The long-acting C5 inhibitor, ravulizumab, is effective and safe in pediatric patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment

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Gema Ariceta[1], Bradley P. Dixon[2], Seong Heon Kim[3], Gaurav Kapur[4], Teri Mauch[5,6], Stephan Ortiz[7], Marc Vallee[8], Andrew E. Denker[9], Hee Gyung Kang[10] and Larry A. Greenbaum[11]; the 312 Study Group[12]

[1]Paediatric Nephrology Department, University Hospital Vall d'Hebron, Barcelona, Spain; [2]Renal Section, Department of Pediatrics, University of Colorado School of Medicine, Aurora, Colorado, USA; [3]Department of Pediatrics, Pusan National University Children's Hospital, Yangsan, Korea; [4]Faculty of Pediatric Sciences, Central Michigan University, Mount Pleasant, Michigan, USA; [5]Division of Pediatric Nephrology, University of Nebraska Medical Center, Omaha Children's Hospital and Medical Center, Omaha, Nebraska, USA; [6]Department of Nephrology and Hypertension, Division of Pediatrics, University of Utah, Salt Lake City, Utah, USA; [7]Clinical and Non-Clinical Pharmacology, Alexion Pharmaceuticals Inc., Boston, Massachusetts, USA; [8]Biostatistics, Alexion Pharmaceuticals Inc., Boston, Massachusetts, USA; [9]Clinical Development, Alexion Pharmaceuticals Inc., Boston, Massachusetts, USA; [10]Division of Pediatric Nephrology, Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea; and [11]Division of Pediatric Nephrology, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, Georgia, USA

Ravulizumab, a long-acting complement C5 inhibitor engineered from eculizumab, allows extending maintenance dosing from every 2–3 weeks to every 4–8 weeks depending on bodyweight. Here, we evaluated the efficacy and safety of ravulizumab in complement inhibitor-naïve children (under 18 years) with atypical hemolytic uremic syndrome. In this phase III, single-arm trial, ravulizumab was administered every eight weeks in patients 20 kg and over, and four weeks in patients under 20 kg. The primary endpoint was a complete thrombotic microangiopathy response (normalization of platelet count and lactate dehydrogenase, and a 25% or more improvement in serum creatinine) through 26 weeks. Secondary endpoints included change in hematologic parameters and kidney function. 18 patients with a median age of 5.2 years were evaluated. At baseline, symptoms of atypical hemolytic uremic syndrome outside the kidney were present in 72.2% of patients and 38.9% had been in intensive care. Baseline estimated glomerular filtration rate was 22 mL/min/1.73 m^2. By week 26, 77.8% of patients achieved a complete thrombotic microangiopathy response; 94.4%, 88.9% and 83.3% of patients achieved platelet normalization, lactate dehydrogenase normalization and a 25% or more improvement in serum creatinine, respectively. By week 50, 94.4% patients had achieved a complete thrombotic microangiopathy response. Median improvement in platelet count was 246 and 213 x10^9/L through week 26 and week 50, respectively. The median increase above baseline in estimated glomerular filtration rate was 80 and 94 mL/min/1.73m^2 through week 26 and week 50, respectively. No unexpected adverse events, deaths, or meningococcal infections occurred. Thus, ravulizumab rapidly improved hematologic and kidney parameters with no unexpected safety concerns in complement inhibitor-naïve children with atypical hemolytic uremic syndrome.

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Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening disease associated with complement dysregulation, characterized by thrombotic microangiopathy (TMA).[1,2] Microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury are hallmarks of aHUS, but aHUS can also affect organs other than the kidneys.[1] Without appropriate treatment, aHUS causes significant morbidity and mortality, with 29% of children requiring dialysis or dying within 1 year and 48% reaching end-stage kidney disease or dying at 3 years, despite plasma therapy.[3,4]

Eculizumab (Alexion Pharmaceuticals Inc., Boston, MA, USA) has been approved for the treatment of aHUS since 2011.[5,6] It has proved highly effective in children with aHUS.[7–10] However, eculizumab treatment regimen involves frequent intravenous infusions (every 2 weeks in patients weighing >10 kg), which can be particularly burdensome for

Correspondence: *Gema Ariceta, Paediatric Nephrology Department, University Hospital Vall d'Hebron, 119, 08035 Barcelona, Spain. E-mail: gariceta@vhebron.net*

[12]Members of the 312 Study Group are listed in the Appendix.

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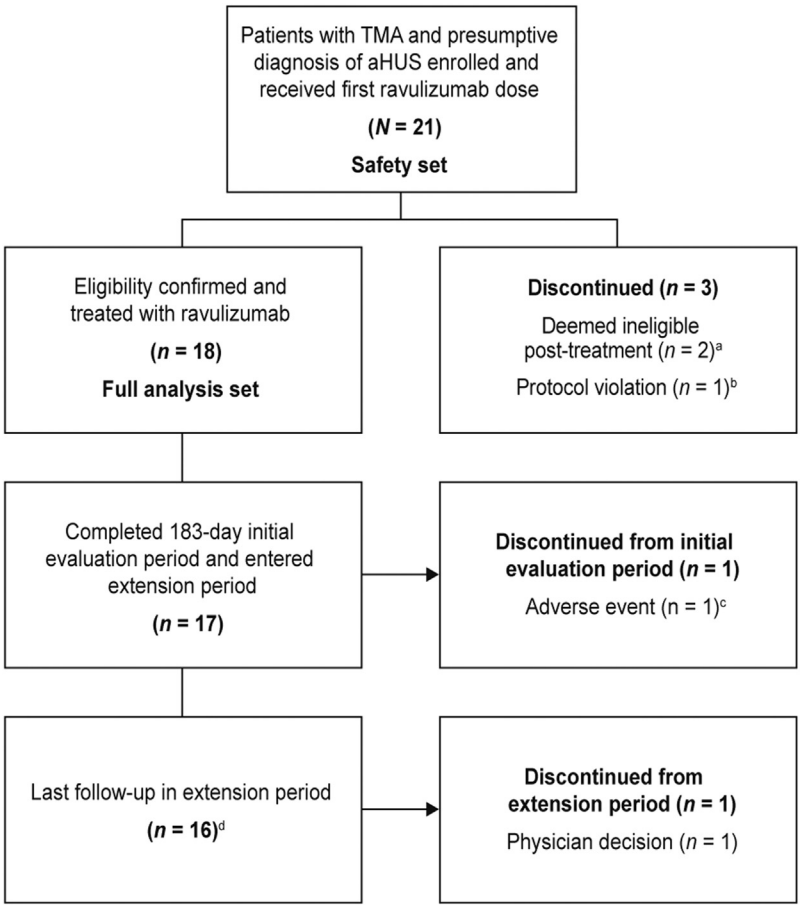


Figure 1 | Patient disposition. [a]One patient was discontinued on day 14 because of laboratory results for platelet count, lactate dehydrogenase (LDH), and hemoglobin not meeting inclusion criteria; one patient was discontinued on day 43 because of positive Shiga toxin-producing *Escherichia coli* test. [b]Patient was discontinued on day 7 because of laboratory results for LDH not meeting inclusion criteria (predose local laboratory results for LDH were also exclusionary). [c]Patient was discontinued on day 21 because of serious adverse events of hypertensive crisis and worsening anemia. [d]At last follow-up. aHUS, atypical hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

pediatric patients and caregivers. A reduction of dosing frequency may improve the quality of life and adherence to treatment.[11–13]

Ravulizumab, a humanized monoclonal antibody, is a long-acting complement C5 inhibitor recently approved for treatment of aHUS in adults and children.[14,15] Ravulizumab was engineered through selective modifications to eculizumab. These modifications included 2 amino acid substitutions made to preserve high binding affinity to C5 at pH 7.4 in blood, but permitting dissociation of C5 from ravulizumab at pH 6.0. Two additional substitutions were made to increase the affinity for neonatal Fc receptor, with all 4 modifications resulting in increased antibody recycling. Overall, these substitutions, while targeting the same C5 epitope, enhanced the duration of terminal complement inhibition, leading to a mean half-life >4 times greater than eculizumab (approximately 51.8 days) because of additional recycling of binding and neutralization of C5 (Supplementary Figure S1).[16] As such, ravulizumab offers a reduced dosing frequency (every 4–8 weeks based on body weight) relative to eculizumab. The clinical efficacy and safety of ravulizumab in adults with aHUS has been demonstrated in a recently published phase 3 trial report (NCT02949128).[17] In this study, we assessed the efficacy and safety of ravulizumab in complement-inhibitor treatment-naïve children with aHUS through an initial evaluation period of 26 weeks and an interim data cut point through the extension period.

RESULTS

Patient characteristics

Twenty-one complement-inhibitor naïve children were enrolled, receiving ≥1 dose of ravulizumab, forming the safety set of this analysis (Figure 1). Two patients were excluded from the full analysis set because of ineligibility after treatment (one patient did not meet laboratory criteria for platelet count, lactate dehydrogenase [LDH], and hemoglobin; and the other had a positive Shiga toxin-producing *Escherichia coli* test), and one patient was excluded because of a protocol violation (did not meet the laboratory criteria for LDH). The full analysis set comprised 18 patients with a median age of 5.2 (range, 0.5–17.3) years (Table 1). Ten patients (55.6%) were female, 9 (50.0%) were White, and the

Table 1 | Baseline demographics, disease characteristics, and laboratory values (full analysis set)

Variable	Overall (N = 18)
Age at time of first infusion, median (range), yr	5.2 (0.5–17.3)
Age at time of first infusion category, yr	
Birth to <2	2 (11.1)
2–<6	9 (50.0)
6–<12	5 (27.8)
12–<18	2 (11.1)
Age at time of first aHUS symptoms, median (range), yr	4.7 (0.8–14.7)
Sex	
Male	8 (44.4)
Female	10 (55.6)
Race[a]	
American Indian or Alaskan Native	1 (5.6)
Asian	5 (27.5)
Black or African American	3 (16.7)
White	9 (50.0)
Unknown	1 (5.6)
Weight at time of first infusion, kg	
≥5–<10	2 (11.1)
≥10–<20	9 (50.0)
≥20–<30	3 (16.7)
≥30–<40	3 (16.7)
≥40–<60	0
≥60	1 (5.6)
Pretreatment extrarenal signs or symptoms of aHUS	13 (72.2)
Any prior kidney transplant[b]	1 (5.6)
Patients who required ICU level of care	7 (38.9)
Time in ICU, mean (SD), d (n = 9)	9.0 (±17.7)
Patients receiving dialysis	6 (33.3)
Birth to <6 yr (n = 11)	2 (18.2)
6–<18 yr (n = 7)	4 (57.1)
Received PE/PI related to this TMA before first infusion of drug	6 (28.6)
Platelet count, median (range), $\times 10^9$/L[c]	51.25 (14–125)
LDH, median (range), U/L[c]	1963.0 (772–4985)
Serum creatinine, median (range), μmol/L[c]	133.0 (35–264)
eGFR, median (range), mL/min per 1.73 m^2[c]	22.0 (10–84)
HGB, median (range), g/L[c]	74.25 (32–106)

aHUS, atypical hemolytic uremic syndrome; eGFR, estimated glomerular filtration rate; HGB, hemoglobin; ICU, intensive care unit; LDH, lactate dehydrogenase; PE, plasma exchange; PI, plasma infusion; TMA, thrombotic microangiopathy.
Data shown as number (percentage) unless otherwise stated.
[a]One patient had 2 races entered (White and American Indian or Alaskan Native).
[b]Transplant related to aHUS, December 2014.
[c]Baseline values may be after PE/PI in some patients.

Table 2 | Complete TMA response at week 26 and week 50

Variable	Initial evaluation period through week 26 (n = 18)	Evaluation through week 50 (n = 18)
Complete TMA response	14 (77.8)	17 (94.4)
Platelet count normalization	17 (94.4)	17 (94.4)
LDH normalization	16 (88.9)	17 (94.4)
25% Improvement in serum creatinine from baseline	15 (83.3)	17 (94.4)
Hematologic normalization	16 (88.9)	17 (94.4)

LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy.
Data shown as number (percentage).

median weight was 16.7 (range, 8.4–69.3) kg. Before ravulizumab treatment, 6 (28.6%) patients had received plasma exchange/plasma infusion. Before the start of screening, 7 (38.9%) patients had been treated in an intensive care unit, for a mean duration of 9.0 (±17.7) days. Extrarenal symptoms of aHUS were present in 13 (72.2%) patients at baseline (Supplementary Table S1). Ten patients were tested using the whole exome sequencing method for genetic variants in complement genes, and 17 were tested for anti-complement factor H (CFH) antibodies. Of those tested with both methods, 9 of 10 (90%) had a pathogenic variant in complement gene and/or anti-CFH antibody (Supplementary Table S2). Pathogenic variants were found in 3 patients (CFH, *MCP*, and *THBD*), and CFH antibodies were found in 7 patients (additional pathogenic variants were identified by local genetic analyses; see supplemental information). The median age of first aHUS symptoms was 4.7 (range, 0.8–14.7) years, and the median age at time of first infusion was 5.2 (range, 0.5–17.3) years. Comorbidities in patients in this study are listed in Supplementary Table S3.

Baseline laboratory values are shown in Table 1. Seventeen patients completed the 26-week initial evaluation period and entered the extension period. One patient discontinued because of an adverse event (AE) during the initial evaluation period. This patient, a 21.6-month-old White female, experienced worsening anemia and hypertensive crisis. She weighed <10 kg and received a loading dose of 300 mg ravulizumab on day 1, and a maintenance dose of 300 mg on day 15. During the loading phase, this patient had a serum C5 level ≥0.5 μg/ml, suggesting incomplete terminal complement inhibition. Following a protocol-specified initial pharmacokinetic (PK)/pharmacodynamic (PD) analysis, the loading dose for this weight category was increased to 600 mg, to ensure adequate target serum concentrations of ravulizumab and corresponding reductions in serum C5. Including the initial evaluation period and extension period, the median duration of follow-up through the current data cut point was 82.6 (range, 3.0–110.6) weeks. Only 1 patient was discontinued from the extension period. This patient had a complete TMA response on day 88 and was discontinued because of physician decision on day 350; the reason for discontinuation was not due to a safety concern. All remaining patients had completed at least 351 days of the study at the data cut.

Primary end point

The primary end point of the study was complete TMA response during the initial evaluation period (Table 2). During the 26-week initial evaluation period, 14 of 18 (77.8%) patients achieved complete TMA response. The median time to complete TMA response considering all available data was 30 (95% confidence interval, 22.0–88.0) days (Figure 2).

During the extension period, through week 50, an additional 3 patients achieved a complete TMA response (resulting complete TMA response in a total of 17/18 [94.4%] patients). Only one patient did not achieve a complete TMA response, as this patient was discontinued during the initial evaluation period (day 21), as mentioned previously, and had

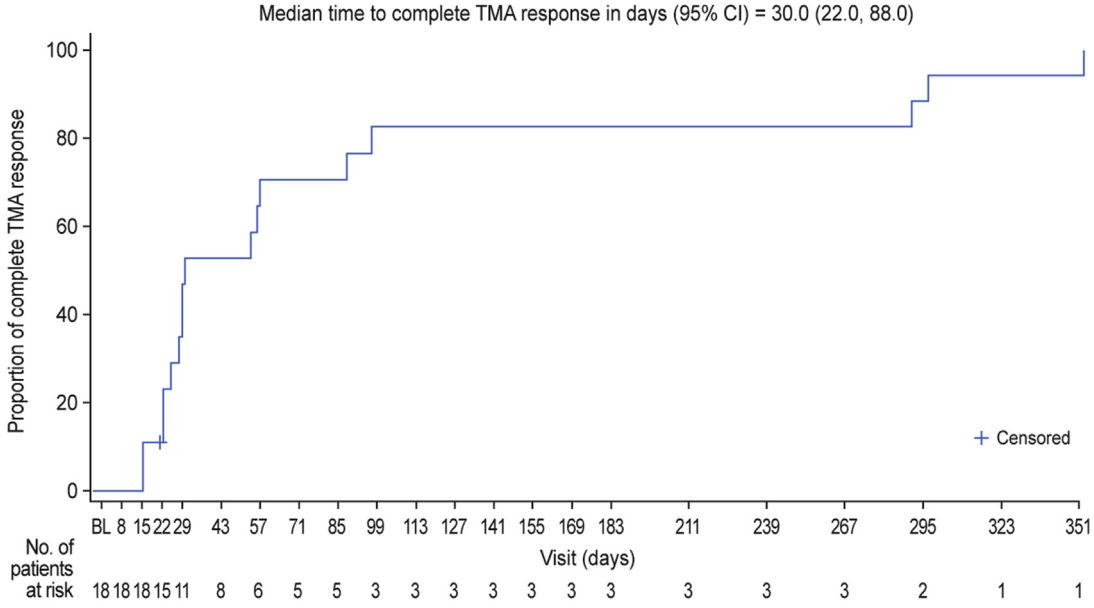


Figure 2 | Time to complete thrombotic microangiopathy (TMA) response through week 50. Kaplan-Meier graph illustrating time to complete TMA response. BL, baseline; CI, confidence interval.

not achieved a response in any of the components of complete TMA response at that point (because a response in any component required confirmation at least 28 days after the initial observation, it was not possible for this patient to have responded in any component).

Hematologic end points

Overall, platelet normalization and ≥25% improvement in serum creatinine were achieved by day 8 in 65% and 47% patients, respectively. By day 15, 88% patients had achieved platelet normalization and 53% achieved ≥25% improvement in serum creatinine.

Platelet count normalization was achieved in 17 (94.4%) patients during the 26-week initial evaluation period and through week 50. The median increase in platelet count from baseline to week 26 was 246.0 × 10^9/L (range, 57.5–368.5 × 10^9/L); and to week 50, 213.0 × 10^9/L (range, 19.5–471.5 × 10^9/L) (Figure 3a).

LDH normalization was achieved in 16 (88.9%) patients during the 26-week initial evaluation period, and in 17 (94.4%) patients through week 50. The median decrease in LDH from baseline to week 26 was 1851.5 U/L (range, –4713 to –513 U/L); and to week 50, 1825.5 U/L (range, –4724 to –579 U/L) (Figure 3b).

Sixteen (88.9%) patients achieved an increase in hemoglobin of ≥20 g/L from baseline, with a confirmatory result through week 26, and 17 patients (94.4%) through week 50. The increase in hemoglobin from baseline to week 26 was 46.5 g/L (range, 26.5–86.0 g/L); and by week 50, 51.5 g/L (range, –19.0 to 80.0 g/L) (Figure 3c).

Renal end points

Renal function substantially improved from baseline, with a median increase in estimated glomerular filtration rate (eGFR) of 80.0 (range, 0–222.0) ml/min per 1.73 m^2 by week 26 and 94.0 (range, 10–230) ml/min per 1.73 m^2 by week 50 (Figure 3d). Of the 6 (28.6%) patients receiving dialysis at baseline, 5 (83.3%) were off dialysis by week 26 and all 6 (100%) were off dialysis by week 50. None of the 12 patients off dialysis at baseline initiated dialysis during the study. Improvement in eGFR (change to a less severe eGFR category between baseline and week 26) was seen in 15 patients (88.2%), with 2 (11.8%) patients remaining in the same category (Figure 4a). By week 50, all 16 patients with evaluable data had improved eGFR category (Figure 4b).

Quality-of-life end points

Nine patients had evaluable Pediatric Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue data at baseline, week 26, and week 50. All 9 patients (100%) had a clinically meaningful improvement (at least 3 points)[18] in Pediatric FACIT-Fatigue score at week 26 and week 50 compared with baseline (Figure 5). The median increase in Pediatric FACIT-Fatigue score was 10.0 (range, 4.0–48.0) and 9.0 (range, 3.0–47.0) at week 26 and week 50, respectively.

PK/PD analysis

Ravulizumab showed immediate, complete, and sustained terminal complement C5 inhibition (serum-free C5, <0.5 μg/ml; Figure 6), with individual free C5 outliers noted at only 3 time points. One outlier (day 15 trough; 0.999 μg/ml) was observed in a patient in the ≤5 to <10 kg group who received the original loading dose. Consequently, following prespecified interim PK/PD analysis, the loading dose for enrolled patients ≤5 to <10 kg was increased from 300 to 600 mg, with no free C5 outliers observed in ≤5 to <10 kg patients receiving the updated loading dose.

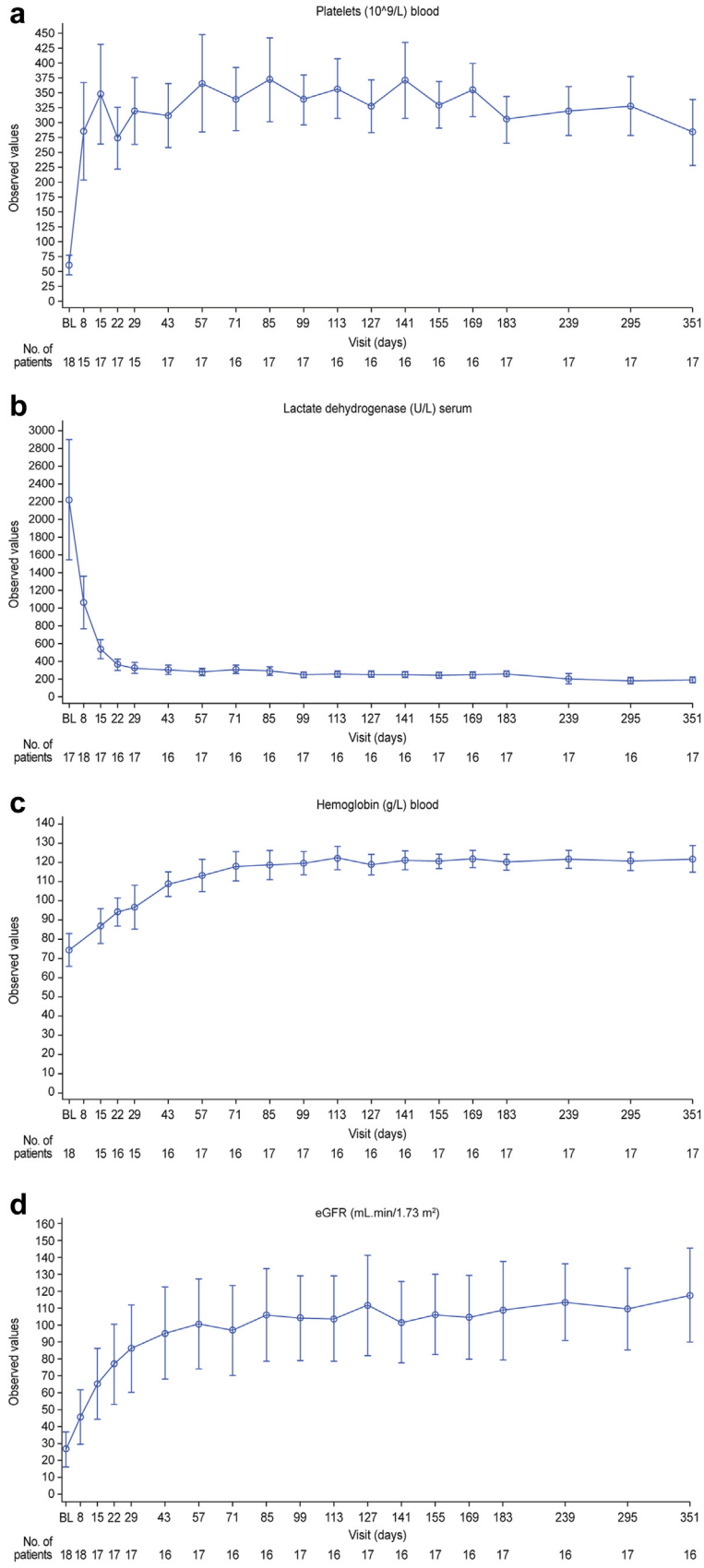


Figure 3 | Observed end points over time: platelet count (a), lactate dehydrogenase (b), hemoglobin (c), and estimated glomerular filtration rate (eGFR) (d). Data are shown as mean (error bars, 95% confidence interval). BL, baseline.

Safety analyses

All 21 patients in the safety analysis experienced AEs (Table 3), with pyrexia, headache, nasopharyngitis, diarrhea, and vomiting occurring most frequently (Table 4). Fourteen patients (66.7%) experienced serious AEs (SAEs), the most frequent of which were viral gastroenteritis and abdominal pain, both occurring in 2 patients each (9.5%; a full list of SAEs is shown in Supplementary Table S4). One patient (4.8%), a 21.6-month-old White female, experienced a grade 3 treatment-emergent AE, listed by the investigator as worsening anemia and hypertensive crisis, which resulted in study discontinuation on day 21. This patient was in the lowest weight category (<10 kg) and received a loading dose of 300 mg (as described previously), resulting in predose serum concentration of ravulizumab of 137 μg/ml, which was below the target threshold. Four patients (19.0%) experienced AEs during study drug infusion, and one of these patients experienced nonsevere hypersensitivity to ravulizumab on 3 separate occasions. These cases resolved with study drug dose interruption, diphenhydramine and paracetamol, and slower rate of infusion; and the patients remained in the study. No deaths or meningococcal infections were reported.

DISCUSSION

This study is the first prospective phase 3 trial evaluating the efficacy and safety of ravulizumab, a long-acting C5 inhibitor with a maintenance dosing interval of 4 to 8 weeks, in pediatric patients with aHUS. Weight-based dosing of ravulizumab resulted in immediate, complete, and sustained terminal complement C5 inhibition, leading to hematologic remission and improvement of renal function in patients with aHUS. The primary end point was met, with 14 (77.8%) patients achieving complete TMA response by week 26. Complete TMA response is a stringent end point requiring platelet count normalization, LDH normalization, and ≥25% improvement in serum creatinine, demonstrated simultaneously at 2 separate assessments at least 28 days apart.

Considering all available follow-up, this end point was met in a median time of 30 days. An additional 3 patients, described below, met the primary end point by week 50 (overall, 94.4% of patients had a complete TMA response). One of these patients had extrarenal symptoms of aHUS and achieved platelet normalization and serum creatinine response on days 18 and 24, respectively. The LDH criterion for response was not met until during the extension period (day 297), which is when the patient formally achieved the complete TMA response. The second patient achieved complete TMA response on day 351. This patient achieved hematologic response during the initial evaluation period (platelets normalized on day 8, and LDH normalized on day 24). Serum creatinine level did not improve ≥25% until day 351, although it was stable throughout the initial evaluation period (range, 160–235 μmol/L). The third patient achieved platelet normalization on day 71 and LDH normalization on day 104. This patient discontinued dialysis on day 193 and only then became evaluable for serum creatinine criteria, which were subsequently met.

a

eGFR categories at baseline (N = 17)		eGFR categories at week 26					
		1 (≥90)	2 (60–89)	3a (45–59)	3b (30–44)	4 (15–29)	5 (<15)
1 (≥90)	0						
2 (60–89)	1 (5.9)	1 (5.9)					
3a (45–59)	1 (5.9)	1 (5.9)					
3b (30–44)	1 (5.9)	1 (5.9)					
4 (15–29)	8 (47.1)	5 (29.4)	1 (5.9)	1 (5.9)		1 (5.9)	
5 (<15)	6 (35.3)	3 (17.6)	2 (11.8)				1 (5.9)

b

eGFR categories at baseline (N = 16)		eGFR categories at week 50					
		1 (≥90)	2 (60–89)	3a (45–59)	3b (30–44)	4 (15–29)	5 (<15)
1 (≥90)	0						
2 (60–89)	1 (6.3)	1 (6.3)					
3a (45–59)	1 (6.3)	1 (6.3)					
3b (30–44)	1 (6.3)	1 (6.3)					
4 (15–29)	8 (50.0)	6 (37.5)		1 (6.3)	1 (6.3)		
5 (<15)	5 (31.3)	3 (18.8)	1 (6.3)	1 (6.3)			

Figure 4 | Shift in estimated glomerular filtration rate (eGFR) category for the initial evaluation period (a) and the extension period (full analysis set) (b). Data shown as number (percentage). eGFR categories are shown in ml/min per 1.73 m^2. Green cells represent improvement from baseline to day 183; red cells represent worsening; and white cells represent no change.

Hematologic normalization was observed in a higher proportion of patients at week 26 than complete TMA response, with 16 (88.9%) patients achieving LDH and platelet count normalization by week 26; by week 50, 17 (94.4%) patients had achieved hematologic normalization. Similar to other studies on complement inhibitors for the

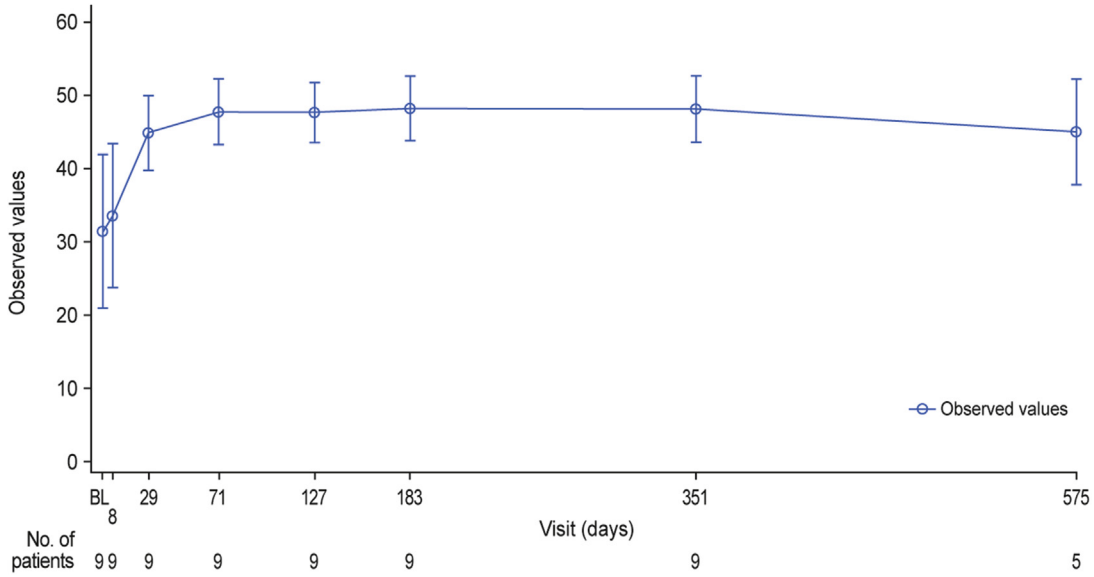


Figure 5 | Pediatric Functional Assessment of Chronic Illness Therapy-Fatigue over time. Data shown as mean (error bars, 95% confidence interval). BL, baseline.

treatment of aHUS,[19,20] platelet normalization occurred earlier than other components of TMA response, observed 8 days after the first ravulizumab dose; and data from this clinical trial demonstrate improvement in efficacy of ravulizumab with increasing treatment duration.

Dialysis is burdensome and debilitating, having a severe impact on the quality of life of children.[21,22] With plasma therapy, close to 50% of children develop end-stage kidney disease within 3 years of diagnosis.[3,4] In this study, 83.3% children who were receiving dialysis at baseline had discontinued dialysis at week 26, and, notably, 100% were off dialysis by week 50, with no patients initiating dialysis during the study. Overall, renal function improved substantially across the cohort, and all patients improved in eGFR category by week 50. As chronic kidney disease staging is not applicable to children aged <2 years as a result of expected physiologic eGFR maturation, this terminology was not applied.[23]

Because TMA leads to the involvement of the microvasculature of other organs, aHUS can also manifest in neurological, gastrointestinal, cardiovascular, and pulmonary systems.[24–26] Thirteen (72.5%) patients in this study had extrarenal symptoms at baseline, similar to the proportion reported in the clinical trial of ravulizumab in adult patients naïve to complement inhibitor therapy.[17] The term "extrarenal symptom," as applied in this trial, refers to any symptom that may be related to aHUS occurring in an organ other than the kidney; this may include symptoms related to the presence of renal failure. The patients in this trial were enrolled at the time of experiencing the primary acute manifestations of aHUS and, thus, presented with severe disease, evidenced by the number hospitalized and the number requiring intensive care unit level of care. Other studies also reported a similar high proportion of patients with extrarenal manifestations of aHUS. For instance, the ALXN1210-aHUS-311 study, the adult equivalent to the current analysis, evaluating the efficacy and safety of ravulizumab in adult patients with aHUS naïve to complement-inhibitor treatment, showed that 92.9% of patients had extrarenal symptoms of aHUS before the first dose. This higher proportion of patients with extrarenal manifestations reported in these recent studies could result from an increased awareness of aHUS as a disease, resulting in increased attribution of these symptoms to aHUS, although an ascertainment bias cannot be excluded as the presence of these symptoms was specifically queried in these trials and not necessarily in earlier ones. Regarding pathogenic variants, the rate of CFH-autoantibody–positive patients in this study was high at 7 (41%). Although it is a higher percentage than expected, it could have been related to the eligibility requirement for being naïve to complement inhibition, as these patients may have been initially treated with alternative therapies. It could also have been due to sampling error, as not all patients consented to genetic testing.

Real-world evidence data from the Global aHUS Registry have shown that dialysis requirement, recent hospitalizations, use of plasma exchange/plasma infusion, and TMA have the largest impact in reduced FACIT-Fatigue scores in patients with aHUS.[27] In this study, all patients with evaluable data had clinically meaningful improvement in FACIT-Fatigue score over time at week 26 and week 50. This improvement is especially important in patients with a chronic disease, such as aHUS, and supports a favorable risk-to-benefit ratio of treatment with ravulizumab.

The availability of a long-term treatment for aHUS that can be given at a reduced frequency compared with

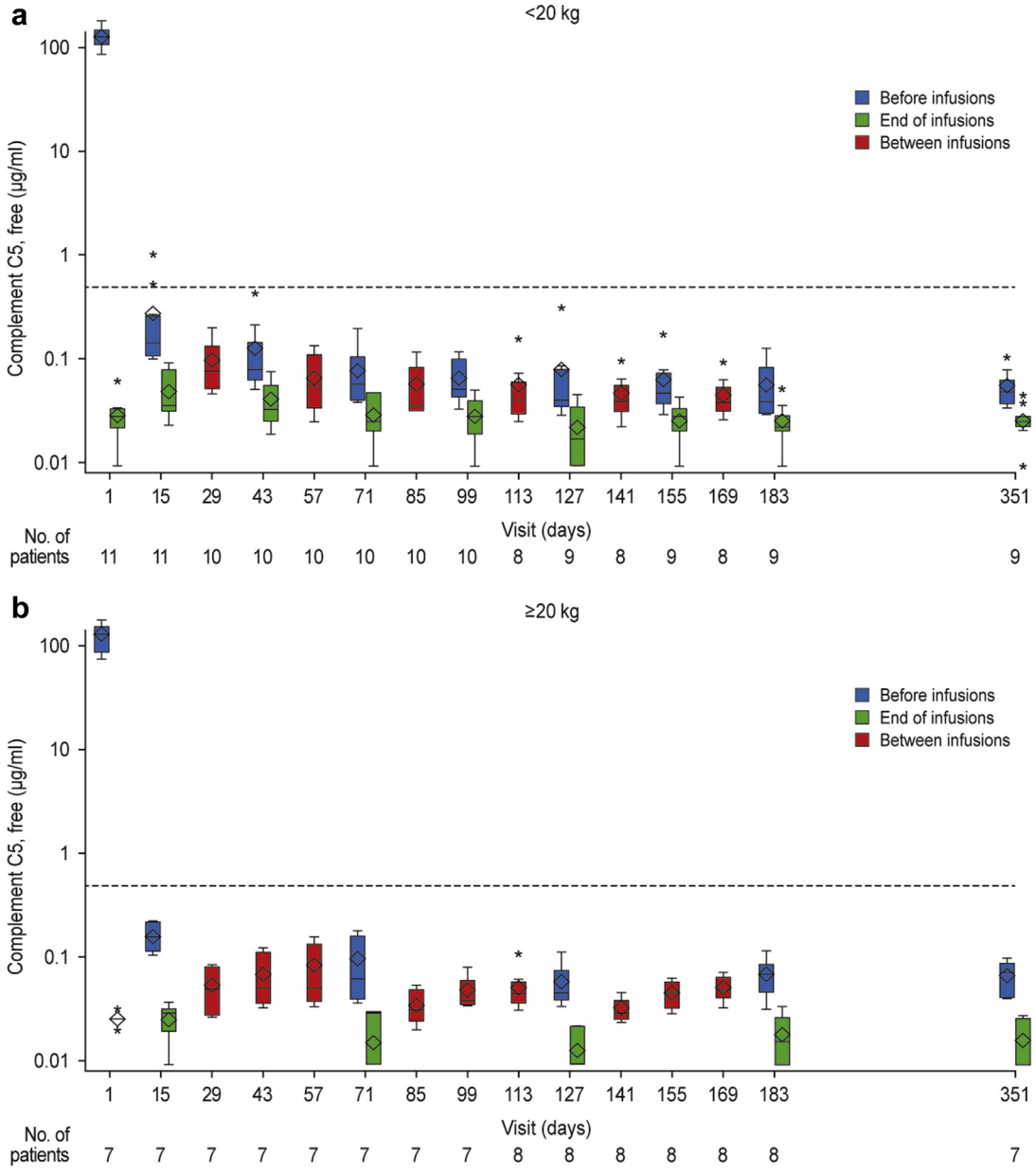


Figure 6 | Serum-free C5 concentrations in patients <20 kg (a) and patients ≥20 kg (b) during the initial evaluation period and extension period (semi–log scale). Free C5 levels shown at the original loading dose of 300 mg for patients <10 kg. Horizontal line is drawn at free C5 at 0.5 µg/ml to denote 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 times the interquartile range from the lower quartile and upper quartile. Outliers are represented by an asterisk.

eculizumab has multiple potential benefits for patients. With a decrease from 26 infusions per year to 13 or 7 infusions (depending on body weight), patients and their caregivers will miss less time at school and work. Moreover, children who may have required a port for vascular access may no longer require a port, with reduced potential for morbidity due to clots or infections and hospital workload. Fewer clinic appointments could also reduce the risk of exposure to nosocomial infections. Children may also feel less sick, and experience reduced fear and pain from repeated venipuncture, and thus have an improved quality of life with potentially greater adherence to treatment regimens, although further studies are required to confirm these hypotheses. Recent data from the hemophilia B literature point to the potential benefit of reduced dosing frequency on burden of therapy and reduced absenteeism from school and work, in children treated with a long-acting recombinant factor IX.[28] It is likely that similar

Table 3 | Summary of AEs through current data cut

AE variable	Overall (N = 21) No. (%)	Events
Any AE	21 (100)	369
Any SAE	14 (66.7)	31
TEAE resulting in drug discontinuation	1 (4.8)	2
TESAE resulting in drug discontinuation	1 (4.8)	2
TEAE resulting in study discontinuation	1 (4.8)	2
TESAE resulting in study discontinuation	1 (4.8)	2
TEAE during study drug infusion	4 (19.0)	7
TESAE during study drug infusion	0	0
Treatment-related AEs	10 (47.6)	33
Meningococcal infections	0	0
Deaths	0	0

AE, adverse event; SAE, serious AE; TEAE, treatment-emergent AE; TESAE, treatment-emergent SAE.

Table 4 | Most frequent treatment-emergent adverse events

Adverse event	Overall (N = 21) No. (%)	Events
Pyrexia	10 (47.6)	22
Nasopharyngitis	7 (33.3)	13
Diarrhea	7 (33.3)	10
Vomiting	7 (33.3)	25
Headache	7 (33.3)	19
Abdominal pain	6 (28.6)	11
Hypertension	6 (28.6)	8
Cough	5 (23.8)	6
Rash	4 (19.0)	5
Rhinorrhea	4 (19.0)	4
Myalgia	4 (19.0)	7
Constipation	4 (19.0)	8
Nausea	4 (19.0)	9

Events occurring in >15% of patients listed. Adverse event terms are as reported by the treating investigator. Patients evaluated for safety include all patients who received ≥1 dose of the study drug.

benefits would be seen in children treated with ravulizumab. In terms of clinical benefits, fewer infusions could free up physician and nursing time in both homecare settings and in the clinic. In patients with aHUS, a recent productivity analysis in the United States shows that less frequent dosing with ravulizumab substantially reduces time spent in treatment; the resulting lost productivity costs for ravulizumab treatment were 60% lower in the clinic and 73% lower in home infusing setting, compared with eculizumab treatment.[29] This suggests that health system and societal costs with ravulizumab therapy are likely to be reduced, and quality of life resulting from increased time available for work and school is likely to improve.[29]

All patients who were enrolled in this study experienced at least one AE, with just under half (47.6%) experiencing treatment-related AEs. One patient discontinued the study after experiencing SAEs of hypertensive crisis and worsening anemia. After discontinuing the study, the investigator chose to treat her with an increased dose of eculizumab (600 mg) on day 21 and day 23.

In the previous study of ravulizumab on adults naïve to complement treatment, AEs were reported in all patients, and SAEs were reported in 51.7%.[17] The most common SAEs were viral gastroenteritis and abdominal pain, occurring in 9.5% of patients each. These data are similar to those reported across the eculizumab trials in adults and children.[7,19,20] Specifically, in children, 90.9% and 59% in the eculizumab trial experienced AEs and SAEs, respectively, similar to the proportions reported in the current study. The most common AEs in eculizumab-treated children were fever, cough, abdominal pain, diarrhea, and respiratory tract infection; and the most common AEs in this study were pyrexia, headache, nasopharyngitis, diarrhea, and vomiting. A recently published 10-year pharmacovigilance study showed that the main risk of eculizumab is meningococcal infection.[30] In the current study, no patients treated with ravulizumab developed meningococcal infections, consistent with previous eculizumab clinical trials in children. Furthermore, no deaths were reported in this study.

This study was designed such that the primary end point required hematologic and renal parameters to be met at 2 separate assessments at least 28 days apart. This meant that patients discontinuing the study within 28 days of first dose were not able to meet this end point. However, this did not have a significant impact on the results as only one patient discontinued during the 26-week initial evaluation period (although this patient discontinued during the first 28 days and thus did not participate long enough to have responded for any parameter). In addition, patients receiving dialysis at baseline were also unable to meet the renal end point until after stopping dialysis, because of serum creatinine level requirement. This could have led to a delay in time to achieve a complete TMA response in some patients, although they had earlier clinical improvement. Also, 2 patients in the current analysis were aged <2 years, so interpretation of both continuous and categorical eGFR data from these patients should be approached with caution. Finally, because of the rarity of the condition, limitations in patient enrollment and sample size meant a comparator or control group was not feasible.

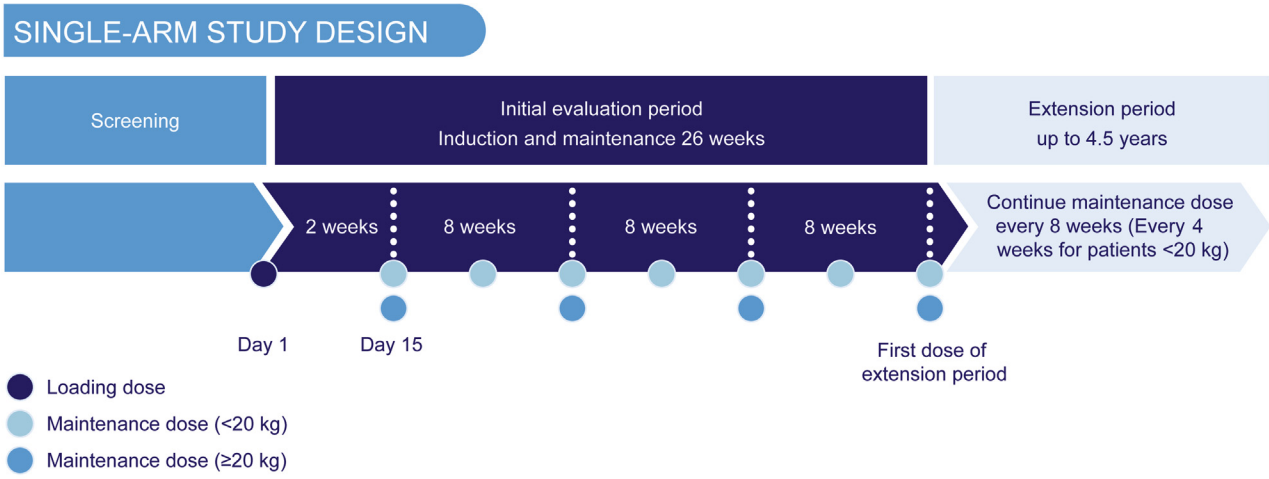
Conclusions

Ravulizumab provided immediate, complete, and sustained complement C5 inhibition, resulting in rapid improvement in renal and hematologic parameters across 26 weeks, and further increase in response rate over longer duration, with no unexpected safety concerns. Treatment with ravulizumab every 4 to 8 weeks provides patients and caregivers with a meaningful reduction in treatment burden. The results from this study support the use of ravulizumab in children for resolution of TMA caused by aHUS for a minimum treatment period of 6 months.

METHODS

Trial oversight and study design

ALXN1210-aHUS-312 (NCT03131219) is a phase 3, single-arm, multicenter study to assess the efficacy and safety of ravulizumab



Patient body weight (kg)	Loading phase (mg)	Maintenance phase (mg)
≥5 to <10[a]	600	300 (every 4 weeks)
≥10 to <20	600	600 (every 4 weeks)
≥20 to <30	900	2100
≥30 to <40	1200	2700
≥40 to <60	2400	3000
≥60 to <100	2700	3300
≥100	3000	3600

Figure 7 | ALXN1210-aHUS-312 study design and dosing schedule. [a]The loading dose for patients <10 kg was increased from 300 to 600 mg following prespecified interim pharmacokinetic/pharmacodynamic analysis. The first 2 patients in this category received 300-mg loading dose.

administered by intravenous infusion to pediatric (aged <18 years) patients with active TMA and kidney injury who were naïve to complement inhibitor treatment. The protocol was approved by the Institutional Review Board or Independent Ethics Committee at all participating centers, and the study was conducted in accordance with the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. The patient's legal guardian was required to provide written informed consent, and the patient, written informed assent, where applicable.

The trial consisted of a screening period (up to 7 days), a 26-week initial evaluation period, and an extension period of 2 years initially, which was increased to 4.5 years by protocol amendment. Ravulizumab dosing was weight based, with each intravenous infusion given over a period of approximately 2 hours. A loading dose was administered, followed by maintenance doses on day 15 and then every 4 to 8 weeks, depending on body weight (Figure 7). Baseline was defined as the period from initial screening until the first study drug infusion, including day 1. Because of the clinical urgency of patients in this analysis, some patients could have received the loading dose before confirmation of eligibility on the basis of central laboratory results and before receiving Shiga toxin-producing *E coli* and a thrombospondin type 1 motif, member 13, test results. All patients were required to have vaccination against *Neisseria meningitidis,* before or at the time of initiating the study drug.

Study population

Male or female patients, aged <18 years and weighing ≥5 kg at the time of consent, who had not been previously treated with complement inhibitors were included if they had evidence of active TMA (hemolysis, thrombocytopenia, and kidney disfunction) per the following laboratory criteria: platelet count, $<150 \times 10^9$/L; LDH, ≥1.5× upper limit of normal; hemoglobin, lower limit of normal or less; and serum creatinine level, ≥97.5th percentile for age. Key exclusion criteria were as follows: deficiency in a thrombospondin type 1 motif, member 13 (activity, <5%); Shiga toxin-producing *E coli* hemolytic uremic syndrome; drug exposure–related hemolytic uremic syndrome; hematopoietic stem cell transplant within last 6 months before start of screening; known genetic defects of cobalamin C metabolism; or other conditions associated with TMA (Supplementary Materials). Patients receiving immunosuppressive therapies were excluded unless specifically for post-transplantation therapy, the patient had anticomplement antibodies, or corticosteroids were being used for another medical condition. Patients receiving plasma exchange/plasma infusion for a period of ≥28 days before screening were excluded (plasma exchange/plasma infusion was allowed up to the first dose of ravulizumab, but not thereafter). Patients receiving long-term dialysis (dialysis on a regular basis for end-stage kidney disease) were also excluded. Patients previously treated with complement inhibitors were also excluded. Full details of inclusion and exclusion criteria are listed in the Supplementary Materials.

Patients must have had vaccination against *N meningitidis* within 3 years before or at the time of initiating the study drug, according to local and national guidance, as well as vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae*. Sexually active female patients were required to use highly effective contraception from screening until at least 8 months after the last dose of ravulizumab and were counseled about avoiding pregnancy during the study period. Patients who received a meningococcal vaccine at study initiation or <2 weeks before initiating treatment with ravulizumab were treated with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients who had not been vaccinated before initiating ravulizumab treatment should have received prophylactic antibiotics before meningococcal vaccination and for at least 2 weeks after. Long-term antibiotic prophylaxis beyond these minimum requirements was based on the practice of the treating physician.

Efficacy end points

The primary end point was complete TMA response during the 26-week initial evaluation period. TMA response was defined by the following criteria: normalization of platelet count ($\geq 150 \times 10^9$/L), normalization of LDH ($\leq$246 U/L), and $\geq$25% improvement in serum creatinine from baseline. Participants had to meet all complete TMA response criteria at 2 separate assessments obtained at least 28 days apart, and any measurement in between. The primary end point was identical to that used in the pediatric eculizumab clinical trial.[7] In cases of a patient receiving dialysis at baseline, the first baseline serum creatinine value that was used was the first available $\geq$6 days after dialysis. For patients receiving dialysis throughout the initial evaluation period, no baseline serum creatinine was calculated during this period, and the renal response component of the analysis was deemed not achieved. eGFR in these patients was set to 10 ml/min per 1.73 m^2.

The secondary end points of the trial included time to complete TMA response; complete TMA response status over time; observed value and change from baseline in hematologic parameters (platelets, LDH, and hemoglobin); proportion of patients with an increase from baseline in hemoglobin $\geq$20 g/L; observed value and change from baseline in eGFR (calculated per the Schwartz formula); eGFR category, as evaluated by eGFR at select target days; dialysis requirement status; and change from baseline in Pediatric FACIT-Fatigue questionnaire (patients aged $\geq$5 years only). The PD and PK end points included serum ravulizumab concentration and serum-free C5 concentrations over time (Supplementary Materials). Free C5 <0.5 μg/ml indicates complete terminal complement inhibition.[31,32]

Exploratory whole exome sequencing of complement pathogenic variants was conducted on the Novaseq 6000 platform with a 2 × 150-bp paired-end module (Illumina Inc., San Diego, CA, USA). Determination of pathogenesis is further detailed in the Supplementary Materials.

Safety end points

The safety of ravulizumab was evaluated by the incidence of AE and SAEs. The proportion of patients who developed antidrug antibodies was also assessed. AEs were coded using MedDRA Version 21.0 and graded using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Physical examinations, vital signs, electrocardiograms, and laboratory assessments were also noted.

Statistical analyses

Efficacy analyses were performed on the full analysis set, which included all patients who received at least one dose of ravulizumab, had at least one postbaseline efficacy assessment, and satisfied specific eligibility criteria that may have been verified only after receiving their first dose. The full analysis set was determined before database lock and before database snapshot for the analysis performed at the end of the 26-week initial evaluation period.

The primary end point, complete TMA response during the 26-week initial evaluation period, was summarized by number and proportion of complete TMA responders (with 2-sided 95% confidence interval) in patients treated with ravulizumab. Complete TMA response through week 50 was also assessed and included all available follow-up.

The secondary end point analyses included a production of Kaplan-Meier distribution of time to complete TMA response. Complete TMA response status over time was summarized by presenting the number and proportion of patients achieving response. Dialysis requirement status, the proportion of patients requiring and no longer requiring dialysis, was calculated (with 2-sided 95% confidence interval). eGFR value and change from baseline were summarized using descriptive statistics. eGFR category was summarized over time, presenting the number and proportion of patients who improved, worsened, and stayed the same compared with eGFR category at baseline.[23] Hematologic parameters (platelets, LDH, and hemoglobin) were summarized using descriptive statistics for observed value and change from baseline. The number and proportion of patients with an increase from baseline in hemoglobin $\geq$20 g/L, observed at 2 separate assessments obtained at least 28 days apart, were summarized. The number and proportion of patients with at least a 3-point improvement from baseline for Pediatric FACIT-Fatigue were also summarized at each time point.

PK/PD analyses were performed in all patients with evaluable PK/PD data who had received at least one infusion of ravulizumab.

All hematologic, renal, and quality-of-life efficacy end points were assessed through week 50.

Safety analyses were performed for the safety set, defined as all patients who received at least one dose of ravulizumab. All AEs, coded using MedDRA Version 18, were summarized by organ system class and preferred term. The data cut point for safety considered all available follow-up.

APPENDIX

Members of the 312 Study Group

Helen Lovell (University of Nebraska Medical Center, Nebraska, USA), Melissa Muff-Luett (University of Nebraska Medical Center, Nebraska, USA), Kristin Malone (University of Nebraska Medical Center, Nebraska, USA), Oluwasegun Adeagbo (Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, Georgia, USA), Alexandria Wilkerson (Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, Georgia, USA), Gloria Fraga (University Hospital Vall d'Hebron, Barcelona, Spain), Scherezade Sarri (University Hospital Vall d'Hebron, Barcelona, Spain), Hae Il Cheong (Division of Pediatric Nephrology, Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea), Yo Han Ahn (Division of Pediatric Nephrology, Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea), Kyoung Hee Han (Jeju National University, School of Medicine, Korea), Elke Wühl (University Hospital Heidelberg for Pediatric and Adolescent Medicine, Heidelberg, Germany), Gianluigi Ardissino (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy), Valentina Capone (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy), Alexandru Constantinescu (Joe DiMaggio Children's Hospital, Hollywood, FL, USA), Ivy Boydstun (Joe DiMaggio Children's Hospital, Hollywood, FL, USA), Reem Raafat (Joe DiMaggio Children's Hospital, Hollywood, FL, USA), Marezhe Mersha (Joe DiMaggio Children's

Hospital, Hollywood, FL, USA), Belkis Wandique-Rapalo (Joe DiMaggio Children's Hospital, Hollywood, FL, USA), Hiroshi Hataya (Tokyo Metropolitan Children's Medical Center, Tokyo, Japan), Dr. Hamada (Tokyo Metropolitan Children's Medical Center, Tokyo, Japan), Dr. Terano (Tokyo Metropolitan Children's Medical Center, Tokyo, Japan), Lesley Rees (Great Ormond Street Hospital, London, UK), Araceli Garcia Pose (Hospital Universitario Infanta Sofía, Madrid, Spain), Inés Vergara Pérez (Hospital Universitario Infanta Sofía, Madrid, Spain), Mercedes Cao Vilariño (Hospital Universitario Infanta Sofía, Madrid, Spain), Brigitte Adams (Hôpital Universitaire des Enfants Reine Fabiola, Brussels, Belgium), and Tram Nathalie (Hôpital Universitaire des Enfants Reine Fabiola, Brussels, Belgium).

DISCLOSURE

LAG has received research support and consultation fees from Alexion Pharmaceuticals Inc. He also serves on the scientific advisory board of the International Atypical Hemolytic Uremic Syndrome (aHUS) Registry, sponsored by Alexion Pharmaceuticals Inc. GA has received lecture and consultation honoraria from Alexion Pharmaceuticals Inc. She is member on the scientific advisory board of the International aHUS Registry, sponsored by Alexion Pharmaceuticals Inc. BPD has received consultation fees from Alexion Pharmaceuticals Inc. GK has received a research grant from Alexion Pharmaceuticals Inc. TM participated in study ALXN1210-312 as an investigator. SO is an employee and shareholder of Alexion Pharmaceuticals Inc. MV was an employee of Alexion Pharmaceuticals Inc. at the time of the clinical trial and owns stock in Alexion Pharmaceuticals Inc. AED was an employee of Alexion Pharmaceuticals Inc. at the time of the clinical trial and owns stock in Alexion Pharmaceuticals Inc. All the other authors declared no competing interests.

DATA STATEMENT

Alexion Pharmaceuticals Inc. will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods like data deidentification, pseudonymization, or anonymization (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion Pharmaceuticals Inc.–sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at http://alexion.com/research-development. Link to Data Request Form (https://alexion.com/contact-alexion/medical-information).

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Patient lay summary.
Supplementary 312 Study group (nonauthor collaborators to be listed in PubMed).
Supplementary inclusion criteria.
Supplementary exclusion criteria.
Supplementary whole-exome sequencing and assessment of variant pathogenicity process. Captured library construction and sequencing; variant calling, filtering, and annotation; assessment of variant pathogenicity; and description of free C5 assay.
Table S1. Extrarenal signs and symptoms.
Table S2. Patient genetics data.
Table S3. Patient comorbidities.
Table S4. All serious adverse events reported during the study.
Figure S1. Graphical representation of the mechanism of ravulizumab half-life prolongation.

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