Long-Term Efficacy and Safety of the Long Acting C5 Inhibitor Ravulizumab for the Treatment of Atypical Hemolytic Uremic Syndrome (aHUS) in Adults

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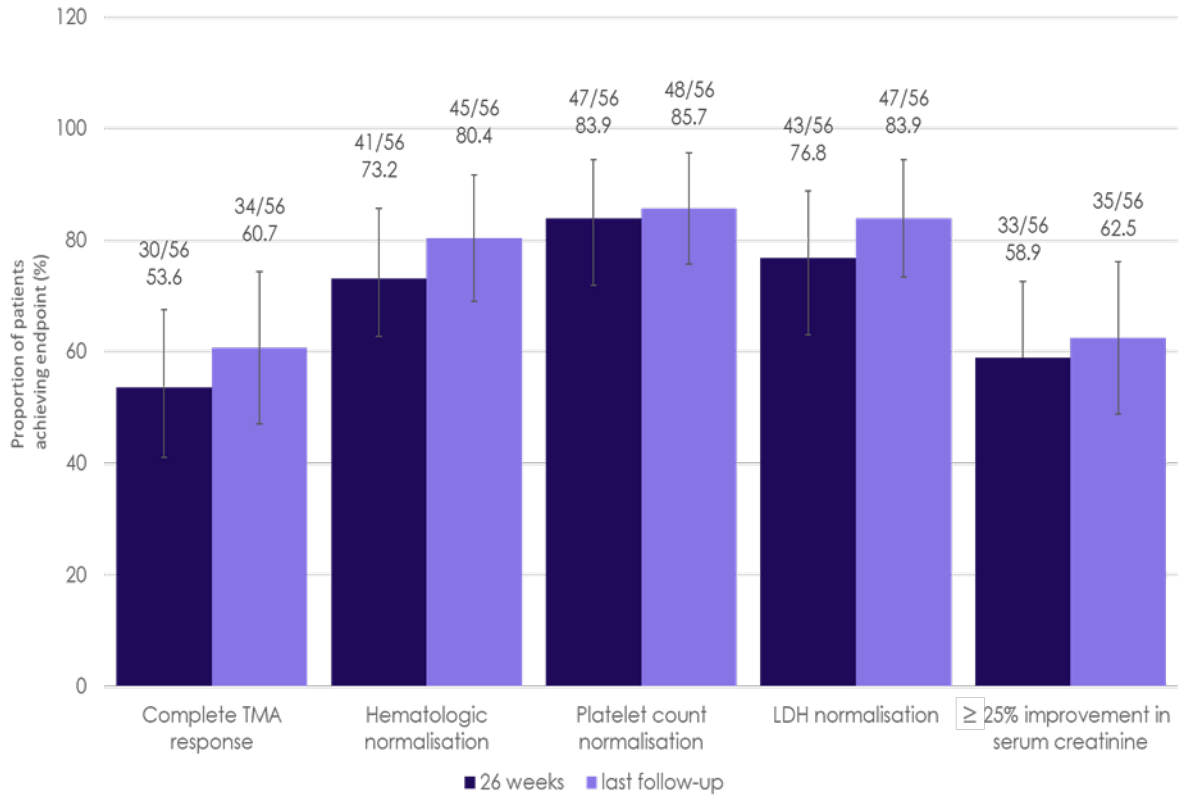
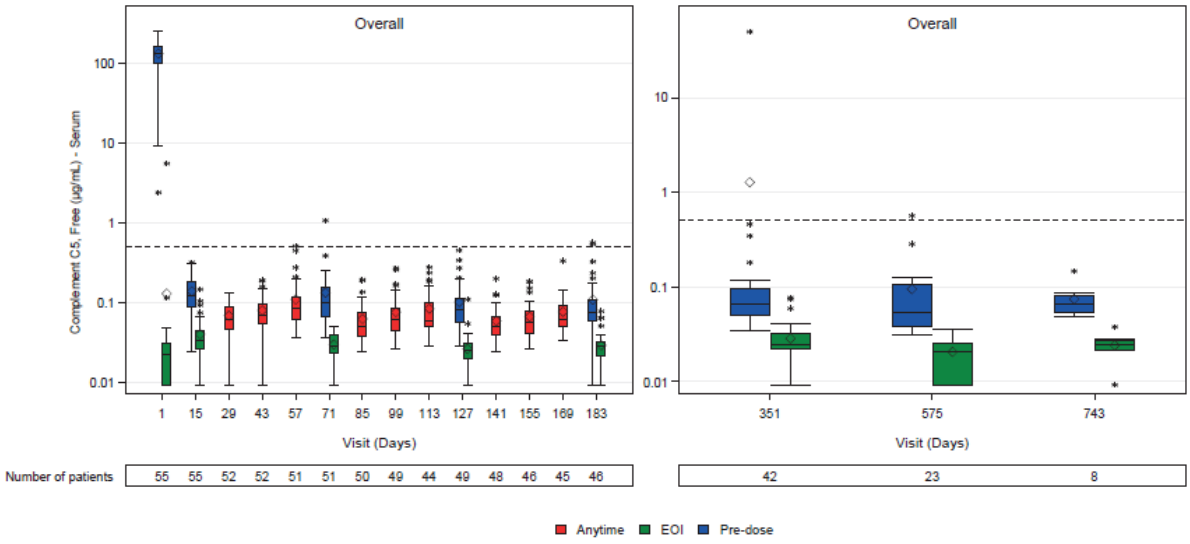
Supplementary materials

Supplementary Figure S1. Complete TMA response and its components during the initial 26 week and last available follow up



Supplementary Figure S2. Free complement C5 concentrations at each study visit following ravulizumab treatment

Pharmacodynamics of free C5 in serum concentration box plots over time (semi-log scale). Horizontal line is drawn at free C5 at 0.5 µg/ml to denote the threshold for complete terminal complement inhibition. The horizontal line in the middle of each box indicates the median, a diamond indicates the mean, and the top border and the bottom border of the boxes mark the 75th and 25th percentiles, respectively. The whiskers represent the highest and lowest values within 1.5 the interquartile range from the lower quartile and upper quartile. Outliers are represented by an asterisk beyond the whiskers.



Supplementary Table S1. Patient clinical characteristics at baseline, 26 weeks and 52 weeks

	Baseline (*N* =56)	**26 weeks (*N* =56)**		**52 weeks (*N* =49)**	
Variable	**Absolute value**	**Absolute value**	**Change from baseline**	**Absolute value**	**Change from baseline**
Serum LDH (U/L), median (min, max)	508.0 (229.5, 3249)	176.5 (118, 342)	-311 (-3072, +9)	187.0 (126, 540)	-294 (-3107, +81)
Platelet count (10^9/L), median (min, max)	95.3 (18, 473)	232 (86, 399)	+125 (-126, +338)	234.5 (115, 422)	+126 (-52, +335)
Hemoglobin (g/L), median (min, max)	85.0 (60.5, 140)	121 (87, 152)	+35 (-9, +69)	128.5 (89, 158)	+42 (-25, +84)
eGFR (mL/min/1.73m^2), median (min, max)[a,b]	10.0 (4, 80)	40 (2, 119)	29.00 (-13, 108)	42.5 (4, 117)	23.00 (-13, 95)
Increase in hemoglobin >20 g/L from baseline, n/m (%)	–	37/49 (66.1)	–	38/44 (86.4)	–

eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase.

[a]Median value is based on patients with eGFR data available at Day 351 only (N=44); [b]Median change from baseline is based on patients with eGFR data available at Day 1 and Day 351 (N=43).

Supplementary Table S2. Patient genetic analysis

Patient ID[a]	Clinician genetics findings summary[a,b]	Trial genetics[c]	Classification[d]	Continued to extension period? (Y/N)	Complete TMA response (Y/N)
1	N/A	Not tested	N/A	Y	N
2	No pathogenic variant	No pathogenic variant	No pathogenic variant	Y	Y
3	CD46	CD46 c.604C>T (p.Leu202Phe)	Likely pathogenic variant	Y	Y
4	N/A	CFB 6:31950377_A/G p.Lys533Arg	Pathogenic variant	Y	Y
5	N/A	Not tested	N/A	Y	N
6 KTx	N/A	No pathogenic variant	No pathogenic variant	Y	Y, in the extension period
7	No pathogenic variant	No pathogenic variant	No pathogenic variant	Y	N
8	CFHR5 c.485_486insAA; p.Glu163Lysfs*10	No pathogenic variant	No pathogenic variant	Y	N
9	N/A	No pathogenic variant	No pathogenic variant	Y	Y
10	N/A	No pathogenic variant	No pathogenic variant	Y	Y
11	No pathogenic variant, CFH autoantibodies not tested	CFH autoantibodies	No pathogenic variant CFH autoantibodies present	Y	Y

Patient ID[a]	Clinician genetics findings summary[a,b]	Trial genetics[c]	Classification[d]	Continued to extension period? (Y/N)	Complete TMA response (Y/N)
12	No pathogenic variant	No pathogenic variant	No pathogenic variant	Y	Y
13	No pathogenic variant	No pathogenic variant	No pathogenic variant	Y	Y
14	N/A	Not tested	N/A	Y	N
15	N/A	Not tested	N/A	Y	Y
16 KTx	N/A	No pathogenic variant	No pathogenic variant	Y	Y
17	No pathogenic variant	Not tested	No pathogenic variant	Y	Y
18	CD46 c.649A>G p. (Ser217Gly) homozygous	CFH autoantibodies; genetics not tested	Likely pathogenic variant CFH autoantibodies present	Y	Y
19	No pathogenic variant	Not tested	No pathogenic variant	Y	Y
20	No pathogenic variant	No pathogenic variant	No pathogenic variant	Y	N
21	N/A	No pathogenic variant	No pathogenic variant	Y	Y
22	No pathogenic variant	No pathogenic variant	No pathogenic variant	Y	Y
23	No pathogenic variant	No pathogenic variant	No pathogenic variant	Y	Y
24	No pathogenic variant	No pathogenic variant	No pathogenic variant	Y	N
25	N/A	CFHR3	No pathogenic variant	Y	N

Patient ID[a]	Clinician genetics findings summary[a,b]	Trial genetics[c]	Classification[d]	Continued to extension period? (Y/N)	Complete TMA response (Y/N)
		1:196790152_C/T; rs138675433			
26	No pathogenic variant	Not tested	No pathogenic variant	Y	Y
27	CFH c.3486del; p.Lys1162AsnfsTer7	CFH c.3226C>G; p.Gln1076Glu CFH c.3486del; p.Lys1162AsnfsTer7	Pathogenic variant	Y	Y
28 KTx	N/A	Not tested	N/A	Y	Y, in the extension period
29	N/A	Not tested	N/A	Y	Y
30	N/A	No pathogenic variant	No pathogenic variant	Y	N
31	N/A	No pathogenic variant	No pathogenic variant	Y	Y
32	N/A	No pathogenic variant	No pathogenic variant	Y	Y
33	CD46 c.286+2T>G	CD46 c.286+2T>G	Pathogenic variant	Y	Y
34	N/A	CFH c.3691del; p.Arg1231AspfsTer40	Pathogenic variant	Y	N
35	N/A	C3 c.481C>T; p.Arg161Trp	Pathogenic variant	Y	N
36	CFH p.Trp314Arg (c.940T>C) heterozygous	Not tested	Pathogenic variant	Y	N
37	No pathogenic variant	No pathogenic variant	No pathogenic variant	Y	Y

Patient ID[a]	Clinician genetics findings summary[a,b]	Trial genetics[c]	Classification[d]	Continued to extension period? (Y/N)	Complete TMA response (Y/N)
38	N/A	CD46 c.175C>T; p.Arg59Ter	Pathogenic variant	Y	Y
39	No pathogenic variant	No pathogenic variant	No pathogenic variant	Y	Y
40 KTx	N/A	No pathogenic variant	No pathogenic variant	Y	Y
41	No pathogenic variant	Not tested	No pathogenic variant	Y	Y
42	N/A	No pathogenic variant	No pathogenic variant	Y	N
43 KTx	N/A	No pathogenic variant	No pathogenic variant	Y	Y, in the extension period
44	N/A	No pathogenic variant	No pathogenic variant	Y	Y
45 KTx	N/A	Not tested	N/A	Y	N
46	N/A	Not tested	N/A	Y	N
47	N/A	Not tested	N/A	Y	N
48	CFH/CFHR1 fusion gene; SCR4 and SCR5 of CFHR1 replacing SCR19 and SCR20 in CFH	No pathogenic variant detected[e]	Pathogenic variant	Y	Y
49	CFH deficiency, but no genetics done	CFH (NM_000186.4) c.341G>A (p.Cys114Tyr)	Pathogenic variant	Y	Y, in the extension period

Patient ID[a]	Clinician genetics findings summary[a,b]	Trial genetics[c]	Classification[d]	Continued to extension period? (Y/N)	Complete TMA response (Y/N)
50	N/A	CFH autoantibodies	No pathogenic variant CFH autoantibodies present	N	N
51 **KTx**	N/A	No pathogenic variant	No pathogenic variant	N	N
52	N/A	No pathogenic variant	No pathogenic variant	N	N
53 **KTx**	N/A	Not tested	N/A	N	N
54	N/A	No pathogenic variant	No pathogenic variant	N	N
55	N/A	CD46 c.565T>G; p.Tyr189Asp	Pathogenic variant	N	N
56	N/A	Not tested	N/A	N	N/A

Greyed-out patients discontinued the study during the initial evaluation period and did not progress into the extension period of this study. [a]Kidney transplant patients are indicated by 'KTx'. [b]Data collected outside of this clinical trial (NCT02949128) and provided by investigators as response to petition by the trial sponsor for patients who consented. [c]Genetic testing carried out in trial patients who consented. [d]Classification based on either clinician genetics findings and/or this trial (NCT02949128). [e]Note that gene fusions are not be detectable by the whole exome sequencing approach used for the trial genetics. N/A, not available.

Supplementary Table S3. Observed median eGFR values at baseline, Day 183 and Day 351

eGFR, estimated glomerular filtration rate

eGFR value (ml/min/1.73m^2)		
Time-point	**Median value (min, max)[a]**	**Median change from baseline (min, max)[b]**
Baseline	10.00 (4, 80)	N/A
Day 183	40.00 (2, 119)	29.00 (-13, 108)
Day 351	42.50 (4, 117)	23.00 (-13, 95)

[a]Median value is based on patients with eGFR data available at Day 351 only (*N* =44); [b]Median change from baseline is based on patients with eGFR data available at Day 1 and Day 351 (*N* =43).

Appendix

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Long-term treatment with ravulizumab improves outcomes in adult patients with atypical hemolytic uremic syndrome (aHUS)

This is an analysis of efficacy and safety outcomes in adult patients with aHUS following long-term (>6 months) treatment with ravulizumab (ULTOMIRIS®) in a clinical study.

- Researchers have been studying ULTOMIRIS® (ravulizumab), which is one of two approved treatments for aHUS (the other being SOLIRIS® [eculizumab]). ULTOMIRIS® was approved in the USA to treat aHUS in October 2019, in the European Union in June 2020, and in Japan in September 2020. Both ULTOMIRIS® and SOLIRIS® work by preventing damage caused by an overactive complement system. In adults, ULTOMIRIS® is given only once every 8 weeks, unlike SOLIRIS® which is given every 2 weeks.

What is aHUS?

- aHUS is a complex disease involving the complement system, which is part of the body's immune system. In patients with aHUS, the complement system becomes overactive and attacks the body's own cells, particularly cells lining small blood vessels, resulting in damage known as thrombotic microangiopathy (TMA). In TMA from aHUS, the linings of small blood vessels become inflamed (swollen) and cause red blood cells to break, such that they stick together with platelets (small particles in the blood that help with clotting) and form tiny blood clots. The multiple small blood clots lead to organ damage, most commonly in the kidneys, but they can also form in other organs. In addition to problems with kidney function, symptoms of aHUS can also include abdominal pain, swelling, seizures, fatigue, bruises, loss of consciousness and, in severe cases, death.

What did this study investigate?

- This study is part of a multi-year clinical trial. The initial results were published in 2020 as a research article entitled "Efficacy and Safety of the Long-Acting C5 Inhibitor, Ravulizumab, in Adult Patients with Atypical Hemolytic Uremic Syndrome Naïve to Complement Inhibitor Treatment". That report showed that ULTOMIRIS® helped improve outcomes in adult patients with aHUS during treatment for 6 months.[1]
- The current study describes the same group of patients in the trial, after they continued to receive ULTOMIRIS® for more than 6 months. These patients were observed for an average of 77 weeks of treatment.
- In this study, 49 patients continued to receive ULTOMIRIS® by an infusion directly into the vein every 8 weeks.
- Researchers measured several markers of response (for example, platelet count, LDH, hemoglobin, creatinine) to confirm that the drug continued to work in patients that had been treated for more than 6 months. Safety was also continuously monitored during treatment.

What did this study find?

- Patients who continued to receive ULTOMIRIS® after 6 months maintained the improvements from the first 6 months of treatment, according to average levels of several markers of response:
  - Platelet count, an important component in blood clotting
  - LDH a measure of damage to the tissues in the body
  - eGFR, a measure of how well kidneys can filter the blood
  - FACIT-Fatigue, a test that measures fatigue (tiredness) in patients
- There was also evidence of continued improvement following long-term treatment (i.e., more than 6 months) with ULTOMIRIS®
  - 61% of patients had a complete TMA response (see glossary), compared with 54% of patients during the first 6 months of treatment
  - 86% achieved platelet count normalization, compared with 84% of patients during the first 6 months of treatment
  - 84% achieved LDH normalization, compared with 77% of patients during the first 6 months of treatment
  - Kidney function (assessed by eGFR category) improved for 30 patients, remained the same for 11 patients and worsened for 2 patients
- The safety of ULTOMIRIS® was measured by looking at adverse events (see glossary). The frequency of adverse events during this study was much lower than during the initial 6 months of treatment.

What are the main conclusions from this study?

- Patients with aHUS receiving ULTOMIRIS® every 8 weeks for more than 6 months maintained improvements in several indicators of response to treatment. Further, ULTOMIRIS® was shown to be well tolerated during treatment for more than 6 months, with a substantial reduction in adverse events during this phase of the study.

- This is a summary of the research article by Dr Thomas Barbour and colleagues, *Long-Term Efficacy and Safety of the Long Acting C5 Inhibitor Ravulizumab for the Treatment of Atypical Hemolytic Uremic Syndrome (aHUS) in Adults.*

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Glossary

Adverse event: An unwanted effect which happens while a patient is taking the drug. These are reported whether or not they are thought to be caused by the drug.

Complete TMA response: A stringent assessment defined by simultaneous improvement in platelet count, LDH levels and serum creatinine levels (measures of kidney damage) at two separate assessments at least 4 weeks apart.

Ravulizumab (ULTOMIRIS®): A drug developed by Alexion Pharmaceuticals, Inc., approved in the USA, the EU and Japan for the treatment of aHUS.

References

1. Rondeau E, Scully M, Ariceta G, *et al*. The long-acting C5 inhibitor, Ravulizumab, is effective and safe in adult patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment. *Kidney Int* 2020; **97:** 1287-1296.