	0.0455	[-0.0161; 0.1070]	0.148
Infections caused by encapsulated bacteria, n (%)	2 (4.5)	1 (4.5)	OR	1.00	[0.09; 11.67]	1.000
			RR	1.00	[0.10; 10.44]	1.000
			RD	0.0000	[-0.1066; 0.1066]	1.000
Severe infections caused by encapsulated bacteria, n (%)	0 (0.0)	1 (4.5)	OR	0.16	[<0.01; 4.12]	0.270
			RR	0.17	[<0.01; 4.02]	0.272
			RD	-0.0455	[-0.1325; 0.0416]	0.306
Serious infections caused by encapsulated bacteria, n (%)	1 (2.3)	1 (4.5)	OR	0.49	[0.03; 8.20]	0.618
			RR	0.50	[0.03; 7.62]	0.618
			RD	-0.0227	[-0.1203; 0.0748]	0.648
PNH Haemolysis and Thrombosis, n (%)	7 (15.9)	7 (31.8)	OR	0.41	[0.12; 1.36]	0.143
			RR	0.50	[0.20; 1.25]	0.137
			RD	-0.1591	[-0.3817; 0.0635]	0.161
Severe pNH Haemolysis and Thrombosis, n (%)	1 (2.3)	2 (9.1)	OR	0.23	[0.02; 2.72]	0.245
			RR	0.25	[0.02; 2.61]	0.247
			RD	-0.0682	[-0.1961; 0.0598]	0.296
Serious pNH Haemolysis and Thrombosis, n (%)	1 (2.3)	2 (9.1)	OR	0.23	[0.02; 2.72]	0.245
			RR	0.25	[0.02; 2.61]	0.247
			RD	-0.0682	[-0.1961; 0.0598]	0.296
Serious or severe infections, n (%)	2 (4.5)	3 (13.6)	OR	0.30	[0.05; 1.96]	0.209
			RR	0.33	[0.06; 1.85]	0.209
			RD	-0.0909	[-0.2470; 0.0651]	0.254
Severe infections, n (%)	1 (2.3)	2 (9.1)	OR	0.23	[0.02; 2.72]	0.245
			RR	0.25	[0.02; 2.61]	0.247
			RD	-0.0682	[-0.1961; 0.0598]	0.296
Serious infections, n (%)	2 (4.5)	3 (13.6)	OR	0.30	[0.05; 1.96]	0.209
			RR	0.33	[0.06; 1.85]	0.209
			RD	-0.0909	[-0.2470; 0.0651]	0.254

	Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
Testicular effects, n (%)	0 (0.0)	0 (0.0)				
Thyroid changes, n (%)	0 (0.0)	0 (0.0)				
<p>N: Number of patients in the analysis set n: Number of patients with event CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference TEAE: Treatment Emergent Adverse Event </p> <p>Analysis methods: OR, RR and RD with Wald 95% CI and p-value. For calculation of OR and RR, in case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>The table shows all pre-specified AESIs which occurred in at least one patient.</p> <p>MedDRA Version: 25.0</p> <p>Cut-off date for analysis: 06-Mar-2023</p>						

Table 4-6 Adverse events overview, disease specific events excluded: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
Any adverse event, n (%)	34 (77.3)	19 (86.4)	OR	0.54	[0.13; 2.19]	0.386
			RR	0.89	[0.71; 1.13]	0.345
			RD	-0.0909	[-0.2804; 0.0986]	0.347
Any severe adverse event, n (%)	3 (6.8)	2 (9.1)	OR	0.73	[0.11; 4.73]	0.743
			RR	0.75	[0.14; 4.17]	0.742
			RD	-0.0227	[-0.1641; 0.1186]	0.753
Any serious adverse event, n (%)	6 (13.6)	4 (18.2)	OR	0.71	[0.18; 2.84]	0.628
			RR	0.75	[0.24; 2.39]	0.626
			RD	-0.0455	[-0.2359; 0.1450]	0.640
<p>N: Number of patients in the analysis set n: Number of patients with event CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference TEAE: Treatment Emergent Adverse Event </p> <p>Analysis methods: OR, RR and RD with Wald 95% CI and p-value. For calculation of OR and RR, in case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>The table displays TEAE, defined as events that started during the on-treatment period. The on-treatment period for Iptacopan is from first dose date until 7 days after the date of last dose administered or the date of the day 168 visit, whichever is earlier. The on-treatment period for Anti-C5 is from first dose date until one day before the next planned dose or the date of the day 168 visit, whichever is earlier.</p> <p>Excluded disease specific events: Preferred Term breakthrough haemolysis or haemoglobinuria.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>						

Table 4-7 Hospitalization: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Para- meter	Esti- mate	[95% CI]	p-value
Any hospitalization, n (%)	5 (11.4)	4 (18.2)	OR	0.58	[0.14; 2.41]	0.450
			RR	0.63	[0.19; 2.10]	0.447
			RD	-0.0682	[-0.2546; 0.1183]	0.474
<p>N: Number of patients in the analysis set n: Number of patients with event CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference TEAE: Treatment Emergent Adverse Event </p> <p>Analysis methods: OR, RR and RD with Wald 95% CI and p-value. For calculation of OR and RR, in case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>The table considers serious TEAE with hospitalization as reason for seriousness. TEAE are defined as events that started during the on-treatment period. The on-treatment period for Iptacopan is from first dose date until 7 days after the date of last dose administered or the date of the day 168 visit, whichever is earlier. The on-treatment period for Anti-C5 is from first dose date until one day before the next planned dose or the date of the day 168 visit, whichever is earlier.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>						

Table 4-8 Number of hospitalizations (Safety Set)

	Treatment Groups	
	Iptacopan (N = 44)	Anti-C5 Antibody (N = 22)
Number of hospitalizations		
0	39 (88.6)	18 (81.8)
1	3 (6.8)	3 (13.6)
2	2 (4.5)	0 (0.0)
3	0 (0.0)	0 (0.0)
4	0 (0.0)	1 (4.5)
<p>N: Number of patients in the analysis set </p> <p>The table considers serious TEAE with hospitalization as reason for seriousness. As one hospitalization may be documented by more than one serious adverse events, the number of hospitalizations was determined by medical review based on the patient narratives. TEAE are defined as events that started during the on-treatment period. The on-treatment period for Iptacopan is from first dose date until 7 days after the date of last dose administered or the date of the day 168 visit, whichever is earlier. The on-treatment period for Anti-C5 is from first dose date until one day before the next planned dose or the date of the day 168 visit, whichever is earlier.</p> <p>N is the denominator for percentage (%) calculation.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>		

5 Subgroup analysis

5-1 Subgroup analysis for efficacy

5-1.1 Reticulocyte counts

Table 5-1.1.1 Reticulocyte counts: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

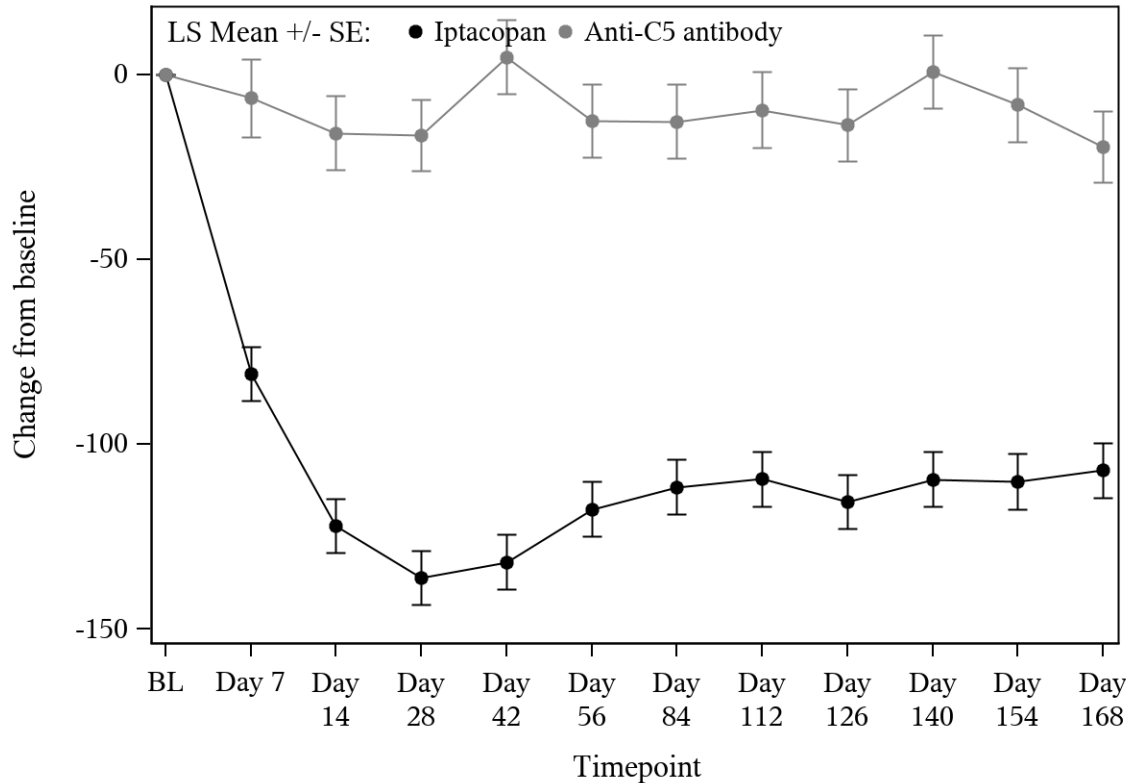
	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Reticulocytes (10⁹/L)					
	N' LS Mean (SE)	N' LS Mean (SE)			
Length of time since diagnosis					
Interaction test	p = 0.760				
< 5 years	11 -103.44 (14.27)	8 -3.92 (17.13)	-99.52	[-137.81; -61.23]	<0.001
≥ 5 years	33 -116.20 (7.22)	14 -4.92 (10.91)	-111.28	[-136.74; -85.81]	<0.001
Age categories					
Interaction test	p = 0.092				
< 45 years	16 -92.93 (16.91)	10 30.95 (17.95)	-123.88	[-166.61; -81.15]	<0.001
≥ 45 years	28 -112.36 (5.96)	12 -21.14 (9.36)	-91.22	[-113.63; -68.80]	<0.001
Sex					
Interaction test	p = 0.593				
Male	14 -105.58 (10.12)	6 -4.10 (13.34)	-101.48	[-131.94; -71.03]	<0.001
Female	30 -115.11 (8.05)	16 -1.11 (11.28)	-114.00	[-141.20; -86.80]	<0.001
Baseline hemoglobin					
Interaction test	p = 0.099				
< 9 g/dL	22 -106.51 (7.08)	10 -15.94 (10.90)	-90.57	[-115.57; -65.56]	<0.001
≥ 9 g/dL	22 -131.01 (11.24)	12 0.58 (12.84)	-131.59	[-162.51; -100.67]	<0.001
History of MAVE prior to screening					
Interaction test	p = 0.229				
No	34 -113.52 (6.13)	15 -11.47 (9.38)	-102.05	[-123.60; -80.49]	<0.001
Yes	10 -111.33 (20.69)	7 13.99 (20.76)	-125.32	[-184.74; -65.91]	<0.001
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.040				
Eculizumab	30 -112.97 (6.24)	17 -12.62 (8.34)	-100.34	[-121.04; -79.64]	<0.001
Ravulizumab	14 -113.78 (13.89)	5 31.19 (24.48)	-144.97	[-203.68; -86.26]	<0.001
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.244				
No	23 -112.51 (9.50)	10 14.63 (14.04)	-127.14	[-161.57; -92.71]	<0.001
Yes	21 -112.86 (8.32)	12 -17.84 (12.20)	-95.02	[-122.94; -67.10]	<0.001

Treatment Groups			Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.089				
< 2	29 -115.12 (7.47)	15 7.79 (10.21)	-122.91	[-147.64; -98.17]	<0.001
≥ 2	15 -123.33 (9.02)	7 -40.37 (13.95)	-82.96	[-112.79; -53.12]	<0.001
Duration of anti-C5 treatment					
N.A. ⁺					
Region					
Interaction test	p = 0.704				
Europe	34 -116.27 (7.43)	18 -5.08 (10.60)	-111.19	[-135.33; -87.06]	<0.001
Other	10 -102.93 (12.71)	4 -2.02 (19.00)	-100.90	[-150.97; -50.83]	<0.001
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>⁺ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Figure 5-1.1.1 Reticulocyte counts: line chart of least squares mean change from baseline - subgroup analysis (Full Analysis Set)

Reticulocytes ($10^9/L$)

Anti-C5 medication history 6 months prior to randomization: Eculizumab



Iptacopan	30	30	28	30	28	28	28	26	30	27	27	28
Anti-C5 antibody	17	13	14	17	14	16	15	12	16	16	15	17

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

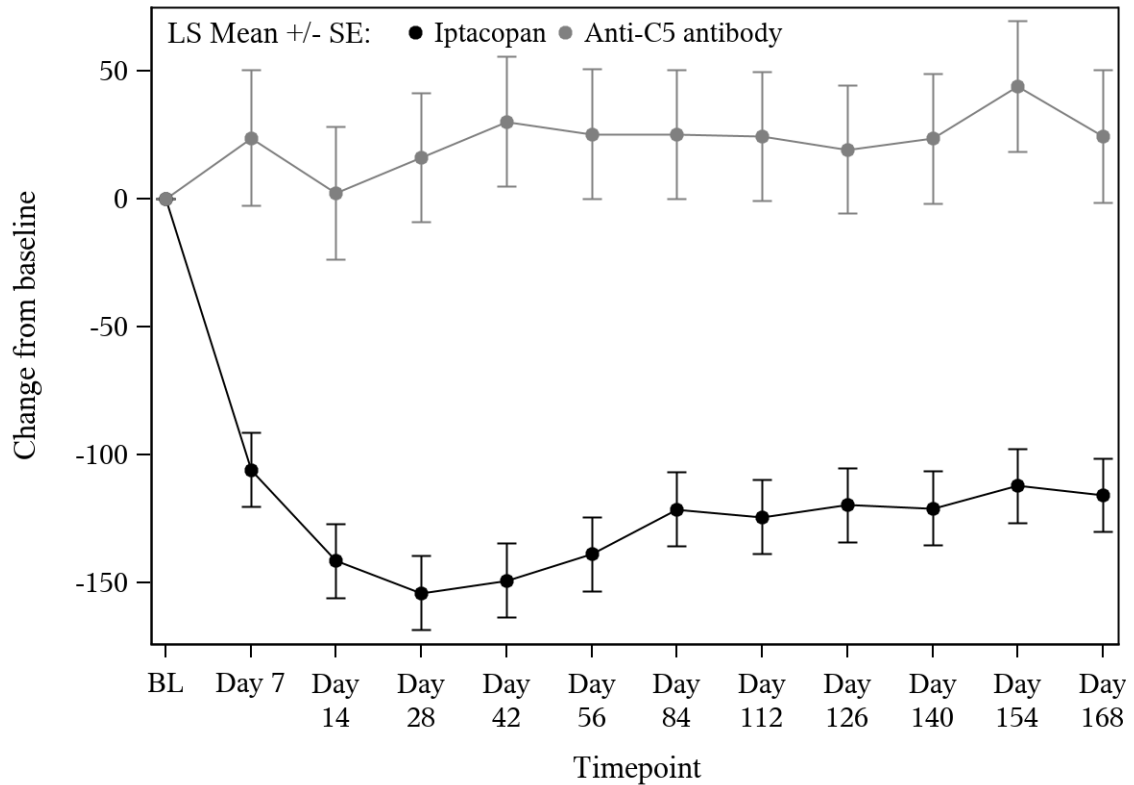
Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

Reticulocytes ($10^9/L$)
Anti-C5 medication history 6 months prior to randomization: Ravulizumab



Iptacopan	14	14	14	13	13	13	14	12	14	14	13	14
Anti-C5 antibody	5	3	3	5	4	4	5	4	5	4	4	4

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.

Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

5-1.2 Transfusion avoidance

Table 5-1.2.1 Transfusion avoidance between Day 1 and Day 168, only actual transfusions: logistic model analysis - subgroup analysis (Full Analysis Set)

Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
Transfusion avoidance between Day 1 and Day 168, only actual transfusions					
	n / N' (%)	n / N' (%)			
Length of time since diagnosis					
Interaction test	p = 0.929				
< 5 years	10 / 11 (90.9)	3 / 8 (37.5)	1.98	[1.08; 6.17]	0.069
≥ 5 years	31 / 33 (93.9)	7 / 14 (50.0)	1.77	[1.23; 3.17]	0.006
Age categories					
Interaction test	p = 0.755				
< 45 years	15 / 16 (93.8)	6 / 10 (60.0)	1.52	[0.99; 2.79]	0.072
≥ 45 years	26 / 28 (92.9)	4 / 12 (33.3)	2.05	[1.31; 4.50]	0.005
Sex					
Interaction test	p = 0.276				
Male	13 / 14 (92.9)	1 / 6 (16.7)	3.57	[1.36; 9.50]	0.025
Female	28 / 30 (93.3)	9 / 16 (56.3)	1.66	[1.10; 2.56]	0.010
Baseline hemoglobin					
Interaction test	p = 0.813				
< 9 g/dL	20 / 22 (90.9)	3 / 10 (30.0)	2.22	[1.21; 10.64]	0.013
≥ 9 g/dL	21 / 22 (95.5)	7 / 12 (58.3)	1.71	[1.27; 2.86]	0.024
History of MAVE prior to screening					
Interaction test	p = 0.658				
No	31 / 34 (91.2)	7 / 15 (46.7)	1.86	[1.20; 3.49]	0.005
Yes	10 / 10 (100.0)	3 / 7 (42.9)	1.66	[0.98; 5.41]	0.174
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.807				
Eculizumab	27 / 30 (90.0)	6 / 17 (35.3)	2.17	[1.45; 4.57]	0.001
Ravulizumab	14 / 14 (100.0)	4 / 5 (80.0)	1.83	[1.30; 3.43]	0.182
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.983				
No	23 / 23 (100.0)	8 / 10 (80.0)	1.37	[1.13; 2.10]	0.077
Yes	18 / 21 (85.7)	2 / 12 (16.7)	3.67	[1.56; 14.49]	0.003
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.831				
< 2	28 / 29 (96.6)	9 / 15 (60.0)	1.59	[1.14; 2.60]	0.010
≥ 2	13 / 15 (86.7)	1 / 7 (14.3)	3.95	[1.48; 13.73]	0.027
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
Region					
Interaction test	p = 0.782				
Europe	32 / 34 (94.1)	8 / 18 (44.4)	1.97	[1.37; 3.34]	0.002
Other	9 / 10 (90.0)	2 / 4 (50.0)	1.34	[0.90; 3.86]	0.395
<p>N: Number of patients in the analysis set N': Number of patients included in the analysis n: Number of patients with response CI: Confidence interval RR: Relative risk N.A.: Not analyzed </p> <p>Analysis method for interaction test: Logistic regression model using Firth's penalized maximum likelihood estimation: Logit(proportion) = treatment + subgroup factor + treatment * subgroup factor + baseline hemoglobin (indicator of hemoglobin \geq 9 g/dL) + transfusion history + prior anti-C5-treatment Covariates baseline hemoglobin, transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: RR and p-value from logistic regression model using Firth's penalized maximum likelihood estimation: Logit(proportion) = treatment + baseline hemoglobin (indicator of hemoglobin \geq 9 g/dL) + transfusion history + prior anti-C5-treatment Covariates baseline hemoglobin, transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. p-value from test on model linear predictor of treatment. Predicted proportions and RR were calculated by marginal standardization from predicted values. First, predicted proportions were calculated by marginal standardization for each treatment group. Then RR was calculated from predicted proportions. Estimates and 95% CI were constructed by median and 2.5% and 97.5% percentiles from 1000 bootstrap samples.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Table 5-1.2.2 Transfusion avoidance between Day 1 and Day 168, only actual transfusions with presence of symptoms: logistic model analysis - subgroup analysis (Full Analysis Set)

Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
Transfusion avoidance between Day 1 and Day 168, only actual transfusions with presence of symptoms					
	n / N' (%)	n / N' (%)			
Length of time since diagnosis					
Interaction test	p = 0.805				
< 5 years	10 / 11 (90.9)	3 / 8 (37.5)	1.98	[1.08; 6.17]	0.069
≥ 5 years	32 / 33 (97.0)	8 / 14 (57.1)	1.67	[1.17; 3.02]	0.008
Age categories					
Interaction test	p = 0.569				
< 45 years	15 / 16 (93.8)	6 / 10 (60.0)	1.52	[0.99; 2.79]	0.072
≥ 45 years	27 / 28 (96.4)	5 / 12 (41.7)	1.92	[1.24; 4.12]	0.005
Sex					
Interaction test	p = 0.353				
Male	13 / 14 (92.9)	1 / 6 (16.7)	3.57	[1.36; 9.50]	0.025
Female	29 / 30 (96.7)	10 / 16 (62.5)	1.56	[1.09; 2.37]	0.012
Baseline hemoglobin					
Interaction test	p = 0.596				
< 9 g/dL	20 / 22 (90.9)	3 / 10 (30.0)	2.22	[1.21; 10.64]	0.013
≥ 9 g/dL	22 / 22 (100.0)	8 / 12 (66.7)	1.57	[1.20; 2.52]	0.024
History of MAVE prior to screening					
Interaction test	p = 0.937				
No	32 / 34 (94.1)	7 / 15 (46.7)	1.93	[1.22; 3.61]	0.003
Yes	10 / 10 (100.0)	4 / 7 (57.1)	1.63	[1.02; 3.28]	0.167
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.780				
Eculizumab	28 / 30 (93.3)	7 / 17 (41.2)	1.97	[1.34; 3.66]	0.002
Ravulizumab	14 / 14 (100.0)	4 / 5 (80.0)	1.83	[1.30; 3.43]	0.182
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.981				
No	23 / 23 (100.0)	8 / 10 (80.0)	1.37	[1.13; 2.10]	0.077
Yes	19 / 21 (90.5)	3 / 12 (25.0)	2.87	[1.40; 9.21]	0.004
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.794				
< 2	28 / 29 (96.6)	9 / 15 (60.0)	1.59	[1.14; 2.60]	0.010
≥ 2	14 / 15 (93.3)	2 / 7 (28.6)	2.80	[1.20; 10.94]	0.032
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
Region					
Interaction test	p = 0.744				
Europe	32 / 34 (94.1)	9 / 18 (50.0)	1.76	[1.24; 2.94]	0.004
Other	10 / 10 (100.0)	2 / 4 (50.0)	1.61	[1.01; 5.47]	0.255
<p>N: Number of patients in the analysis set N': Number of patients included in the analysis n: Number of patients with response CI: Confidence interval RR: Relative risk N.A.: Not analyzed </p> <p>Analysis method for interaction test: Logistic regression model using Firth's penalized maximum likelihood estimation: Logit(proportion) = treatment + subgroup factor + treatment * subgroup factor + baseline hemoglobin (indicator of hemoglobin \geq 9 g/dL) + transfusion history + prior anti-C5-treatment Covariates baseline hemoglobin, transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: RR and p-value from logistic regression model using Firth's penalized maximum likelihood estimation: Logit(proportion) = treatment + baseline hemoglobin (indicator of hemoglobin \geq 9 g/dL) + transfusion history + prior anti-C5-treatment Covariates baseline hemoglobin, transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. p-value from test on model linear predictor of treatment. Predicted proportions and RR were calculated by marginal standardization from predicted values. First, predicted proportions were calculated by marginal standardization for each treatment group. Then RR was calculated from predicted proportions. Estimates and 95% CI were constructed by median and 2.5% and 97.5% percentiles from 1000 bootstrap samples.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Table 5-1.2.3 Transfusion avoidance between Day 1 and Day 336, only actual transfusions: logistic model analysis - subgroup analysis (Full Analysis Set)

Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
Transfusion avoidance between Day 1 and Day 336, only actual transfusions					
	n / N' (%)	n / N' (%)			
Length of time since diagnosis					
Interaction test	p = 0.753				
< 5 years	9 / 11 (81.8)	3 / 8 (37.5)	1.94	[1.00; 6.40]	0.119
≥ 5 years	30 / 33 (90.9)	7 / 14 (50.0)	1.77	[1.23; 3.69]	0.010
Age categories					
Interaction test	p = 0.915				
< 45 years	15 / 16 (93.8)	6 / 10 (60.0)	1.52	[0.99; 2.79]	0.072
≥ 45 years	24 / 28 (85.7)	4 / 12 (33.3)	1.98	[1.25; 4.78]	0.015
Sex					
Interaction test	p = 0.438				
Male	12 / 14 (85.7)	1 / 6 (16.7)	3.49	[1.09; 18.20]	0.047
Female	27 / 30 (90.0)	9 / 16 (56.3)	1.63	[1.09; 2.55]	0.020
Baseline hemoglobin					
Interaction test	p = 0.977				
< 9 g/dL	19 / 22 (86.4)	3 / 10 (30.0)	2.41	[1.25; 14.52]	0.018
≥ 9 g/dL	20 / 22 (90.9)	7 / 12 (58.3)	1.63	[1.22; 2.72]	0.039
History of MAVE prior to screening					
Interaction test	p = 0.488				
No	29 / 34 (85.3)	7 / 15 (46.7)	1.79	[1.14; 3.43]	0.015
Yes	10 / 10 (100.0)	3 / 7 (42.9)	1.66	[0.98; 5.41]	0.174
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.754				
Eculizumab	26 / 30 (86.7)	6 / 17 (35.3)	2.10	[1.40; 4.65]	0.003
Ravulizumab	13 / 14 (92.9)	4 / 5 (80.0)	1.71	[0.88; 3.19]	0.181
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.494				
No	22 / 23 (95.7)	8 / 10 (80.0)	1.32	[1.01; 2.02]	0.144
Yes	17 / 21 (81.0)	2 / 12 (16.7)	3.42	[1.49; 14.19]	0.006
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.691				
< 2	27 / 29 (93.1)	9 / 15 (60.0)	1.56	[1.11; 2.52]	0.018
≥ 2	12 / 15 (80.0)	1 / 7 (14.3)	3.43	[1.36; 13.25]	0.049
Duration of anti-C5 treatment					
N.A. ⁺					

Treatment Groups			Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
Region					
Interaction test	p = 0.443				
Europe	31 / 34 (91.2)	8 / 18 (44.4)	1.88	[1.29; 3.15]	0.004
Other	8 / 10 (80.0)	2 / 4 (50.0)	1.25	[0.61; 4.22]	0.662
<p>N: Number of patients in the analysis set N': Number of patients included in the analysis n: Number of patients with response CI: Confidence interval RR: Relative risk N.A.: Not analyzed </p> <p>Analysis method for interaction test: Logistic regression model using Firth's penalized maximum likelihood estimation: Logit(proportion) = treatment + subgroup factor + treatment * subgroup factor + baseline hemoglobin (indicator of hemoglobin \geq 9 g/dL) + transfusion history + prior anti-C5-treatment Covariates baseline hemoglobin, transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: RR and p-value from logistic regression model using Firth's penalized maximum likelihood estimation: Logit(proportion) = treatment + baseline hemoglobin (indicator of hemoglobin \geq 9 g/dL) + transfusion history + prior anti-C5-treatment Covariates baseline hemoglobin, transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. p-value from test on model linear predictor of treatment. Predicted proportions and RR were calculated by marginal standardization from predicted values. First, predicted proportions were calculated by marginal standardization for each treatment group. Then RR was calculated from predicted proportions. Estimates and 95% CI were constructed by median and 2.5% and 97.5% percentiles from 1000 bootstrap samples.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Table 5-1.2.4 Transfusion avoidance between Day 1 and Day 336, only actual transfusions with presence of symptoms: logistic model analysis - subgroup analysis (Full Analysis Set)

Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
Transfusion avoidance between Day 1 and Day 336, only actual transfusions with presence of symptoms					
	n / N' (%)	n / N' (%)			
Length of time since diagnosis					
Interaction test	p = 0.683				
< 5 years	9 / 11 (81.8)	3 / 8 (37.5)	1.94	[1.00; 6.40]	0.119
≥ 5 years	31 / 33 (93.9)	8 / 14 (57.1)	1.70	[1.17; 3.57]	0.012
Age categories					
Interaction test	p = 0.982				
< 45 years	15 / 16 (93.8)	6 / 10 (60.0)	1.52	[0.99; 2.79]	0.072
≥ 45 years	25 / 28 (89.3)	5 / 12 (41.7)	1.85	[1.17; 4.39]	0.017
Sex					
Interaction test	p = 0.501				
Male	12 / 14 (85.7)	1 / 6 (16.7)	3.49	[1.09; 18.20]	0.047
Female	28 / 30 (93.3)	10 / 16 (62.5)	1.55	[1.09; 2.40]	0.021
Baseline hemoglobin					
Interaction test	p = 0.971				
< 9 g/dL	19 / 22 (86.4)	3 / 10 (30.0)	2.41	[1.25; 14.52]	0.018
≥ 9 g/dL	21 / 22 (95.5)	8 / 12 (66.7)	1.49	[1.08; 2.41]	0.035
History of MAVE prior to screening					
Interaction test	p = 0.708				
No	30 / 34 (88.2)	7 / 15 (46.7)	1.86	[1.16; 3.50]	0.009
Yes	10 / 10 (100.0)	4 / 7 (57.1)	1.63	[1.02; 3.28]	0.167
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.810				
Eculizumab	27 / 30 (90.0)	7 / 17 (41.2)	1.91	[1.28; 3.62]	0.003
Ravulizumab	13 / 14 (92.9)	4 / 5 (80.0)	1.71	[0.88; 3.19]	0.181
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.537				
No	22 / 23 (95.7)	8 / 10 (80.0)	1.32	[1.01; 2.02]	0.144
Yes	18 / 21 (85.7)	3 / 12 (25.0)	2.70	[1.30; 9.46]	0.008
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.760				
< 2	27 / 29 (93.1)	9 / 15 (60.0)	1.56	[1.11; 2.52]	0.018
≥ 2	13 / 15 (86.7)	2 / 7 (28.6)	2.32	[1.10; 10.73]	0.066
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
Region					
Interaction test	p = 0.829				
Europe	31 / 34 (91.2)	9 / 18 (50.0)	1.67	[1.17; 2.77]	0.009
Other	9 / 10 (90.0)	2 / 4 (50.0)	1.57	[0.75; 6.25]	0.345
<p>N: Number of patients in the analysis set N': Number of patients included in the analysis n: Number of patients with response CI: Confidence interval RR: Relative risk N.A.: Not analyzed </p> <p>Analysis method for interaction test: Logistic regression model using Firth's penalized maximum likelihood estimation: Logit(proportion) = treatment + subgroup factor + treatment * subgroup factor + baseline hemoglobin (indicator of hemoglobin \geq 9 g/dL) + transfusion history + prior anti-C5-treatment Covariates baseline hemoglobin, transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: RR and p-value from logistic regression model using Firth's penalized maximum likelihood estimation: Logit(proportion) = treatment + baseline hemoglobin (indicator of hemoglobin \geq 9 g/dL) + transfusion history + prior anti-C5-treatment Covariates baseline hemoglobin, transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. p-value from test on model linear predictor of treatment. Predicted proportions and RR were calculated by marginal standardization from predicted values. First, predicted proportions were calculated by marginal standardization for each treatment group. Then RR was calculated from predicted proportions. Estimates and 95% CI were constructed by median and 2.5% and 97.5% percentiles from 1000 bootstrap samples.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

5-1.3 Hemoglobin levels

Table 5-1.3.1 Increase in hemoglobin levels ≥ 2 g/dL from baseline without requiring pRBC transfusions: logistic model analysis - subgroup analysis (Full Analysis Set)

		Treatment Groups		Comparison		
		Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
Increase in hemoglobin levels ≥ 2 g/dL from baseline^a without requiring pRBC transfusions^b						
		n / N' (%)	n / N' (%)			
Length of time since diagnosis						
Interaction test		p = 0.680				
< 5 years		9 / 11 (81.8)	0 / 8 (0.0)	8.44	[3.57; 16.66]	0.019
≥ 5 years		28 / 33 (84.8)	0 / 14 (0.0)	21.57	[10.86; 46.18]	<0.001
Age categories						
Interaction test		p = 0.982				
< 45 years		14 / 16 (87.5)	0 / 10 (0.0)	9.99	[4.13; 18.14]	0.005
≥ 45 years		23 / 28 (82.1)	0 / 12 (0.0)	17.43	[7.40; 39.22]	0.002
Sex						
Interaction test		p = 0.417				
Male		11 / 14 (78.6)	0 / 6 (0.0)	6.07	[1.48; 18.41]	0.039
Female		26 / 30 (86.7)	0 / 16 (0.0)	21.17	[11.44; 39.05]	<0.001
Baseline hemoglobin						
Interaction test		p = 0.674				
< 9 g/dL		17 / 22 (77.3)	0 / 10 (0.0)	17.20	[7.53; 34.02]	0.007
≥ 9 g/dL		20 / 22 (90.9)	0 / 12 (0.0)	16.48	[8.41; 30.16]	0.002
History of MAVE prior to screening						
Interaction test		p = 0.669				
No		27 / 34 (79.4)	0 / 15 (0.0)	20.19	[10.30; 34.32]	0.002
Yes		10 / 10 (100.0)	0 / 7 (0.0)	7.04	[3.79; 10.14]	0.025
Anti-C5 medication history 6 months prior to randomization						
Interaction test		p = 0.651				
Eculizumab		26 / 30 (86.7)	0 / 17 (0.0)	23.43	[12.52; 42.33]	<0.001
Ravulizumab		11 / 14 (78.6)	0 / 5 (0.0)	8.80	[3.49; 17.13]	0.045
Transfusion in the last 6 months prior to randomization						
Interaction test		p = 0.732				
No		21 / 23 (91.3)	0 / 10 (0.0)	14.86	[6.25; 27.96]	0.003
Yes		16 / 21 (76.2)	0 / 12 (0.0)	13.95	[5.44; 25.54]	0.008
Number of transfusions in the last 6 months prior to randomization						
Interaction test		p = 0.676				
< 2		25 / 29 (86.2)	0 / 15 (0.0)	21.95	[11.68; 33.38]	<0.001
≥ 2		12 / 15 (80.0)	0 / 7 (0.0)	10.50	[4.68; 17.61]	0.020
Duration of anti-C5 treatment						
N.A. ⁺						

Treatment Groups			Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
Region					
Interaction test	p = 0.408				
Europe	29 / 34 (85.3)	0 / 18 (0.0)	24.18	[12.69; 44.36]	<0.001
Other	8 / 10 (80.0)	0 / 4 (0.0)	3.60	[0.94; 14.29]	0.120
<p>N: Number of patients in the analysis set N': Number of patients included in the analysis n: Number of patients with response CI: Confidence interval RR: Relative risk N.A.: Not analyzed </p> <p>Analysis method for interaction test: Logistic regression model using Firth's penalized maximum likelihood estimation: Logit(proportion) = treatment + subgroup factor + treatment * subgroup factor + baseline hemoglobin (indicator of hemoglobin \geq 9 g/dL) + transfusion history + prior anti-C5-treatment Covariates baseline hemoglobin, transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: RR and p-value from logistic regression model using Firth's penalized maximum likelihood estimation: Logit(proportion) = treatment + baseline hemoglobin (indicator of hemoglobin \geq 9 g/dL) + transfusion history + prior anti-C5-treatment Covariates baseline hemoglobin, transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. p-value from test on model linear predictor of treatment. Predicted proportions and RR were calculated by marginal standardization from predicted values. First, predicted proportions were calculated by marginal standardization for each treatment group. Then RR was calculated from predicted proportions. Estimates and 95% CI were constructed by median and 2.5% and 97.5% percentiles from 1000 bootstrap samples.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>a: between Day 126 and Day 168 (at least 3 out of 4 scheduled assessments) b: between Day 14 and Day 168</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Table 5-1.3.2 Hemoglobin levels ≥ 12 g/dL without requiring pRBC transfusions: logistic model analysis - subgroup analysis (Full Analysis Set)

Treatment Groups		Comparison			
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
Hemoglobin levels ≥ 12 g/dL^a without requiring pRBC transfusions^b					
	n / N' (%)	n / N' (%)			
Length of time since diagnosis					
Interaction test	p = 0.622				
< 5 years	7 / 11 (63.6)	0 / 8 (0.0)	6.94	[2.64; 11.30]	0.037
≥ 5 years	24 / 33 (72.7)	0 / 14 (0.0)	25.06	[11.39; 52.28]	0.001
Age categories					
Interaction test	p = 0.989				
< 45 years	12 / 16 (75.0)	0 / 10 (0.0)	10.02	[2.87; 17.73]	0.011
≥ 45 years	19 / 28 (67.9)	0 / 12 (0.0)	16.67	[4.83; 36.69]	0.008
Sex					
Interaction test	p = 0.396				
Male	9 / 14 (64.3)	0 / 6 (0.0)	4.62	[0.95; 10.96]	0.062
Female	22 / 30 (73.3)	0 / 16 (0.0)	26.99	[11.10; 55.65]	0.002
Baseline hemoglobin					
Interaction test	p = 0.177				
< 9 g/dL	11 / 22 (50.0)	0 / 10 (0.0)	6.53	[2.25; 15.26]	0.085
≥ 9 g/dL	20 / 22 (90.9)	0 / 12 (0.0)	16.48	[8.41; 30.16]	0.002
History of MAVE prior to screening					
Interaction test	p = 0.637				
No	22 / 34 (64.7)	0 / 15 (0.0)	24.37	[8.34; 62.45]	0.003
Yes	9 / 10 (90.0)	0 / 7 (0.0)	6.10	[2.00; 10.00]	0.045
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.777				
Eculizumab	21 / 30 (70.0)	0 / 17 (0.0)	18.87	[6.89; 34.21]	0.002
Ravulizumab	10 / 14 (71.4)	0 / 5 (0.0)	10.31	[4.17; 19.47]	0.055
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.244				
No	21 / 23 (91.3)	0 / 10 (0.0)	14.86	[6.25; 27.96]	0.003
Yes	10 / 21 (47.6)	0 / 12 (0.0)	6.69	[2.40; 16.42]	0.063
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.286				
< 2	24 / 29 (82.8)	0 / 15 (0.0)	22.60	[11.58; 36.38]	0.001
≥ 2	7 / 15 (46.7)	0 / 7 (0.0)	6.86	[1.24; 14.83]	0.102
Duration of anti-C5 treatment					
N.A. ⁺					

Treatment Groups			Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
Region					
Interaction test	p = 0.862				
Europe	23 / 34 (67.6)	0 / 18 (0.0)	26.87	[6.90; 59.11]	0.002
Other	8 / 10 (80.0)	0 / 4 (0.0)	3.60	[0.94; 14.29]	0.120
<p>N: Number of patients in the analysis set N': Number of patients included in the analysis n: Number of patients with response CI: Confidence interval RR: Relative risk N.A.: Not analyzed </p> <p>Analysis method for interaction test: Logistic regression model using Firth's penalized maximum likelihood estimation: Logit(proportion) = treatment + subgroup factor + treatment * subgroup factor + baseline hemoglobin (indicator of hemoglobin \geq 9 g/dL) + transfusion history + prior anti-C5-treatment Covariates baseline hemoglobin, transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: RR and p-value from logistic regression model using Firth's penalized maximum likelihood estimation: Logit(proportion) = treatment + baseline hemoglobin (indicator of hemoglobin \geq 9 g/dL) + transfusion history + prior anti-C5-treatment Covariates baseline hemoglobin, transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. p-value from test on model linear predictor of treatment. Predicted proportions and RR were calculated by marginal standardization from predicted values. First, predicted proportions were calculated by marginal standardization for each treatment group. Then RR was calculated from predicted proportions. Estimates and 95% CI were constructed by median and 2.5% and 97.5% percentiles from 1000 bootstrap samples.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>a: between Day 126 and Day 168 (at least 3 out of 4 scheduled assessments) b: between Day 14 and Day 168</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

5-2 Subgroup analysis for PRO

5-2.1 FACIT Fatigue

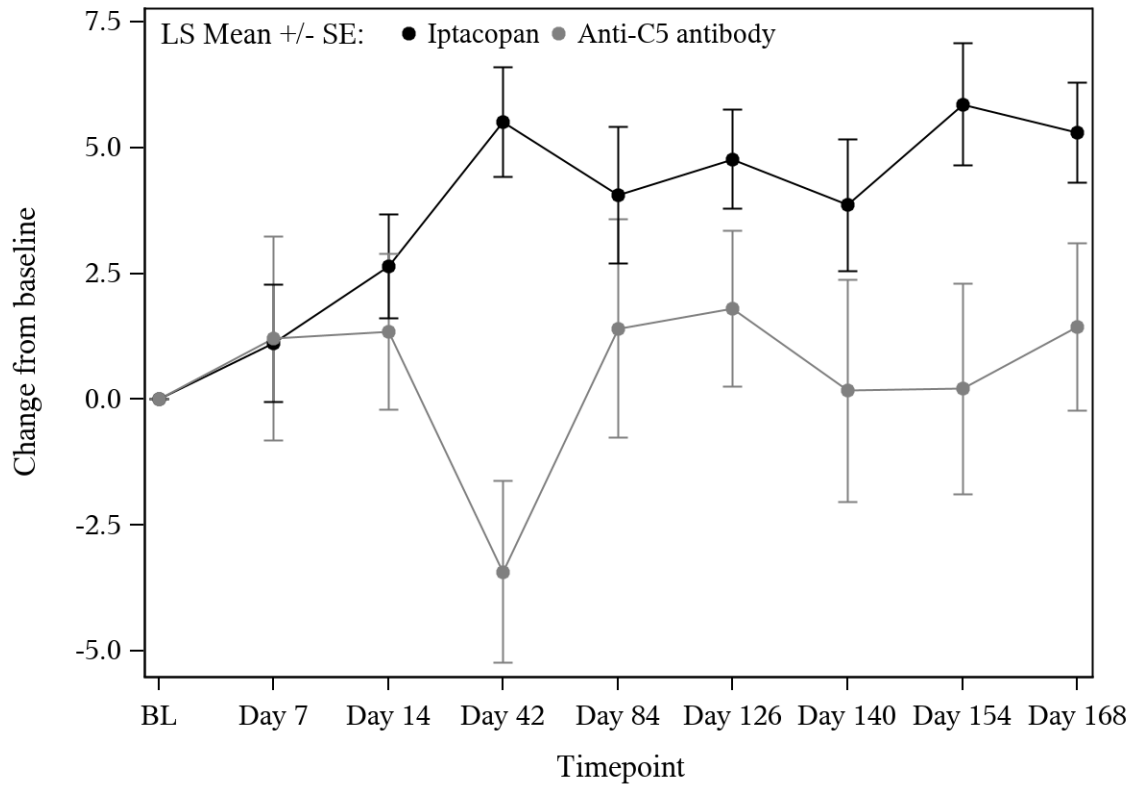
Table 5-2.1.1 FACIT Fatigue: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
FACIT Fatigue					
	N' LS Mean (SE)	N' LS Mean (SE)			
Length of time since diagnosis					
Interaction test	p = 0.096				
< 5 years	11 4.77 (2.40)	7 -0.67 (2.88)	5.44	[-1.86; 12.73]	0.128
≥ 5 years	33 7.04 (0.95)	12 -2.77 (1.53)	9.81	[6.23; 13.38]	<0.001
Age categories					
Interaction test	p = 0.088				
< 45 years	16 9.20 (2.03)	8 -2.50 (2.34)	11.70	[6.14; 17.27]	<0.001
≥ 45 years	28 4.30 (1.03)	11 -0.88 (1.71)	5.18	[1.15; 9.21]	0.013
Sex					
Interaction test	p = 0.0501				
Male	14 4.26 (2.07)	6 0.78 (2.32)	3.49	[-2.25; 9.22]	0.225
Female	30 6.69 (0.94)	13 -3.04 (1.43)	9.73	[6.35; 13.10]	<0.001
Baseline hemoglobin					
Interaction test	p = 0.723				
< 9 g/dL	22 4.71 (1.40)	8 -3.47 (2.68)	8.18	[2.04; 14.32]	0.011
≥ 9 g/dL	22 7.63 (1.40)	11 -0.27 (1.70)	7.90	[3.78; 12.02]	<0.001
History of MAVE prior to screening					
Interaction test	p = 0.554				
No	34 6.06 (1.17)	12 -0.99 (1.90)	7.05	[2.63; 11.46]	0.002
Yes	10 5.09 (1.98)	7 -3.91 (2.24)	9.00	[2.60; 15.40]	0.010
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.595				
Eculizumab	30 4.72 (1.00)	14 -3.43 (1.54)	8.15	[4.47; 11.83]	<0.001
Ravulizumab	14 7.17 (1.26)	5 1.43 (2.12)	5.74	[0.77; 10.71]	0.025
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.039				
No	23 6.49 (1.05)	8 2.45 (1.62)	4.04	[0.27; 7.81]	0.037
Yes	21 6.07 (1.60)	11 -3.64 (2.47)	9.72	[4.09; 15.35]	0.001
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.885				
< 2	29 5.61 (1.07)	13 -1.25 (1.47)	6.86	[3.12; 10.59]	<0.001
≥ 2	15 5.03 (2.48)	6 -3.44 (3.97)	8.47	[0.24; 16.71]	0.044

Figure 5-2.1.1 FACIT Fatigue: line chart of least squares mean change from baseline - subgroup analysis (Full Analysis Set)

FACIT Fatigue

Transfusion in the last 6 months prior to randomization: No



Iptacopan	23	22	21	23	22	22	23	23	23
Anti-C5 antibody	9	7	9	8	8	8	7	6	7

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

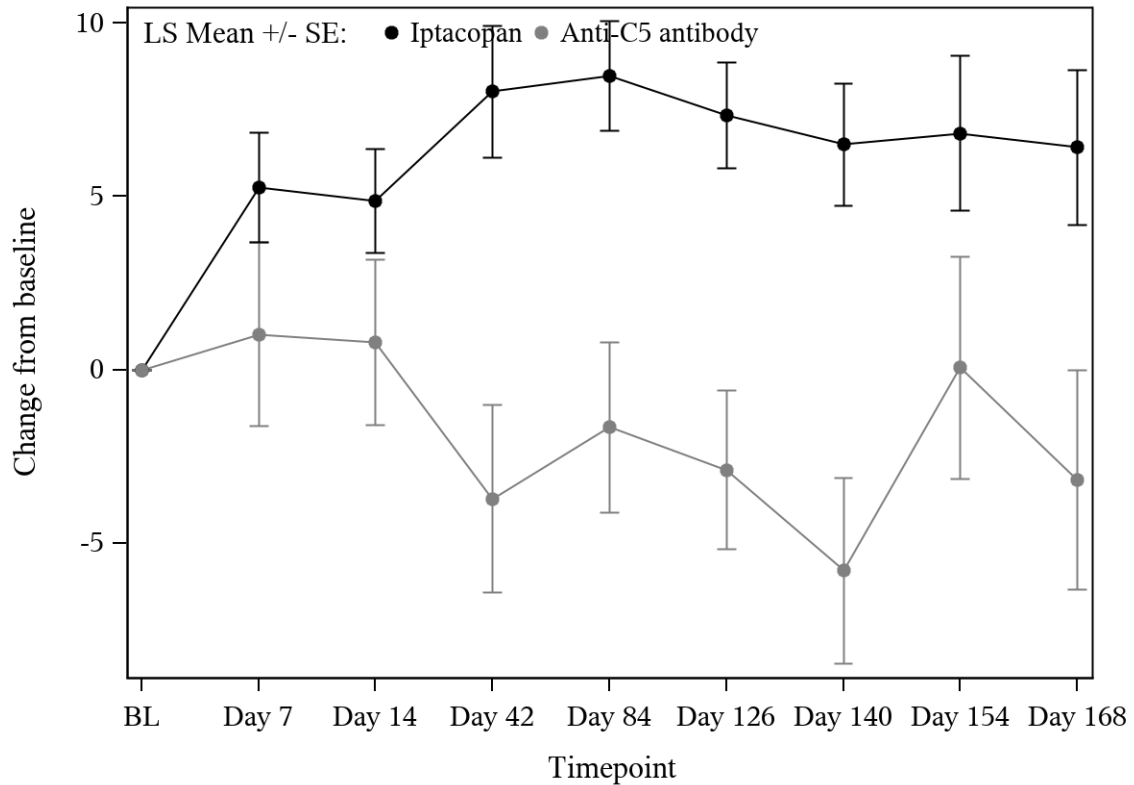
Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

FACIT Fatigue

Transfusion in the last 6 months prior to randomization: Yes



Iptacopan	21	20	18	21	18	19	19	18	19
Anti-C5 antibody	12	8	8	12	9	9	9	10	11

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.

Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

5-2.2 EORTC QLQ-C30 Symptoms

Table 5-2.2.1.1 QLQ-C30 - Fatigue: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Fatigue					
	N' LS Mean (SE)	N' LS Mean (SE)			
Length of time since diagnosis					
Interaction test	p = 0.536				
< 5 years	11 -9.85 (16.59)	7 -1.21 (18.22)	-8.64	[-25.27; 7.99]	0.300
≥ 5 years	33 -17.21 (2.42)	12 2.19 (3.90)	-19.40	[-28.59; -10.21]	<0.001
Age categories					
Interaction test	p = 0.148				
< 45 years	16 -16.46 (5.41)	8 7.99 (6.60)	-24.45	[-39.73; -9.17]	0.003
≥ 45 years	28 -10.99 (2.62)	11 -0.02 (4.30)	-10.96	[-21.15; -0.77]	0.036
Sex					
Interaction test	p = 0.182				
Male	14 -16.07 (5.73)	6 -4.24 (6.87)	-11.82	[-28.28; 4.63]	0.147
Female	30 -15.18 (2.60)	13 2.84 (3.96)	-18.01	[-27.49; -8.53]	<0.001
Baseline hemoglobin					
Interaction test	p = 0.766				
< 9 g/dL	22 -11.08 (2.92)	8 6.60 (5.55)	-17.68	[-30.22; -5.14]	0.007
≥ 9 g/dL	22 -17.91 (3.63)	11 -3.71 (4.48)	-14.21	[-25.33; -3.08]	0.014
History of MAVE prior to screening					
Interaction test	p = 0.837				
No	34 -13.67 (2.43)	12 1.02 (3.93)	-14.69	[-23.75; -5.64]	0.002
Yes	10 -20.77 (5.81)	7 6.50 (6.58)	-27.28	[-46.73; -7.83]	0.011
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.859				
Eculizumab	30 -10.41 (2.74)	14 7.06 (4.13)	-17.47	[-27.64; -7.30]	0.001
Ravulizumab	14 -18.71 (3.56)	5 -4.64 (6.02)	-14.08	[-28.98; 0.82]	0.062
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.201				
No	23 -18.16 (3.00)	8 -7.62 (4.92)	-10.54	[-22.08; 1.00]	0.072
Yes	21 -10.63 (3.12)	11 9.20 (4.95)	-19.83	[-31.18; -8.48]	0.001
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.418				
< 2	29 -17.61 (2.67)	13 0.08 (3.82)	-17.69	[-27.16; -8.22]	<0.001
≥ 2	15 -5.79 (4.12)	6 12.22 (6.66)	-18.00	[-33.12; -2.89]	0.022
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.696				
Europe	34 -14.30 (2.74)	15 2.21 (4.36)	-16.50	[-26.31; -6.70]	0.001
Other	10 -17.77 (7.49)	4 -8.57 (12.06)	-9.20	[-40.64; 22.24]	0.515
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

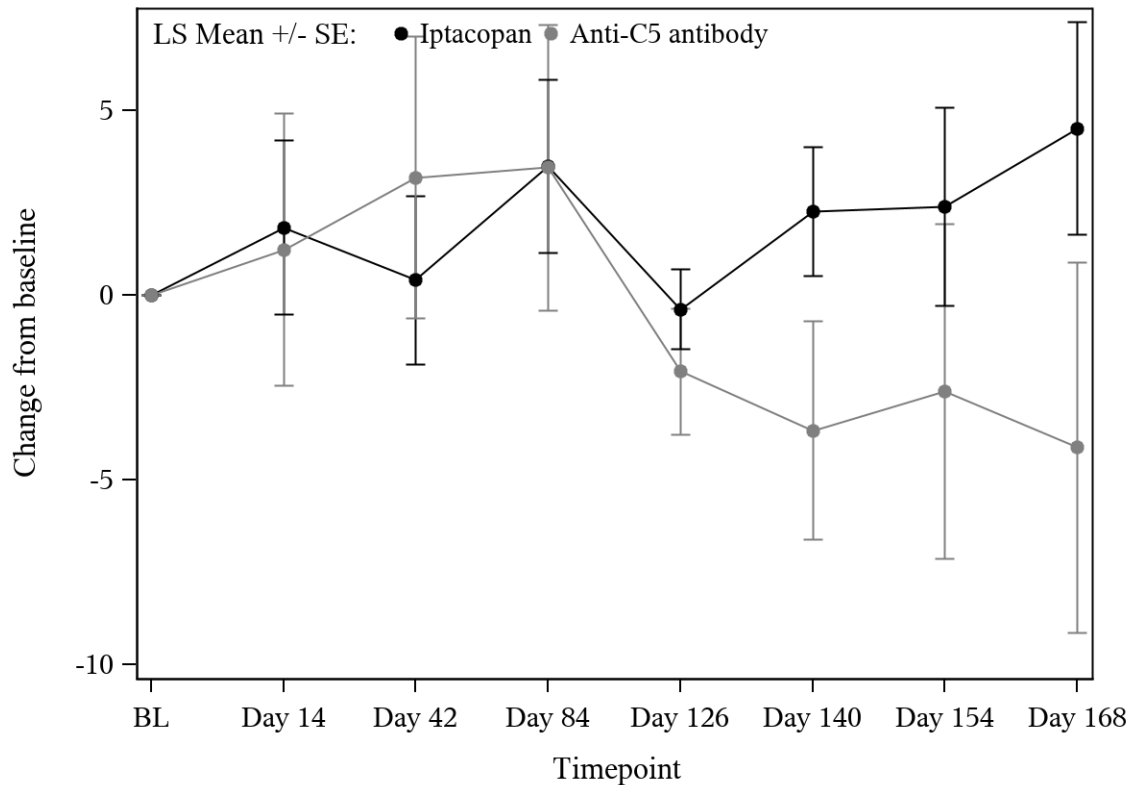
Table 5-2.2.2.1 QLQ-C30 - Nausea and vomiting: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Nausea and vomiting					
N' LS Mean (SE) N' LS Mean (SE)					
Length of time since diagnosis					
Interaction test	p = 0.382				
< 5 years	11 -2.47 (2.66)	7 2.10 (3.16)	-4.57	[-11.80; 2.65]	0.206
≥ 5 years	33 -0.06 (1.09)	12 1.25 (1.80)	-1.31	[-5.47; 2.85]	0.534
Age categories					
Interaction test	p = 0.273				
< 45 years	16 1.66 (2.55)	8 -0.09 (2.87)	1.75	[-4.99; 8.49]	0.605
≥ 45 years	28 -1.55 (1.04)	11 2.67 (1.75)	-4.22	[-8.31; -0.13]	0.043
Sex					
Interaction test	p = 0.551				
Male	14 -1.81 (2.25)	6 2.06 (2.74)	-3.88	[-10.21; 2.46]	0.224
Female	30 0.18 (1.21)	13 1.11 (1.85)	-0.93	[-5.28; 3.42]	0.672
Baseline hemoglobin					
Interaction test	p = 0.101				
< 9 g/dL	22 -0.88 (1.50)	8 2.48 (2.82)	-3.36	[-9.63; 2.92]	0.288
≥ 9 g/dL	22 -0.92 (1.34)	11 -0.47 (1.70)	-0.45	[-4.51; 3.62]	0.827
History of MAVE prior to screening					
Interaction test	p = 0.202				
No	34 -0.41 (1.16)	12 0.80 (1.98)	-1.21	[-5.68; 3.26]	0.593
Yes	10 0.54 (2.09)	7 4.43 (2.24)	-3.89	[-9.32; 1.55]	0.155
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.982				
Eculizumab	30 0.80 (1.32)	14 3.56 (2.07)	-2.76	[-7.70; 2.18]	0.271
Ravulizumab	14 -1.59 (0.86)	5 -1.62 (1.53)	0.03	[-3.45; 3.51]	0.985
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.043				
No	23 1.86 (1.63)	8 -3.46 (2.66)	5.32	[-0.95; 11.59]	0.093
Yes	21 -2.00 (1.69)	11 5.10 (2.52)	-7.10	[-13.27; -0.93]	0.026
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.008				
< 2	29 0.76 (1.14)	13 -1.49 (1.71)	2.25	[-1.81; 6.30]	0.274
≥ 2	15 -2.52 (1.88)	6 8.42 (3.20)	-10.93	[-17.62; -4.25]	0.002
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.444				
Europe	34 -0.29 (1.09)	15 1.44 (1.69)	-1.73	[-5.56; 2.10]	0.372
Other	10 0.57 (1.78)	4 7.55 (2.57)	-6.98	[-13.54; -0.42]	0.038
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Figure 5-2.2.2.1 QLQ-C30 - Nausea and vomiting: line chart of least squares mean change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Nausea and vomiting
Transfusion in the last 6 months prior to randomization: No



Iptacopan	23	21	23	22	22	23	23	23
Anti-C5 antibody	9	9	8	8	8	7	6	7

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

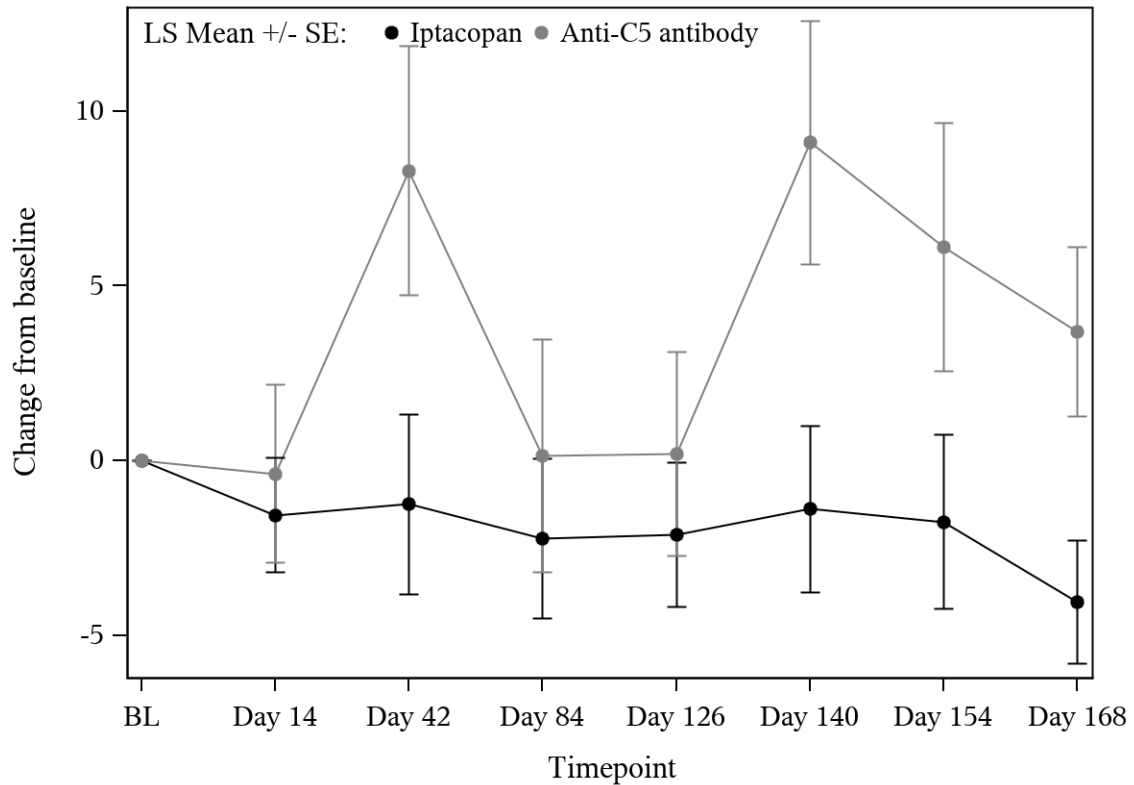
Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Nausea and vomiting
Transfusion in the last 6 months prior to randomization: Yes



Iptacopan	21	18	21	18	19	19	18	19
Anti-C5 antibody	12	8	12	9	9	9	10	11

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

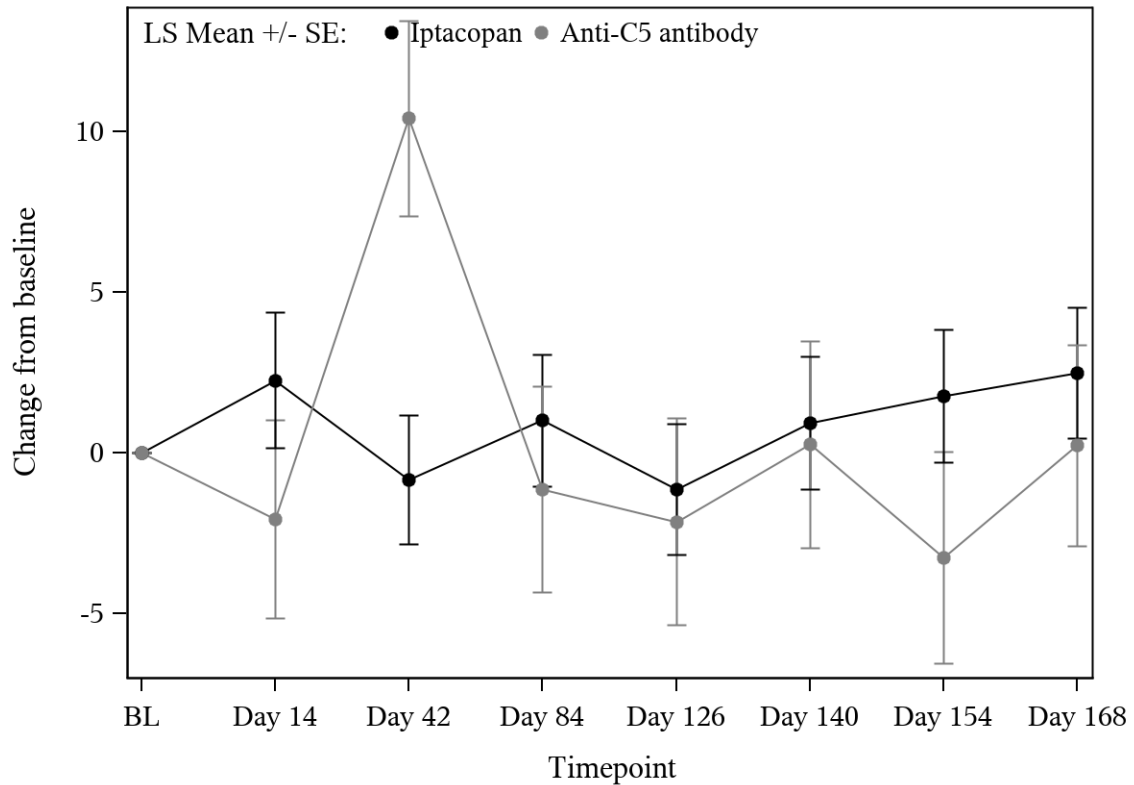
Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.

Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Nausea and vomiting

Number of transfusions in the last 6 months prior to randomization: < 2



Iptacopan	29	26	29	28	28	27	27	28
Anti-C5 antibody	14	12	13	12	11	11	11	12

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

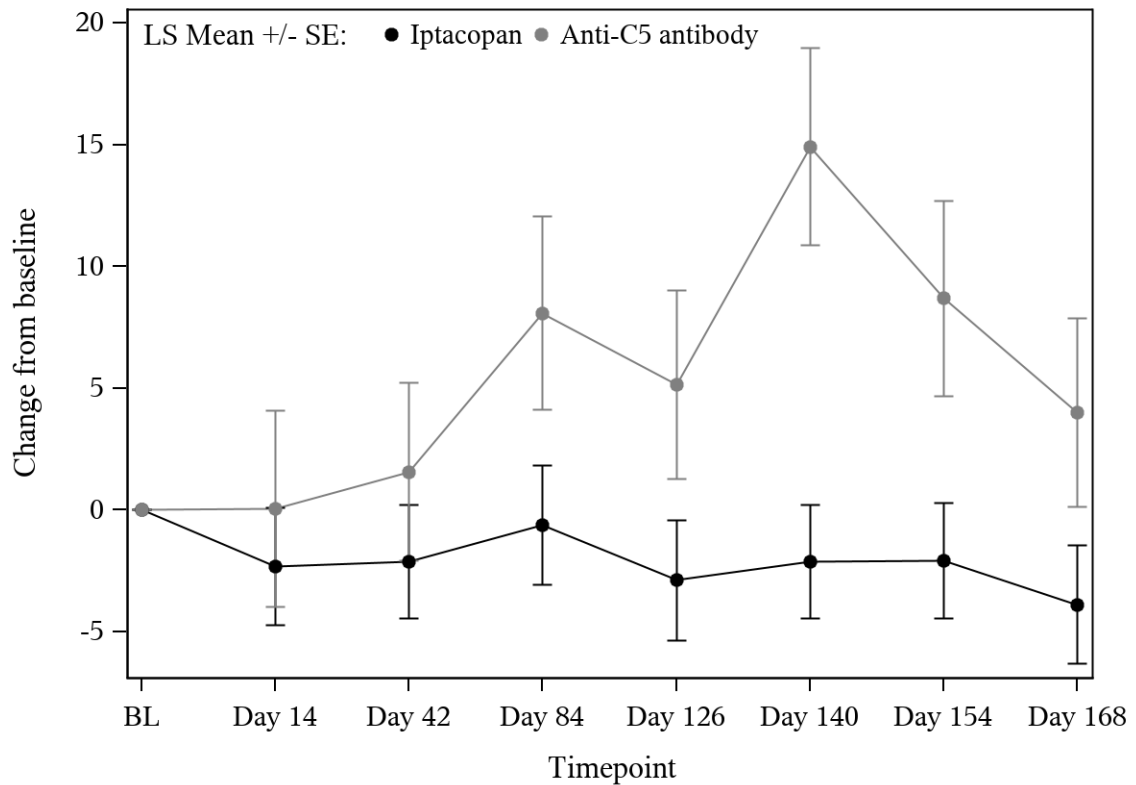
Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.

Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Nausea and vomiting

Number of transfusions in the last 6 months prior to randomization: ≥ 2



Iptacopan	15	13	15	12	13	15	14	14
Anti-C5 antibody	7	5	7	5	6	5	5	6

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.

Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

Table 5-2.2.3.1 QLQ-C30 - Pain: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

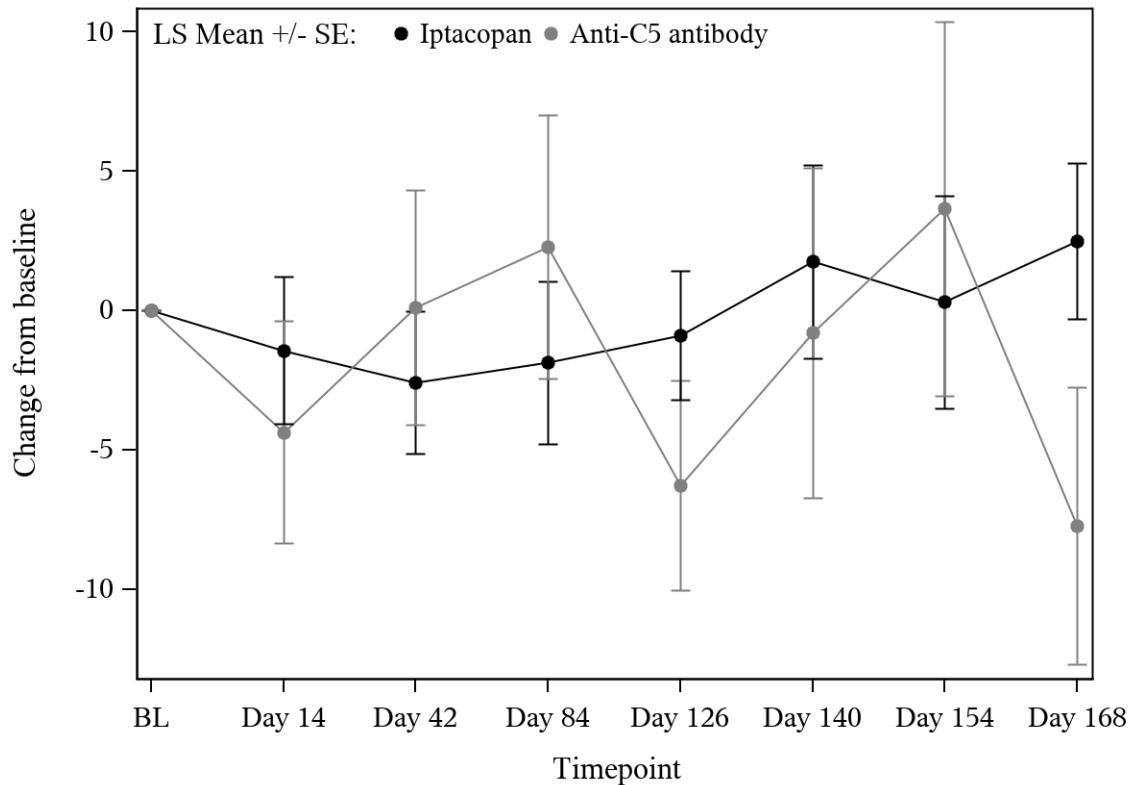
	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Pain					
	N' LS Mean (SE)				
Length of time since diagnosis					
Interaction test	p = 0.629				
< 5 years	11 -1.32 (3.96)	7 2.90 (4.91)	-4.22	[-17.23; 8.80]	0.499
≥ 5 years	33 -0.83 (2.63)	12 4.85 (4.31)	-5.68	[-16.12; 4.76]	0.277
Age categories					
Interaction test	p = 0.432				
< 45 years	16 2.61 (4.51)	8 2.80 (5.10)	-0.19	[-12.28; 11.89]	0.974
≥ 45 years	28 -0.80 (2.11)	11 1.66 (3.51)	-2.46	[-10.96; 6.03]	0.559
Sex					
Interaction test	p = 0.233				
Male	14 -1.24 (4.05)	6 -1.56 (5.86)	0.31	[-15.32; 15.95]	0.967
Female	30 -1.05 (2.61)	13 5.15 (3.87)	-6.20	[-15.56; 3.16]	0.187
Baseline hemoglobin					
Interaction test	p = 0.104				
< 9 g/dL	22 -0.22 (2.17)	8 3.41 (3.94)	-3.63	[-12.76; 5.50]	0.421
≥ 9 g/dL	22 -0.89 (3.28)	11 1.31 (4.21)	-2.21	[-12.67; 8.26]	0.670
History of MAVE prior to screening					
Interaction test	p = 0.520				
No	34 -0.06 (2.33)	12 1.25 (3.88)	-1.31	[-10.22; 7.60]	0.770
Yes	10 -2.67 (3.34)	7 7.78 (3.44)	-10.44	[-19.66; -1.23]	0.028
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.421				
Eculizumab	30 -3.76 (2.66)	14 4.52 (4.02)	-8.28	[-18.33; 1.77]	0.103
Ravulizumab	14 4.46 (3.11)	5 3.35 (5.40)	1.10	[-12.29; 14.50]	0.859
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.007				
No	23 -2.20 (2.60)	8 -5.91 (4.25)	3.70	[-6.27; 13.68]	0.454
Yes	21 -1.12 (2.41)	11 7.99 (3.83)	-9.11	[-17.82; -0.41]	0.041
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.374				
< 2	29 -1.45 (2.69)	13 0.69 (3.85)	-2.14	[-11.78; 7.49]	0.653
≥ 2	15 -1.97 (3.20)	6 5.66 (5.72)	-7.63	[-19.99; 4.74]	0.210
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.789				
Europe	34 -0.35 (2.24)	15 6.32 (3.51)	-6.67	[-14.61; 1.26]	0.098
Other	10 -4.67 (11.06)	4 -2.49 (10.04)	-2.18	[-13.21; 8.85]	0.685
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Figure 5-2.2.3.1 QLQ-C30 - Pain: line chart of least squares mean change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Pain

Transfusion in the last 6 months prior to randomization: No



Iptacopan	23	21	23	22	22	23	23	23
Anti-C5 antibody	9	9	8	8	8	7	6	7

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

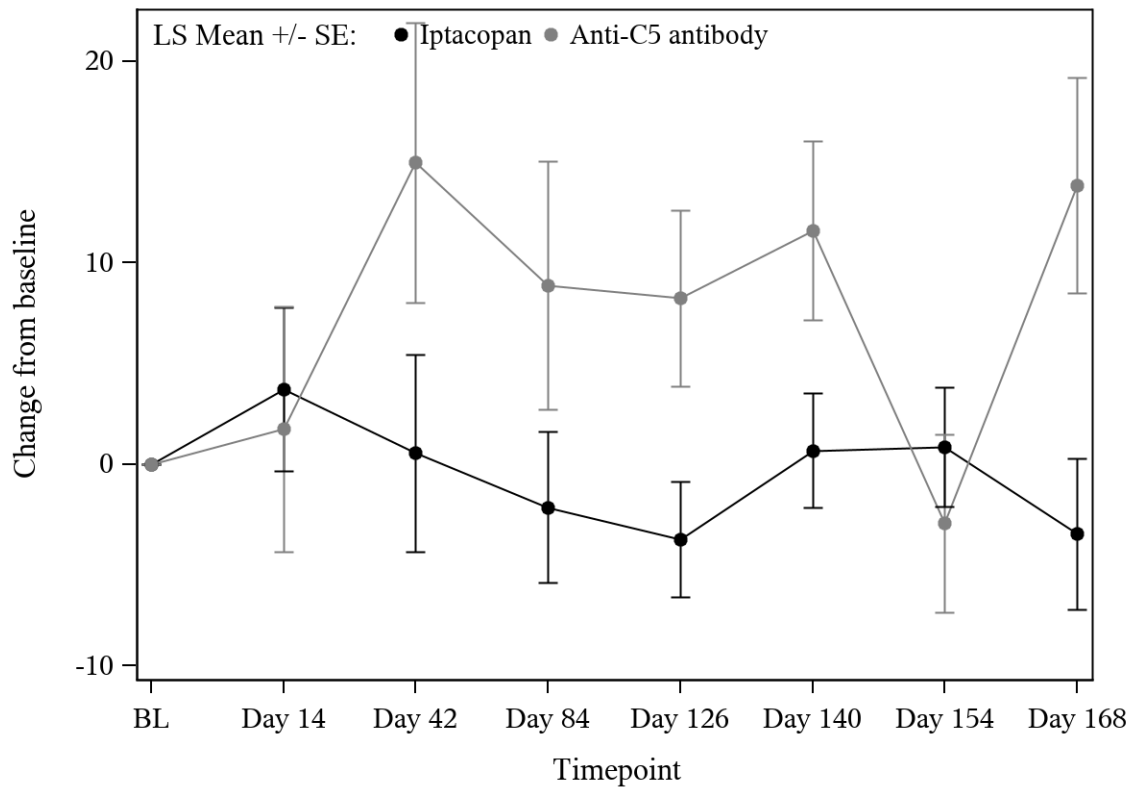
Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Pain

Transfusion in the last 6 months prior to randomization: Yes



Iptacopan	21	18	21	18	19	19	18	19
Anti-C5 antibody	12	8	12	9	9	9	10	11

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.

Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

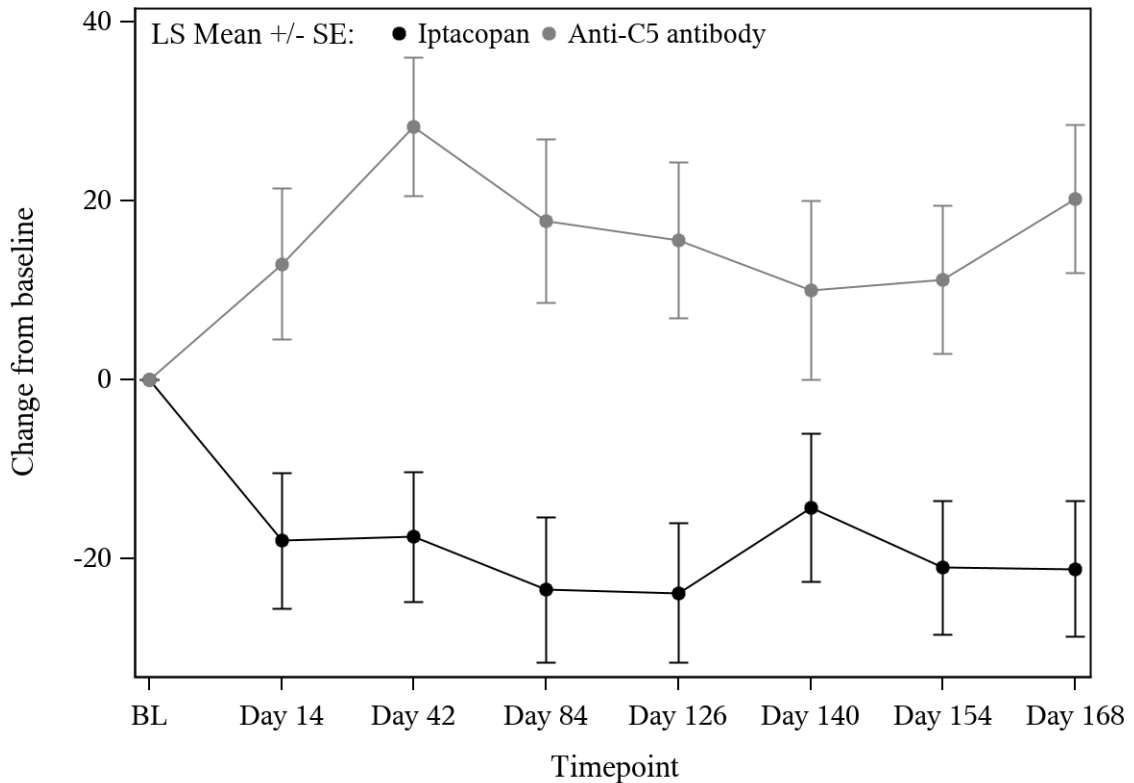
Table 5-2.2.4.1 QLQ-C30 - Dyspnoea: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Dyspnoea					
	N' LS Mean (SE)				
Length of time since diagnosis					
Interaction test	p = 0.525				
< 5 years	11 -19.51 (7.23)	7 -0.52 (8.92)	-18.99	[-39.12; 1.14]	0.063
≥ 5 years	33 -18.64 (2.52)	12 3.69 (4.12)	-22.34	[-31.86; -12.81]	<0.001
Age categories					
Interaction test	p = 0.022				
< 45 years	16 -22.20 (6.92)	8 12.13 (7.13)	-34.33	[-50.52; -18.14]	<0.001
≥ 45 years	28 -16.74 (2.87)	11 -1.29 (4.82)	-15.45	[-26.77; -4.13]	0.009
Sex					
Interaction test	p = 0.621				
Male	14 -11.99 (5.16)	6 3.88 (6.84)	-15.86	[-32.33; 0.60]	0.058
Female	30 -18.18 (2.76)	13 0.61 (4.29)	-18.80	[-29.02; -8.58]	<0.001
Baseline hemoglobin					
Interaction test	p = 0.224				
< 9 g/dL	22 -13.31 (3.43)	8 0.50 (6.68)	-13.80	[-28.58; 0.97]	0.066
≥ 9 g/dL	22 -25.83 (4.21)	11 1.62 (4.87)	-27.45	[-39.28; -15.63]	<0.001
History of MAVE prior to screening					
Interaction test	p = 0.019				
No	34 -16.63 (2.88)	12 -1.84 (4.79)	-14.79	[-25.73; -3.85]	0.009
Yes	10 -20.59 (98.46)	7 12.20 (82.56)	-32.79	[-1455.38; 1389.80]	0.819
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.862				
Eculizumab	30 -14.98 (2.95)	14 5.66 (4.38)	-20.64	[-31.49; -9.78]	<0.001
Ravulizumab	14 -22.68 (4.55)	5 -1.50 (7.98)	-21.18	[-40.75; -1.61]	0.036
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.921				
No	23 -22.91 (3.29)	8 -2.66 (5.27)	-20.25	[-32.45; -8.06]	0.002
Yes	21 -14.61 (4.05)	11 3.98 (6.71)	-18.59	[-33.05; -4.12]	0.014
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.377				
< 2	29 -23.16 (2.73)	13 2.87 (3.91)	-26.04	[-35.64; -16.43]	<0.001
≥ 2	15 -7.71 (6.15)	6 10.54 (10.56)	-18.26	[-38.87; 2.36]	0.079
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.145				
Europe	34 -19.70 (2.94)	15 5.72 (4.67)	-25.42	[-35.82; -15.01]	<0.001
Other	10 -15.91 (3.49)	4 -4.59 (5.03)	-11.32	[-24.23; 1.60]	0.083
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Figure 5-2.2.4.1 QLQ-C30 - Dyspnoea: line chart of least squares mean change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Dyspnoea
Age categories: < 45 years



Iptacopan	16	15	16	15	14	15	15	15
Anti-C5 antibody	9	8	9	9	7	7	7	8

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

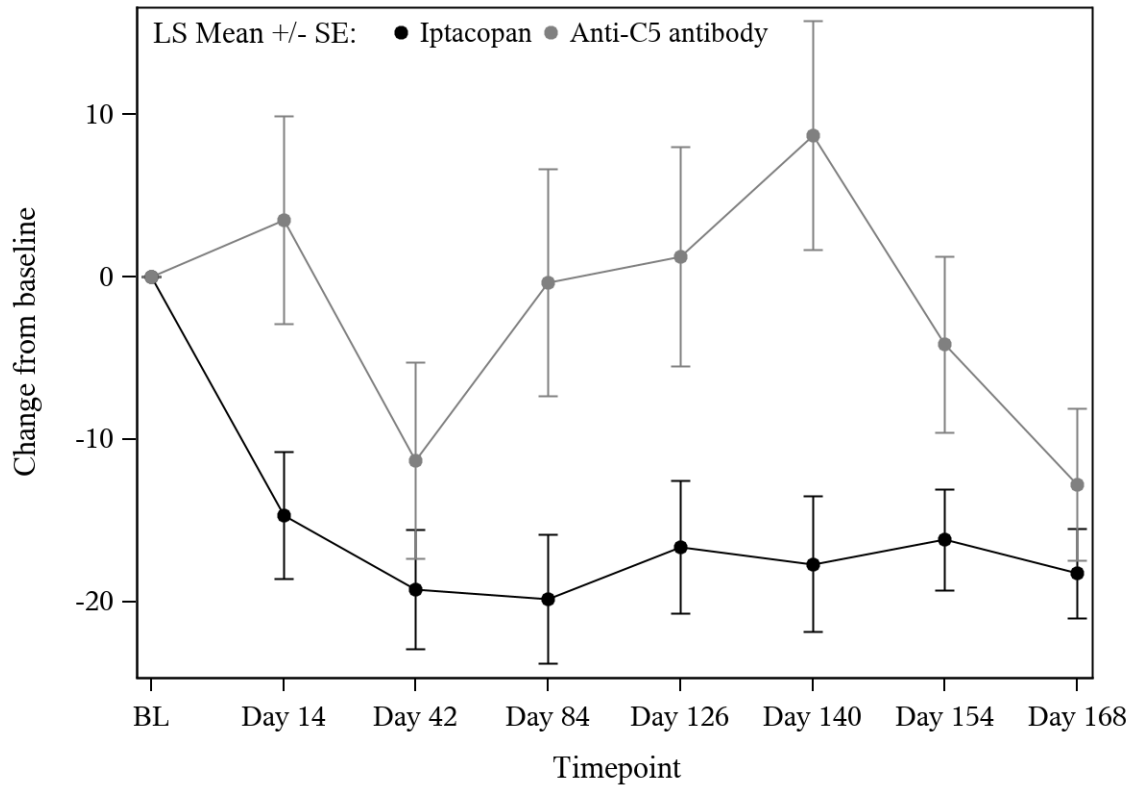
Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Dyspnoea
Age categories: ≥ 45 years



Iptacopan	28	24	28	25	27	27	26	27
Anti-C5 antibody	12	9	11	8	10	9	9	10

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

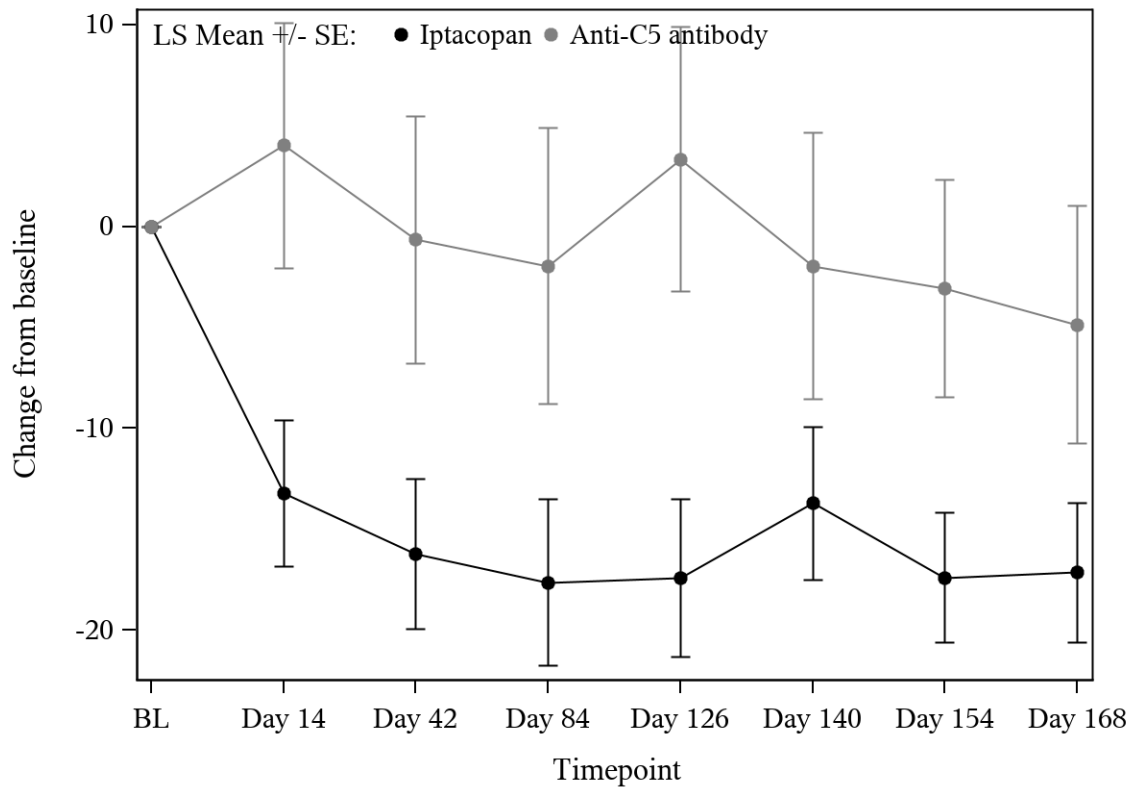
Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.

Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Dyspnoea
History of MAVE prior to screening: No



Iptacopan	34	29	34	31	31	32	31	32
Anti-C5 antibody	14	10	13	11	10	10	11	11

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

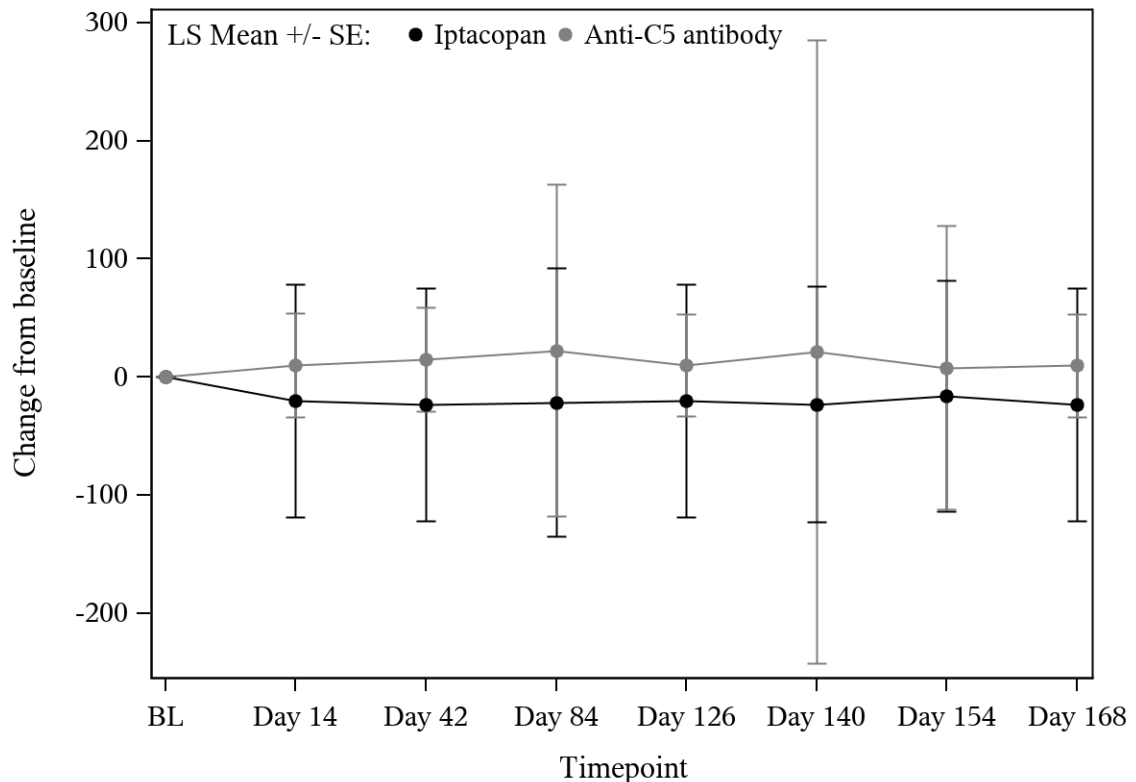
Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.

Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Dyspnoea
History of MAVE prior to screening: Yes



Iptacopan	10	10	10	9	10	10	10	10
Anti-C5 antibody	7	7	7	6	7	6	5	7

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.

Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

Table 5-2.2.5.1 QLQ-C30 - Insomnia: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Insomnia					
	N' LS Mean (SE)				
Length of time since diagnosis					
Interaction test	p = 0.145				
< 5 years	11 -2.12 (6.37)	7 -4.71 (7.41)	2.59	[-13.97; 19.15]	0.743
≥ 5 years	33 -10.72 (3.15)	12 -0.52 (5.19)	-10.21	[-22.29; 1.88]	0.096
Age categories					
Interaction test	p = 0.902				
< 45 years	16 -16.20 (5.87)	8 -7.71 (6.50)	-8.49	[-23.49; 6.52]	0.252
≥ 45 years	28 -9.75 (3.41)	11 -3.45 (5.64)	-6.30	[-19.59; 7.00]	0.343
Sex					
Interaction test	p = 0.259				
Male	14 -18.18 (5.05)	6 -5.85 (5.31)	-12.33	[-23.77; -0.89]	0.036
Female	30 -5.51 (3.59)	13 -3.54 (5.32)	-1.96	[-14.73; 10.80]	0.757
Baseline hemoglobin					
Interaction test	p = 0.635				
< 9 g/dL	22 -7.50 (4.25)	8 -0.39 (7.73)	-7.11	[-24.64; 10.42]	0.413
≥ 9 g/dL	22 -10.10 (3.98)	11 -6.10 (5.02)	-4.00	[-16.43; 8.42]	0.515
History of MAVE prior to screening					
Interaction test	p = 0.505				
No	34 -7.18 (3.03)	12 -3.43 (5.04)	-3.76	[-15.29; 7.78]	0.515
Yes	10 -18.59 (6.74)	7 -1.02 (8.00)	-17.57	[-40.56; 5.42]	0.118
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.394				
Eculizumab	30 -8.12 (3.05)	14 -0.39 (4.55)	-7.72	[-18.73; 3.28]	0.164
Ravulizumab	14 -10.76 (5.35)	5 -13.39 (8.47)	2.63	[-18.33; 23.59]	0.792
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.890				
No	23 -9.85 (3.98)	8 -6.28 (6.65)	-3.57	[-19.50; 12.36]	0.650
Yes	21 -8.76 (3.71)	11 -2.90 (5.82)	-5.86	[-18.74; 7.02]	0.357
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.432				
< 2	29 -9.62 (3.56)	13 -1.35 (5.28)	-8.26	[-21.04; 4.52]	0.198
≥ 2	15 -7.02 (4.58)	6 -3.21 (8.06)	-3.81	[-19.56; 11.93]	0.617
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.368				
Europe	34 -10.31 (2.61)	15 -3.46 (4.09)	-6.85	[-15.92; 2.23]	0.138
Other	10 -5.85 (4.68)	4 -15.01 (6.96)	9.17	[-8.94; 27.27]	0.301
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Table 5-2.2.6.1 QLQ-C30 - Appetite loss: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Appetite loss					
	N' LS Mean (SE)	N' LS Mean (SE)			
Length of time since diagnosis					
Interaction test	p = 0.391				
< 5 years	11 0.69 (4.37)	7 4.71 (5.05)	-4.02	[-15.88; 7.84]	0.495
≥ 5 years	33 -5.67 (1.30)	12 5.49 (2.15)	-11.16	[-16.13; -6.18]	<0.001
Age categories					
Interaction test	p = 0.067				
< 45 years	16 -3.59 (3.08)	8 11.48 (3.45)	-15.06	[-23.19; -6.93]	<0.001
≥ 45 years	28 -3.98 (1.61)	11 1.59 (2.70)	-5.56	[-11.82; 0.70]	0.081
Sex					
Interaction test	p = 0.988				
Male	14 -2.07 (3.24)	6 6.19 (3.84)	-8.26	[-16.56; 0.04]	0.051
Female	30 -4.08 (1.80)	13 4.89 (2.73)	-8.97	[-15.40; -2.54]	0.007
Baseline hemoglobin					
Interaction test	p = 0.310				
< 9 g/dL	22 -4.39 (2.97)	8 10.76 (5.27)	-15.15	[-27.34; -2.96]	0.017
≥ 9 g/dL	22 -4.02 (1.85)	11 2.99 (2.43)	-7.01	[-12.97; -1.05]	0.023
History of MAVE prior to screening					
Interaction test	p = 0.423				
No	34 -4.64 (1.48)	12 3.54 (2.50)	-8.18	[-13.83; -2.53]	0.005
Yes	10 -1.81 (4.34)	7 8.55 (4.54)	-10.36	[-22.90; 2.19]	0.102
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.850				
Eculizumab	30 -4.91 (1.73)	14 6.20 (2.68)	-11.11	[-17.46; -4.76]	<0.001
Ravulizumab	14 -3.66 (2.17)	5 3.42 (3.64)	-7.08	[-15.74; 1.57]	0.105
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.634				
No	23 -6.33 (1.03)	8 -1.18 (1.92)	-5.15	[-9.52; -0.77]	0.023
Yes	21 -2.69 (2.94)	11 9.40 (4.40)	-12.09	[-22.38; -1.81]	0.023
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.244				
< 2	29 -6.39 (1.51)	13 4.18 (2.29)	-10.58	[-15.94; -5.22]	<0.001
≥ 2	15 -1.39 (2.88)	6 7.64 (4.88)	-9.03	[-19.38; 1.33]	0.085
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.157				
Europe	34 -3.17 (1.74)	15 8.38 (2.72)	-11.55	[-17.65; -5.45]	<0.001
Other	10 -8.32 (1.65)	4 -2.22 (2.38)	-6.10	[-12.11; -0.09]	0.047
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

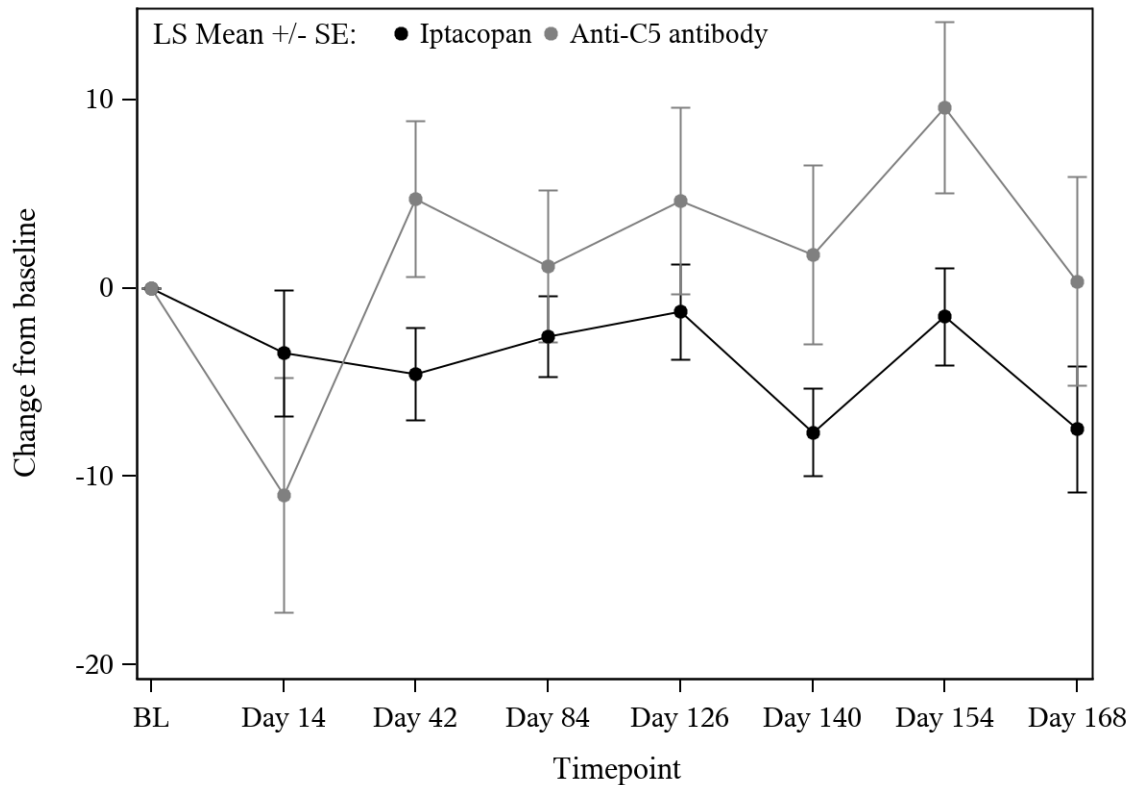
Table 5-2.2.7.1 QLQ-C30 - Constipation: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Constipation					
	N' LS Mean (SE)				
Length of time since diagnosis					
Interaction test	p = 0.919				
< 5 years	11 3.50 (2.40)	7 5.48 (2.94)	-1.98	[-8.76; 4.80]	0.554
≥ 5 years	33 -1.41 (1.27)	12 1.11 (2.10)	-2.52	[-7.33; 2.29]	0.302
Age categories					
Interaction test	p = 0.250				
< 45 years	16 0.98 (1.68)	8 -1.39 (1.95)	2.37	[-2.12; 6.85]	0.295
≥ 45 years	28 -1.47 (1.72)	11 2.88 (2.99)	-4.35	[-11.20; 2.51]	0.210
Sex					
Interaction test	p = 0.092				
Male	14 -1.06 (3.02)	6 -1.32 (3.96)	0.26	[-8.80; 9.31]	0.954
Female	30 -0.67 (1.26)	13 3.26 (1.92)	-3.93	[-8.45; 0.59]	0.088
Baseline hemoglobin					
Interaction test	p = 0.038				
< 9 g/dL	22 -2.63 (1.86)	8 5.94 (3.55)	-8.58	[-16.45; -0.70]	0.034
≥ 9 g/dL	22 -0.51 (2.06)	11 -3.80 (2.70)	3.29	[-3.16; 9.73]	0.306
History of MAVE prior to screening					
Interaction test	p = 0.950				
No	34 0.51 (1.29)	12 2.24 (2.18)	-1.72	[-6.65; 3.20]	0.489
Yes	10 -6.55 (2.41)	7 0.18 (2.54)	-6.73	[-13.61; 0.16]	0.055
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.157				
Eculizumab	30 -0.77 (1.41)	14 0.28 (2.17)	-1.05	[-6.18; 4.08]	0.686
Ravulizumab	14 0.36 (2.14)	5 6.63 (3.19)	-6.27	[-14.14; 1.60]	0.114
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.908				
No	23 -2.61 (1.30)	8 -1.29 (2.27)	-1.32	[-6.52; 3.89]	0.615
Yes	21 1.28 (1.98)	11 2.61 (3.03)	-1.33	[-8.28; 5.62]	0.702
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.408				
< 2	29 -1.92 (1.20)	13 0.39 (1.83)	-2.30	[-6.60; 2.00]	0.290
≥ 2	15 2.12 (2.79)	6 3.39 (4.99)	-1.27	[-11.90; 9.36]	0.810
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.084				
Europe	34 -0.90 (1.37)	15 0.05 (2.07)	-0.95	[-5.56; 3.66]	0.684
Other	10 2.19 (2.22)	4 11.55 (3.41)	-9.36	[-17.42; -1.31]	0.025
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Figure 5-2.2.7.1 QLQ-C30 - Constipation: line chart of least squares mean change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Constipation
Baseline hemoglobin: < 9 g/dL



Iptacopan	22	19	22	19	20	20	19	20
Anti-C5 antibody	9	6	9	7	6	6	7	8

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

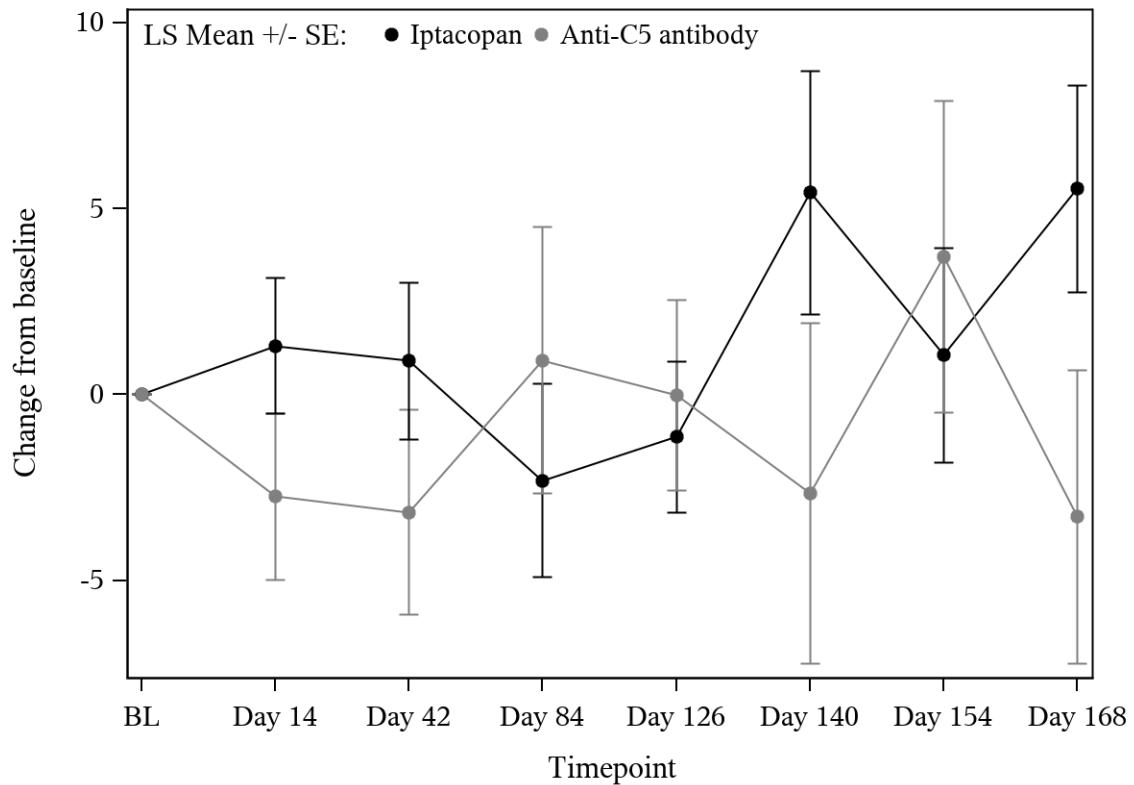
Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Constipation
Baseline hemoglobin: ≥ 9 g/dL



Iptacopan	22	20	22	21	21	22	22	22
Anti-C5 antibody	12	11	11	10	11	10	9	10

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.

Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

Table 5-2.2.8.1 QLQ-C30 - Diarrhoea: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Diarrhoea					
	N' LS Mean (SE)		N' LS Mean (SE)		
Length of time since diagnosis					
Interaction test	p = 0.480				
< 5 years	11 2.07 (3.87)	7 4.14 (4.57)	-2.07	[-11.21; 7.07]	0.647
≥ 5 years	33 1.48 (2.71)	12 6.13 (4.50)	-4.65	[-14.98; 5.69]	0.374
Age categories					
Interaction test	p = 0.951				
< 45 years	16 2.50 (3.36)	8 3.97 (3.80)	-1.46	[-10.28; 7.35]	0.740
≥ 45 years	28 2.12 (2.89)	11 5.23 (4.87)	-3.11	[-14.40; 8.18]	0.584
Sex					
Interaction test	p = 0.717				
Male	14 2.73 (5.70)	6 7.67 (8.59)	-4.94	[-26.52; 16.64]	0.634
Female	30 0.08 (1.80)	13 2.51 (2.69)	-2.44	[-8.85; 3.98]	0.445
Baseline hemoglobin					
Interaction test	p = 0.136				
< 9 g/dL	22 -1.32 (2.45)	8 8.06 (4.44)	-9.37	[-19.30; 0.55]	0.064
≥ 9 g/dL	22 1.19 (3.48)	11 1.19 (4.27)	-0.00	[-10.37; 10.36]	1.000
History of MAVE prior to screening					
Interaction test	p = 0.557				
No	34 0.05 (2.02)	12 0.67 (3.23)	-0.62	[-7.93; 6.69]	0.864
Yes	10 10.06 (7.54)	7 16.06 (8.75)	-6.00	[-30.92; 18.91]	0.612
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.313				
Eculizumab	30 0.87 (2.57)	14 7.07 (3.91)	-6.19	[-15.55; 3.17]	0.192
Ravulizumab	14 2.28 (3.03)	5 0.33 (5.32)	1.95	[-10.61; 14.51]	0.751
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.084				
No	23 5.24 (3.22)	8 -1.12 (5.19)	6.36	[-6.13; 18.86]	0.307
Yes	21 -1.86 (2.06)	11 6.67 (2.98)	-8.53	[-15.78; -1.29]	0.023
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.111				
< 2	29 2.31 (2.57)	13 0.20 (3.85)	2.12	[-7.01; 11.24]	0.646
≥ 2	15 2.90 (2.87)	6 15.70 (4.71)	-12.80	[-23.05; -2.55]	0.016
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.658				
Europe	34 3.02 (2.52)	15 6.38 (3.83)	-3.36	[-12.15; 5.43]	0.450
Other	10 -0.15 (4.34)	4 -4.22 (6.14)	4.07	[-12.74; 20.88]	0.613
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

5-2.3 EORTC QLQ-C30 QoL

Table 5-2.3.1.1 QLQ-C30 - Global health status: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Global health status					
	N' LS Mean (SE)		N' LS Mean (SE)		
Length of time since diagnosis					
Interaction test	p = 0.352				
< 5 years	11 9.01 (3.79)	7 -1.59 (4.88)	10.60	[-1.55; 22.75]	0.082
≥ 5 years	33 12.59 (1.74)	12 -3.37 (2.81)	15.96	[9.42; 22.49]	<0.001
Age categories					
Interaction test	p = 0.686				
< 45 years	16 14.44 (4.01)	8 -1.18 (4.09)	15.63	[6.12; 25.13]	0.003
≥ 45 years	28 9.47 (2.00)	11 -4.06 (3.44)	13.52	[5.56; 21.49]	0.002
Sex					
Interaction test	p = 0.130				
Male	14 8.08 (3.11)	6 2.07 (4.36)	6.01	[-4.43; 16.44]	0.241
Female	30 11.54 (2.04)	13 -5.53 (3.09)	17.07	[9.73; 24.41]	<0.001
Baseline hemoglobin					
Interaction test	p = 0.803				
< 9 g/dL	22 9.35 (1.96)	8 -7.60 (3.84)	16.96	[8.40; 25.52]	<0.001
≥ 9 g/dL	22 13.36 (3.16)	11 0.08 (3.76)	13.29	[4.19; 22.38]	0.006
History of MAVE prior to screening					
Interaction test	p = 0.867				
No	34 10.50 (1.99)	12 -4.53 (3.27)	15.03	[7.68; 22.38]	<0.001
Yes	10 10.56 (3.77)	7 -3.35 (4.08)	13.91	[1.88; 25.94]	0.027
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.437				
Eculizumab	30 11.10 (2.12)	14 -5.39 (3.13)	16.50	[8.88; 24.11]	<0.001
Ravulizumab	14 9.57 (2.32)	5 1.25 (4.06)	8.32	[-1.43; 18.08]	0.089
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.051				
No	23 11.73 (2.22)	8 4.88 (3.64)	6.85	[-1.77; 15.47]	0.115
Yes	21 9.62 (2.16)	11 -8.30 (3.30)	17.92	[10.46; 25.38]	<0.001
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.709				
< 2	29 11.78 (2.14)	13 -1.50 (3.04)	13.28	[5.88; 20.68]	<0.001
≥ 2	15 14.01 (4.19)	6 -2.46 (6.41)	16.47	[1.57; 31.38]	0.033
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.229				
Europe	34 12.31 (1.73)	15 -3.82 (2.68)	16.13	[10.12; 22.14]	<0.001
Other	10 10.65 (3.14)	4 3.87 (4.87)	6.78	[-4.54; 18.10]	0.227
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Table 5-2.3.2.1 QLQ-C30 - Physical functioning: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Physical functioning					
	N' LS Mean (SE)		N' LS Mean (SE)		
Length of time since diagnosis					
Interaction test	p = 0.057				
< 5 years	11 6.19 (4.39)	7 1.05 (5.30)	5.14	[-7.02; 17.31]	0.355
≥ 5 years	33 12.80 (2.16)	12 -3.25 (3.53)	16.05	[7.74; 24.37]	<0.001
Age categories					
Interaction test	p = 0.545				
< 45 years	16 15.76 (2.89)	8 1.55 (2.96)	14.21	[6.94; 21.48]	<0.001
≥ 45 years	28 7.68 (1.99)	11 -3.51 (3.36)	11.19	[3.29; 19.08]	0.007
Sex					
Interaction test	p = 0.365				
Male	14 6.97 (3.83)	6 -4.74 (4.57)	11.71	[0.63; 22.78]	0.040
Female	30 12.10 (2.25)	13 -1.31 (3.39)	13.41	[5.30; 21.52]	0.002
Baseline hemoglobin					
Interaction test	p = 0.548				
< 9 g/dL	22 6.72 (2.63)	8 -4.03 (4.93)	10.76	[-0.39; 21.90]	0.058
≥ 9 g/dL	22 13.90 (2.34)	11 -0.17 (2.84)	14.08	[7.07; 21.08]	<0.001
History of MAVE prior to screening					
Interaction test	p = 0.743				
No	34 11.14 (2.22)	12 -0.96 (3.62)	12.10	[3.71; 20.49]	0.006
Yes	10 6.85 (3.25)	7 -1.59 (3.15)	8.44	[-0.70; 17.59]	0.068
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.330				
Eculizumab	30 9.71 (1.98)	14 -4.65 (2.96)	14.36	[7.11; 21.61]	<0.001
Ravulizumab	14 11.17 (2.89)	5 5.54 (4.82)	5.62	[-6.49; 17.74]	0.334
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.433				
No	23 14.95 (1.60)	8 5.38 (2.50)	9.57	[3.79; 15.36]	0.002
Yes	21 6.82 (2.88)	11 -6.07 (4.45)	12.89	[2.94; 22.84]	0.013
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.473				
< 2	29 11.94 (2.27)	13 -1.53 (3.12)	13.47	[5.66; 21.29]	0.001
≥ 2	15 9.51 (4.42)	6 -1.74 (7.25)	11.25	[-0.98; 23.47]	0.069
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.105				
Europe	34 10.28 (1.96)	15 -4.68 (3.01)	14.96	[8.26; 21.67]	<0.001
Other	10 12.15 (3.57)	4 1.10 (5.25)	11.05	[-3.49; 25.60]	0.119
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Table 5-2.3.3.1 QLQ-C30 - Role functioning: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Role functioning					
	N' LS Mean (SE)		N' LS Mean (SE)		
Length of time since diagnosis					
Interaction test	p = 0.597				
< 5 years	11 12.09 (6.95)	7 -2.34 (8.18)	14.43	[-4.19; 33.05]	0.118
≥ 5 years	33 12.73 (3.09)	12 -8.85 (5.00)	21.58	[9.91; 33.25]	<0.001
Age categories					
Interaction test	p = 0.572				
< 45 years	16 13.23 (6.63)	8 -11.45 (6.91)	24.68	[8.67; 40.69]	0.004
≥ 45 years	28 7.91 (2.91)	11 -7.60 (4.90)	15.51	[4.02; 27.00]	0.010
Sex					
Interaction test	p = 0.360				
Male	14 8.42 (7.72)	6 -9.93 (8.83)	18.35	[-1.08; 37.79]	0.062
Female	30 13.18 (3.25)	13 -7.24 (4.89)	20.41	[8.68; 32.14]	0.001
Baseline hemoglobin					
Interaction test	p = 0.397				
< 9 g/dL	22 8.08 (3.95)	8 -17.45 (7.19)	25.53	[9.29; 41.78]	0.003
≥ 9 g/dL	22 14.93 (4.05)	11 -1.74 (4.98)	16.67	[4.47; 28.87]	0.009
History of MAVE prior to screening					
Interaction test	p = 0.363				
No	34 12.48 (3.32)	12 -8.13 (5.43)	20.61	[8.12; 33.11]	0.002
Yes	10 3.85 (3.99)	7 -7.36 (4.69)	11.21	[-1.73; 24.15]	0.084
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.391				
Eculizumab	30 9.34 (3.28)	14 -11.77 (4.85)	21.12	[9.27; 32.96]	<0.001
Ravulizumab	14 10.77 (4.10)	5 -3.87 (7.01)	14.64	[-2.57; 31.85]	0.090
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.279				
No	23 15.01 (3.33)	8 0.21 (5.37)	14.80	[2.32; 27.28]	0.022
Yes	21 7.04 (4.20)	11 -12.96 (6.36)	20.00	[5.58; 34.42]	0.008
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.922				
< 2	29 12.60 (3.30)	13 -6.54 (4.62)	19.13	[7.74; 30.53]	0.002
≥ 2	15 8.84 (6.73)	6 -12.31 (9.93)	21.15	[0.47; 41.83]	0.045
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.417				
Europe	34 11.78 (3.30)	15 -9.44 (5.05)	21.22	[9.79; 32.65]	<0.001
Other	10 11.76 (6.67)	4 -7.57 (10.30)	19.33	[-7.50; 46.17]	0.133
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

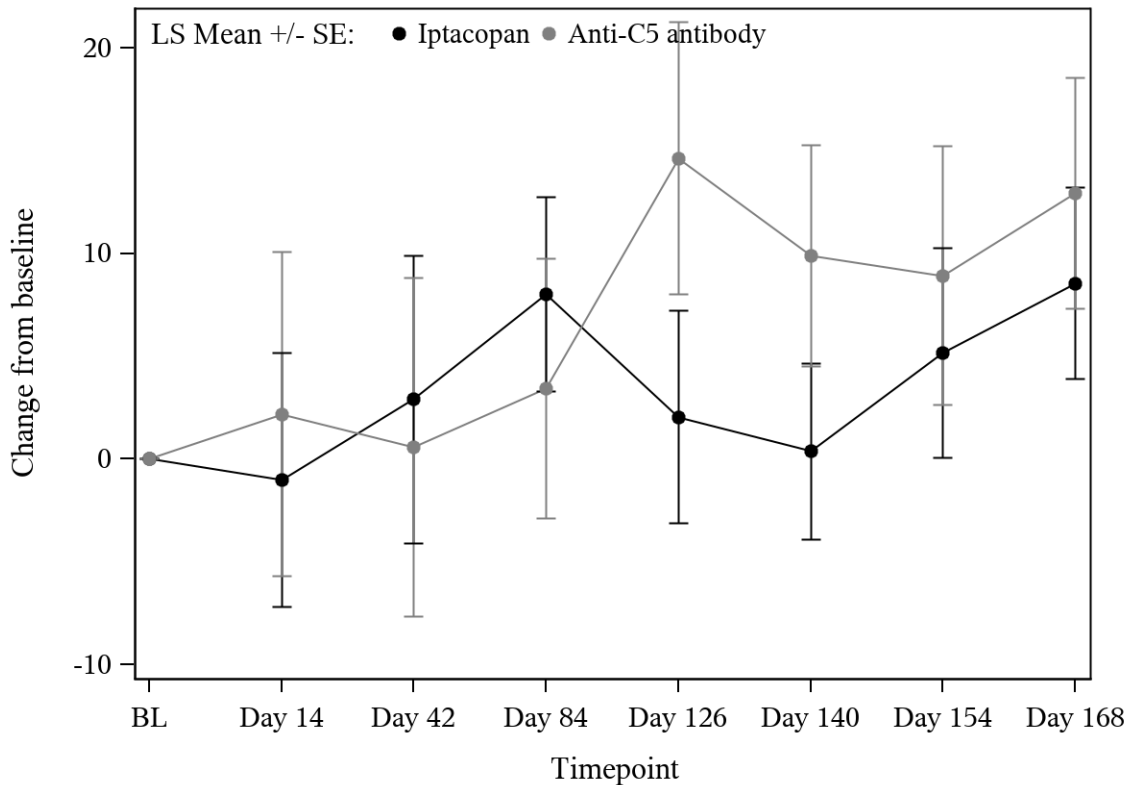
Table 5-2.3.4.1 QLQ-C30 - Emotional functioning: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Emotional functioning					
	N' LS Mean (SE)	N' LS Mean (SE)			
Length of time since diagnosis					
Interaction test	p = 0.009				
< 5 years	11 5.00 (4.19)	7 12.56 (5.15)	-7.56	[-20.63; 5.51]	0.236
≥ 5 years	33 9.09 (2.77)	12 -4.36 (4.51)	13.45	[2.91; 24.00]	0.014
Age categories					
Interaction test	p = 0.450				
< 45 years	16 10.63 (6.58)	8 1.63 (6.30)	9.01	[-5.19; 23.20]	0.201
≥ 45 years	28 4.09 (2.81)	11 -0.24 (4.59)	4.34	[-6.47; 15.15]	0.421
Sex					
Interaction test	p = 0.297				
Male	14 4.90 (4.33)	6 -5.06 (5.27)	9.96	[-2.25; 22.18]	0.103
Female	30 6.40 (2.93)	13 2.36 (4.40)	4.04	[-6.47; 14.56]	0.442
Baseline hemoglobin					
Interaction test	p = 0.923				
< 9 g/dL	22 2.71 (3.77)	8 -0.85 (6.64)	3.56	[-11.90; 19.02]	0.641
≥ 9 g/dL	22 10.93 (3.46)	11 3.91 (4.13)	7.02	[-3.16; 17.21]	0.169
History of MAVE prior to screening					
Interaction test	p = 0.139				
No	34 5.72 (2.74)	12 2.11 (4.58)	3.61	[-6.86; 14.08]	0.491
Yes	10 12.24 (5.85)	7 -2.54 (6.61)	14.79	[-3.74; 33.31]	0.108
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.522				
Eculizumab	30 6.04 (2.71)	14 -2.58 (4.03)	8.62	[-1.22; 18.46]	0.084
Ravulizumab	14 8.39 (4.33)	5 6.18 (7.33)	2.21	[-16.18; 20.61]	0.801
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.860				
No	23 8.35 (3.06)	8 2.19 (5.09)	6.16	[-6.11; 18.43]	0.313
Yes	21 5.94 (3.65)	11 -1.12 (5.50)	7.06	[-5.63; 19.75]	0.265
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.787				
< 2	29 8.24 (2.67)	13 0.15 (3.94)	8.08	[-1.43; 17.59]	0.093
≥ 2	15 0.87 (5.31)	6 -6.39 (8.57)	7.26	[-10.01; 24.53]	0.385
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.188				
Europe	34 6.81 (2.29)	15 -2.71 (3.52)	9.52	[1.68; 17.36]	0.018
Other	10 5.48 (5.63)	4 6.93 (9.54)	-1.44	[-22.13; 19.25]	0.884
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Figure 5-2.3.4.1 QLQ-C30 - Emotional functioning: line chart of least squares mean change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Emotional functioning
Length of time since diagnosis: < 5 years



Iptacopan	11	10	11	9	9	11	11	11
Anti-C5 antibody	8	6	8	6	6	6	6	7

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

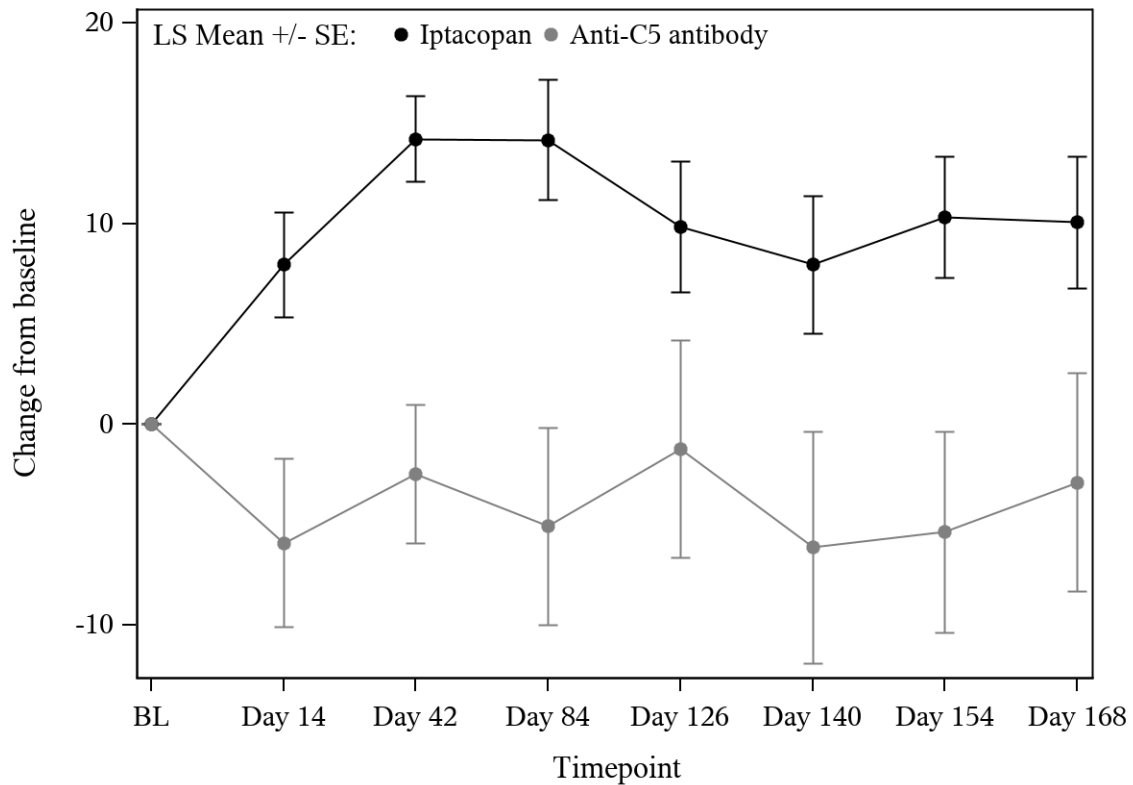
Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Emotional functioning
Length of time since diagnosis: ≥ 5 years



Iptacopan	33	29	33	31	32	31	30	31
Anti-C5 antibody	13	11	12	11	11	10	10	11

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.

Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

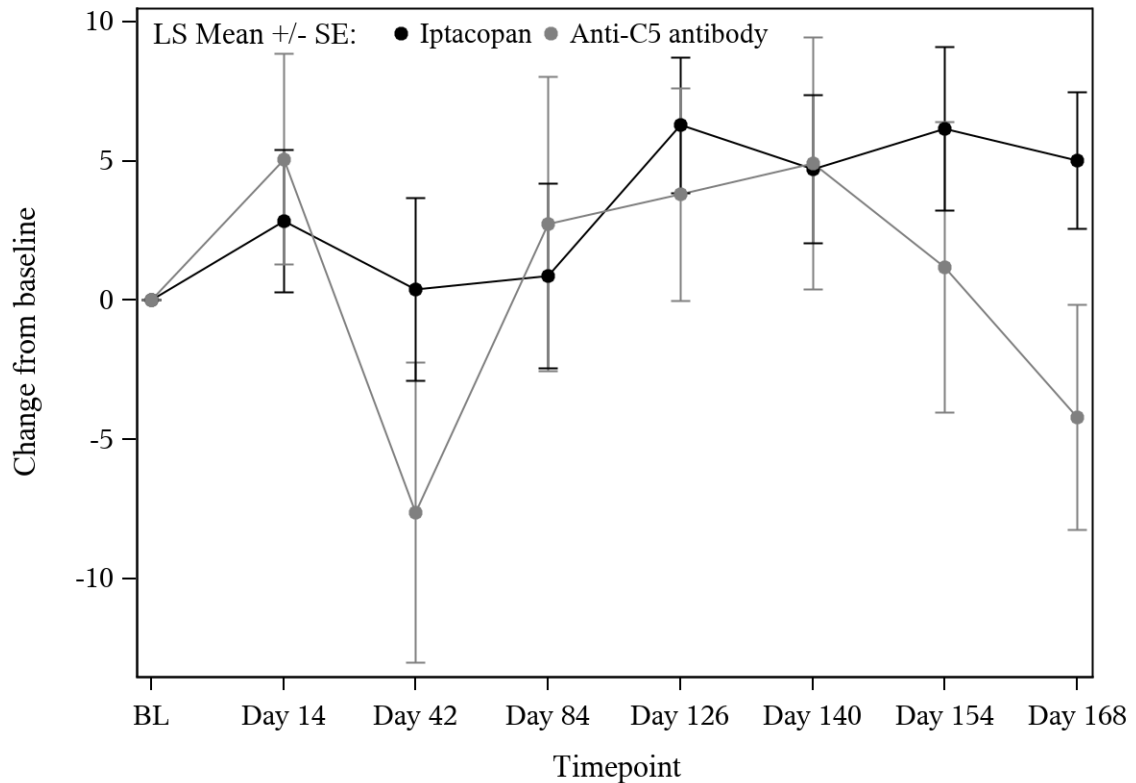
Table 5-2.3.5.1 QLQ-C30 - Cognitive functioning: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Cognitive functioning					
	N' LS Mean (SE)	N' LS Mean (SE)			
Length of time since diagnosis					
Interaction test	p = 0.753				
< 5 years	11 15.69 (8.18)	7 9.00 (10.45)	6.69	[-19.40; 32.77]	0.525
≥ 5 years	33 9.12 (2.21)	12 -7.40 (3.66)	16.52	[7.94; 25.09]	<0.001
Age categories					
Interaction test	p = 0.502				
< 45 years	16 13.82 (7.00)	8 -5.28 (7.37)	19.11	[4.28; 33.93]	0.014
≥ 45 years	28 5.72 (2.09)	11 -6.74 (3.46)	12.46	[4.37; 20.56]	0.004
Sex					
Interaction test	p = 0.553				
Male	14 6.93 (5.95)	6 -7.15 (7.04)	14.09	[-3.23; 31.41]	0.100
Female	30 8.45 (2.34)	13 -4.98 (3.52)	13.43	[4.98; 21.88]	0.003
Baseline hemoglobin					
Interaction test	p = 0.746				
< 9 g/dL	22 4.56 (2.72)	8 -8.39 (5.06)	12.95	[1.64; 24.27]	0.026
≥ 9 g/dL	22 13.51 (3.49)	11 -3.50 (4.22)	17.00	[6.71; 27.30]	0.002
History of MAVE prior to screening					
Interaction test	p = 0.163				
No	34 7.24 (2.26)	12 -2.50 (3.66)	9.73	[1.37; 18.10]	0.024
Yes	10 4.31 (4.99)	7 -12.52 (5.08)	16.83	[2.18; 31.48]	0.028
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.550				
Eculizumab	30 7.12 (2.49)	14 -7.85 (3.65)	14.97	[5.99; 23.95]	0.002
Ravulizumab	14 8.34 (3.49)	5 -2.99 (6.17)	11.34	[-3.70; 26.37]	0.130
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.009				
No	23 8.93 (2.19)	8 4.81 (3.56)	4.12	[-4.16; 12.39]	0.318
Yes	21 6.44 (3.37)	11 -15.48 (5.19)	21.92	[10.45; 33.39]	<0.001
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.961				
< 2	29 9.63 (2.63)	13 -4.33 (3.68)	13.96	[4.93; 22.99]	0.003
≥ 2	15 4.02 (3.96)	6 -13.98 (6.54)	18.01	[4.32; 31.69]	0.013
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.199				
Europe	34 8.07 (2.39)	15 -9.02 (3.80)	17.09	[8.61; 25.57]	<0.001
Other	10 5.55 (2.67)	4 -5.63 (4.88)	11.18	[1.13; 21.23]	0.031
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Figure 5-2.3.5.1 QLQ-C30 - Cognitive functioning: line chart of least squares mean change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Cognitive functioning
Transfusion in the last 6 months prior to randomization: No



Iptacopan	23	21	23	22	22	23	23	23
Anti-C5 antibody	9	9	8	8	8	7	6	7

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

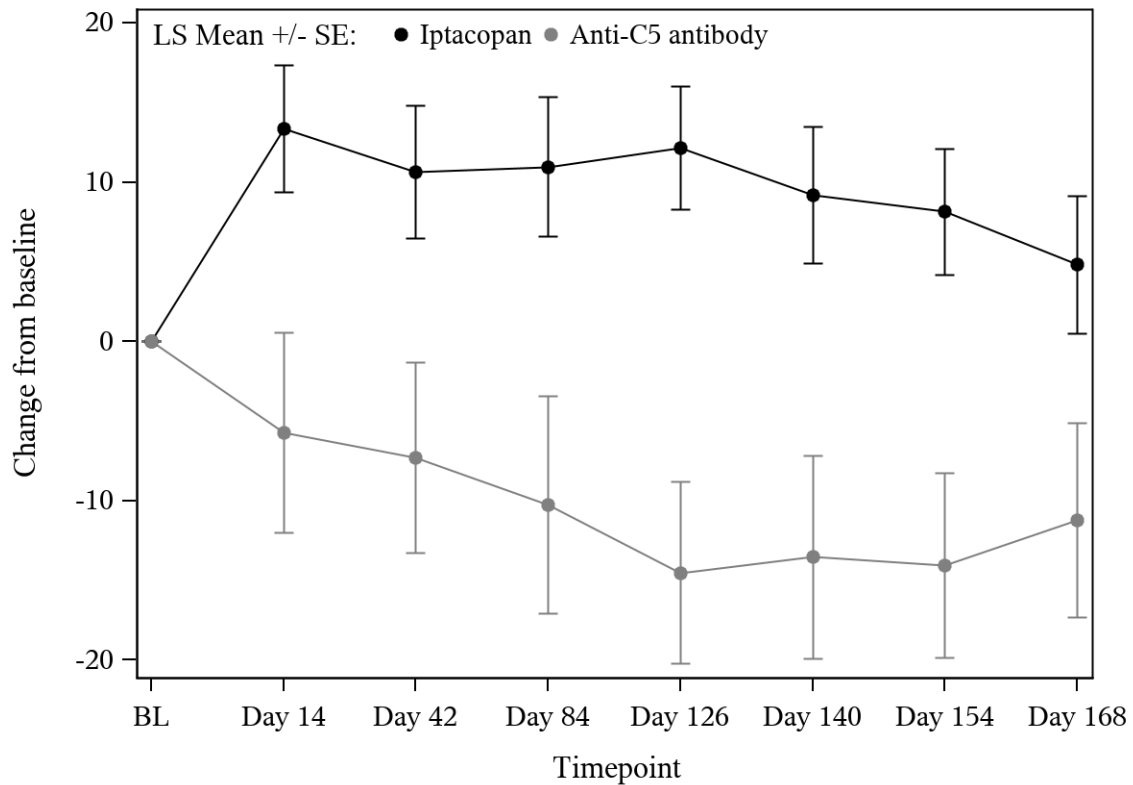
Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Cognitive functioning
Transfusion in the last 6 months prior to randomization: Yes



Iptacopan	21	18	21	18	19	19	18	19
Anti-C5 antibody	12	8	12	9	9	9	10	11

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.

Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

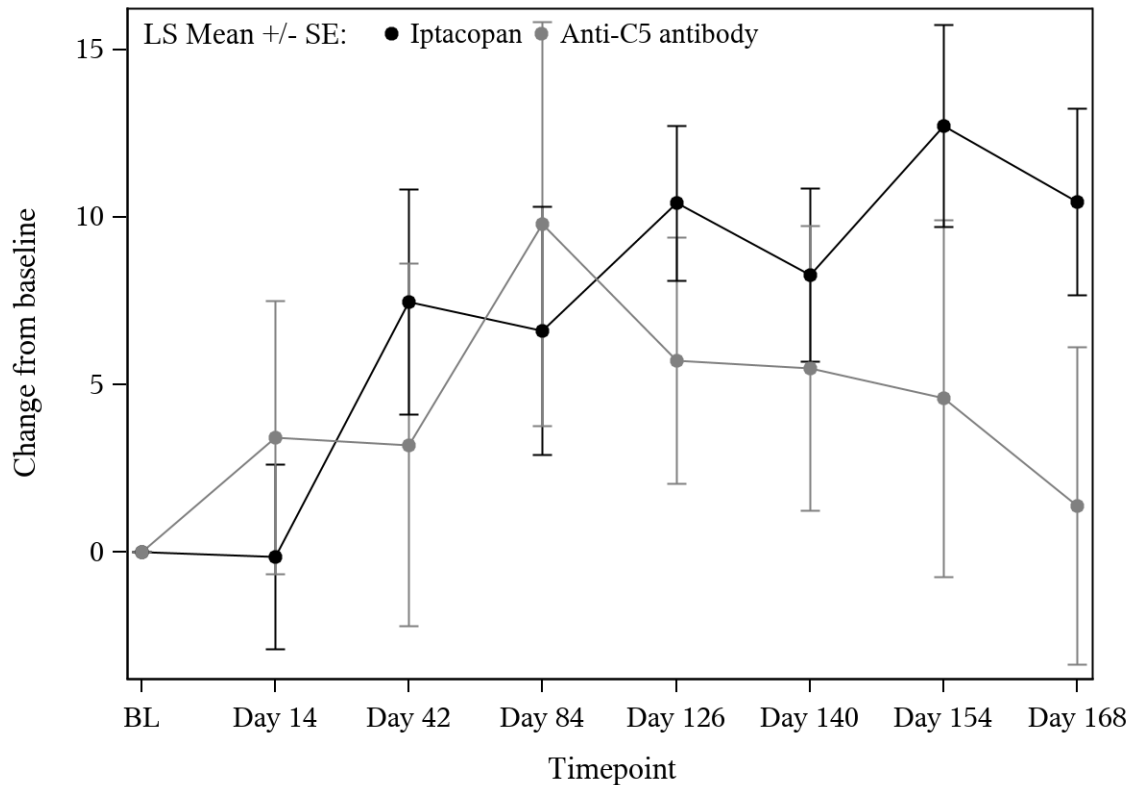
Table 5-2.3.6.1 QLQ-C30 - Social functioning: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
QLQ-C30 - Social functioning					
	N' LS Mean (SE)		N' LS Mean (SE)		
Length of time since diagnosis					
Interaction test	p = 0.429				
< 5 years	11 25.32 (7.24)	7 17.35 (8.75)	7.97	[-15.44; 31.39]	0.468
≥ 5 years	33 11.58 (2.39)	12 -6.65 (3.81)	18.23	[9.29; 27.16]	<0.001
Age categories					
Interaction test	p = 0.361				
< 45 years	16 19.16 (5.82)	8 -3.86 (6.23)	23.02	[8.90; 37.13]	0.003
≥ 45 years	28 5.01 (2.28)	11 -6.10 (3.74)	11.11	[2.39; 19.84]	0.014
Sex					
Interaction test	p = 0.473				
Male	14 9.51 (7.10)	6 -4.35 (7.56)	13.86	[-2.83; 30.55]	0.097
Female	30 10.79 (2.78)	13 -5.21 (4.15)	16.01	[6.05; 25.96]	0.002
Baseline hemoglobin					
Interaction test	p = 0.419				
< 9 g/dL	22 6.97 (3.58)	8 -13.83 (6.60)	20.81	[5.94; 35.68]	0.008
≥ 9 g/dL	22 13.43 (3.20)	11 0.62 (3.84)	12.81	[3.19; 22.44]	0.011
History of MAVE prior to screening					
Interaction test	p = 0.446				
No	34 10.51 (2.52)	12 -7.17 (4.22)	17.68	[8.12; 27.25]	<0.001
Yes	10 2.29 (4.39)	7 -5.93 (4.48)	8.22	[-4.40; 20.83]	0.191
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.119				
Eculizumab	30 9.96 (2.59)	14 -10.83 (4.02)	20.79	[11.24; 30.35]	<0.001
Ravulizumab	14 8.44 (2.72)	5 1.35 (4.69)	7.08	[-3.85; 18.01]	0.194
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.006				
No	23 13.40 (2.30)	8 7.23 (3.58)	6.17	[-2.39; 14.73]	0.151
Yes	21 5.97 (3.88)	11 -18.00 (5.80)	23.97	[10.78; 37.16]	<0.001
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.328				
< 2	29 10.22 (2.48)	13 -1.66 (3.42)	11.88	[3.26; 20.50]	0.008
≥ 2	15 3.41 (5.70)	6 -19.18 (9.32)	22.59	[3.66; 41.52]	0.022
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.438				
Europe	34 9.62 (2.49)	15 -7.97 (3.92)	17.58	[8.75; 26.41]	<0.001
Other	10 11.60 (4.02)	4 -3.53 (6.51)	15.13	[0.00; 30.26]	0.0499 9
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Figure 5-2.3.6.1 QLQ-C30 - Social functioning: line chart of least squares mean change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Social functioning
Transfusion in the last 6 months prior to randomization: No



Iptacopan	23	21	23	22	22	23	23	23
Anti-C5 antibody	9	9	8	8	8	7	6	7

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

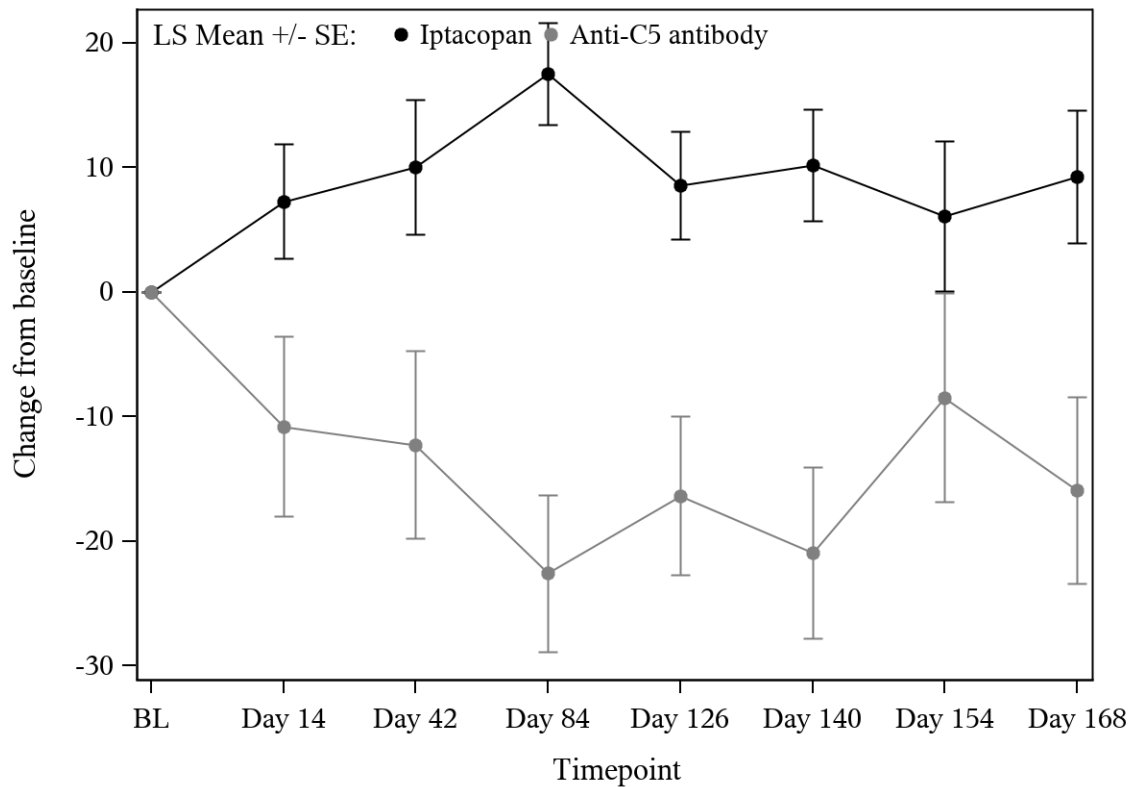
Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.
 Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

QLQ-C30 - Social functioning
Transfusion in the last 6 months prior to randomization: Yes



Iptacopan	21	18	21	18	19	19	18	19
Anti-C5 antibody	12	8	12	9	9	9	10	11

LS Mean: Least square mean
 SE: Standard error

Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
 Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment

If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor.

Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.

Intercurrent events stemming from breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values.

Missing values were not imputed, i.e. the analysis was based on observed data only.

Cut-off date for analysis: 06-Mar-2023

5-2.4 EQ-5D VAS

Table 5-2.4.1 EQ-5D VAS: MMRM analysis of change from baseline - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
EQ-5D VAS					
	N' LS Mean (SE)		N' LS Mean (SE)		
Length of time since diagnosis					
Interaction test	p = 0.122				
< 5 years	11 3.20 (3.95)	7 -2.48 (4.74)	5.68	[-5.80; 17.15]	0.307
≥ 5 years	33 11.75 (1.91)	12 -5.46 (3.04)	17.21	[10.09; 24.33]	<0.001
Age categories					
Interaction test	p = 0.666				
< 45 years	16 9.49 (3.92)	8 -5.29 (4.04)	14.78	[4.93; 24.64]	0.005
≥ 45 years	28 9.17 (2.25)	11 -2.98 (3.73)	12.16	[3.37; 20.94]	0.008
Sex					
Interaction test	p = 0.904				
Male	14 9.87 (3.05)	6 -1.56 (4.04)	11.43	[2.08; 20.77]	0.018
Female	30 9.11 (2.02)	13 -4.63 (3.08)	13.74	[6.42; 21.05]	<0.001
Baseline hemoglobin					
Interaction test	p = 0.912				
< 9 g/dL	22 7.04 (2.66)	8 -7.29 (4.80)	14.32	[3.43; 25.22]	0.012
≥ 9 g/dL	22 9.69 (2.75)	11 -3.66 (3.32)	13.35	[5.18; 21.52]	0.002
History of MAVE prior to screening					
Interaction test	p = 0.892				
No	34 9.46 (2.17)	12 -3.04 (3.47)	12.50	[4.49; 20.50]	0.003
Yes	10 4.57 (3.23)	7 -6.74 (3.12)	11.30	[2.22; 20.39]	0.018
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.855				
Eculizumab	30 7.72 (2.11)	14 -6.81 (3.10)	14.53	[6.95; 22.11]	<0.001
Ravulizumab	14 10.94 (2.88)	5 1.54 (4.95)	9.40	[-2.71; 21.51]	0.119
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.234				
No	23 9.66 (1.85)	8 0.88 (2.96)	8.78	[1.79; 15.77]	0.016
Yes	21 9.08 (3.02)	11 -6.07 (4.51)	15.14	[4.80; 25.48]	0.005
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.953				
< 2	29 8.58 (1.79)	13 -3.96 (2.48)	12.54	[6.34; 18.74]	<0.001
≥ 2	15 8.52 (4.63)	6 -3.45 (6.82)	11.97	[-3.43; 27.37]	0.121
Duration of anti-C5 treatment					
N.A. ⁺					

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	Adj. mean difference	[95% CI]	p-value
Region					
Interaction test	p = 0.335				
Europe	34 8.82 (1.78)	15 -6.57 (2.77)	15.39	[9.19; 21.59]	<0.001
Other	10 15.51 (3.09)	4 6.39 (4.58)	9.12	[-2.27; 20.51]	0.110
<p>N: Number of patients in the analysis set N': Number of patients with evaluable baseline and post-baseline score at visit CI: Confidence interval LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed </p> <p>Analysis method for interaction test: MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. The interaction test p-value is the type III p-value for the 2-fold interaction treatment * subgroup factor.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: Change from baseline = treatment + visit + treatment * visit + baseline value + baseline value * visit + transfusion history + prior anti-C5-treatment If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. Covariates transfusion history, prior anti-C5-treatment, sex and age were excluded from the model equation if they were connected to the subgroup factor. Anti-C5 antibody was the reference group for treatment group comparison. LS Means and comparisons are calculated at Day 126 - 168 as linear function of the parameter estimates.</p> <p>Patients with an evaluable baseline value and at least one evaluable post-baseline value were included in the analysis.</p> <p>Intercurrent events stemming from discontinuation of treatment, breakthrough haemolysis events, MAVEs and red blood cell transfusions were handled with a treatment policy strategy, i.e. data obtained after the occurrence were not replaced by imputed values. Missing values were not imputed, i.e. the analysis was based on observed data only.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

5-3 Subgroup analysis for safety

5-3.1 Adverse events overview

Table 5-3.1.1 Any adverse event: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
Any adverse event					
	n / N (%)	n / N (%)			
Length of time since diagnosis					
Interaction test	p = 0.177				
< 5 years	10 / 11 (90.9)	7 / 8 (87.5)	1.04	[0.75; 1.43]	0.816
≥ 5 years	24 / 33 (72.7)	13 / 14 (92.9)	0.78	[0.61; 1.01]	0.060
Age categories					
Interaction test	p = 0.899				
< 45 years	12 / 16 (75.0)	9 / 10 (90.0)	0.83	[0.59; 1.18]	0.308
≥ 45 years	22 / 28 (78.6)	11 / 12 (91.7)	0.86	[0.66; 1.11]	0.241
Sex					
Interaction test	p = 0.579				
Male	11 / 14 (78.6)	6 / 6 (100.0)	0.79	[0.60; 1.03]	0.084
Female	23 / 30 (76.7)	14 / 16 (87.5)	0.88	[0.67; 1.15]	0.339
Baseline hemoglobin					
Interaction test	p = 0.758				
< 9 g/dL	18 / 22 (81.8)	10 / 10 (100.0)	0.82	[0.67; 1.00]	0.046
≥ 9 g/dL	16 / 22 (72.7)	10 / 12 (83.3)	0.87	[0.61; 1.25]	0.458
History of MAVE prior to screening					
Interaction test	p = 0.111				
No	28 / 34 (82.4)	13 / 15 (86.7)	0.95	[0.74; 1.22]	0.692
Yes	6 / 10 (60.0)	7 / 7 (100.0)	0.60	[0.36; 1.00]	0.048
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.517				
Eculizumab	23 / 30 (76.7)	16 / 17 (94.1)	0.81	[0.65; 1.03]	0.081
Ravulizumab	11 / 14 (78.6)	4 / 5 (80.0)	0.98	[0.59; 1.65]	0.946
Transfusion in the last 6 months prior to randomization					
Interaction test	p = 0.273				
No	18 / 23 (78.3)	8 / 10 (80.0)	0.98	[0.67; 1.43]	0.909
Yes	16 / 21 (76.2)	12 / 12 (100.0)	0.76	[0.60; 0.97]	0.026
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.288				
< 2	23 / 29 (79.3)	13 / 15 (86.7)	0.92	[0.70; 1.20]	0.523
≥ 2	11 / 15 (73.3)	7 / 7 (100.0)	0.73	[0.54; 1.00]	0.046

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
Duration of anti-C5 treatment					
N.A. ⁺					
Region					
Interaction test					
	p = 0.189				
Europe	25 / 34 (73.5)	17 / 18 (94.4)	0.78	[0.62; 0.98]	0.033
Other	9 / 10 (90.0)	3 / 4 (75.0)	1.20	[0.66; 2.19]	0.553
<p>N: Number of patients in the analysis set n: Number of patients with event N.A.: Not applicable CI: Confidence interval RR: Relative risk TEAE: Treatment Emergent Adverse Event </p> <p>Analysis method for interaction test: Q-test for homogeneity of RR. In case of zero events in only one treatment arm in a subgroup, one patient with 0.5 events was added to each treatment arm in this subgroup.</p> <p>Analysis methods for within-subgroup analysis: OR, RR and RD with Wald 95% CI and p-value. For calculation of OR and RR, in case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>⁺ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p> <p>The table displays TEAE, defined as events that started during the on-treatment period. The on-treatment period for Iptacopan is from first dose date until 7 days after the date of last dose administered or the date of the day 168 visit, whichever is earlier. The on-treatment period for Anti-C5 is from first dose date until one day before the next planned dose or the date of the day 168 visit, whichever is earlier.</p> <p>Cut-off date for analysis: 06-Mar-2023</p>					

Table 5-3.1.2 Any severe adverse event: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.1.3 Any serious adverse event: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

5-3.2 Adverse events by SOC and PT

There is no data meeting the display criteria for this table.

5-3.3 Severe adverse events by SOC and PT

There is no data meeting the display criteria for this table.

5-3.4 Serious adverse events by SOC and PT

There is no data meeting the display criteria for this table.

5-3.5 Adverse events of special interest

Table 5-3.5.1 Decreased platelets: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.2 Severe decreased platelets: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.3 Serious decreased platelets: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.4 Infections caused by encapsulated bacteria: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.5 Severe infections caused by encapsulated bacteria: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.6 Serious infections caused by encapsulated bacteria: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.7 PNH Haemolysis and Thrombosis: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
PNH Haemolysis and Thrombosis					
	n / N (%)	n / N (%)			
Length of time since diagnosis					
Interaction test	p = 0.379				
< 5 years	0 / 11 (0.0)	2 / 8 (25.0)	0.15	[<0.01; 2.76]	0.201
≥ 5 years	7 / 33 (21.2)	5 / 14 (35.7)	0.59	[0.23; 1.55]	0.289
Age categories					
N.A.*					
Sex					
N.A.*					
Baseline hemoglobin					
N.A.*					
History of MAVE prior to screening					
Interaction test	p = 0.380				
No	6 / 34 (17.6)	4 / 15 (26.7)	0.66	[0.22; 2.01]	0.466
Yes	1 / 10 (10.0)	3 / 7 (42.9)	0.23	[0.03; 1.81]	0.163
Anti-C5 medication history 6 months prior to randomization					
Interaction test	p = 0.304				
Eculizumab	5 / 30 (16.7)	7 / 17 (41.2)	0.40	[0.15; 1.08]	0.071
Ravulizumab	2 / 14 (14.3)	0 / 5 (0.0)	2.00	[0.11; 35.81]	0.638
Transfusion in the last 6 months prior to randomization					
N.A.*					
Number of transfusions in the last 6 months prior to randomization					
Interaction test	p = 0.433				
< 2	6 / 29 (20.7)	5 / 15 (33.3)	0.62	[0.23; 1.70]	0.355
≥ 2	1 / 15 (6.7)	2 / 7 (28.6)	0.23	[0.03; 2.16]	0.200
Duration of anti-C5 treatment					
N.A.+					
Region					
Interaction test	p = 0.244				
Europe	5 / 34 (14.7)	7 / 18 (38.9)	0.38	[0.14; 1.02]	0.056
Other	2 / 10 (20.0)	0 / 4 (0.0)	2.27	[0.13; 39.15]	0.572

Treatment Groups		Comparison		
Iptacopan (N = 44)	Anti-C5 antibody (N = 22)	RR	[95% CI]	p-value
<p>N: Number of patients in the analysis set n: Number of patients with event N.A.: Not applicable CI: Confidence interval RR: Relative risk TEAE: Treatment Emergent Adverse Event </p> <p>Analysis method for interaction test: Q-test for homogeneity of RR. In case of zero events in only one treatment arm in a subgroup, one patient with 0.5 events was added to each treatment arm in this subgroup.</p> <p>Analysis methods for within-subgroup analysis: OR, RR and RD with Wald 95% CI and p-value. For calculation of OR and RR, in case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. Anti-C5 antibody was the reference group for treatment group comparison.</p> <p>[†] The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis. [*] The subgroup analysis is not presented as all subgroups have less than 10 events.</p> <p>The table shows all pre-specified AESIs which occurred in at least one patient.</p> <p>MedDRA Version: 25.0</p> <p>Cut-off date for analysis: 06-Mar-2023</p>				

Table 5-3.5.8 Severe pNH Haemolysis and Thrombosis: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.9 Serious pNH Haemolysis and Thrombosis: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.10 Serious or severe infections: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.11 Severe infections: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.12 Serious infections: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.13 Testicular effects: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.14 Severe testicular effects: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.15 Serious testicular effects: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.16 Thyroid changes: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.17 Severe thyroid changes: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.

Table 5-3.5.18 Serious thyroid changes: binary analysis - subgroup analysis (Safety Set)

There is no data meeting the display criteria for this table.
