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**Introduction:** Atypical hemolytic uremic syndrome (aHUS) is a rare, complex, multisystem disease of dysregulated complement activity, characterized by progressive thrombotic microangiopathy (TMA), acute kidney injury, and multiorgan dysfunction, which often progresses to chronic kidney disease. Results from the prospective clinical trial of ravulizumab (NCT02949128) reveal rapid resolution of TMA in patients with aHUS, with sustained efficacy and safety in a 26-week initial evaluation period.

**Methods:** The aim of this analysis was to characterize the long-term efficacy and the safety profile of ravulizumab in adults with aHUS who had completed the initial evaluation period of the trial. Complete TMA response, hematologic and kidney functions, and safety were evaluated for all patients available for follow-up in the extension period (median follow-up: 76.7 weeks; range: 0.6–118.3). This trial included a total of 58 patients, 49 of whom entered the extension period.

**Results:** A total of 4 additional patients achieved complete TMA response during the follow-up period. Normalization of platelet count, serum lactate dehydrogenase (LDH), and hemoglobin observed in the 26-week initial evaluation period was sustained until the last available follow-up, as were the improvements in the estimated glomerular filtration rate (eGFR) and patient quality of life. All efficacy endpoints were correlated with the sustained inhibition of complement C5. Most adverse events (AEs) occurred early during the initial evaluation period and decreased substantially during the extension period. No patient developed a meningococcal infection or died during the extension period.

**Conclusion:** This analysis reveals that ravulizumab administered every 8 weeks is efficacious with an acceptable safety profile for the long-term treatment of adults with aHUS and provides additional clinical benefit beyond 6 months of treatment.

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aHUS is a rare, multisystem disease caused by dysregulation of complement activation. It is characterized by TMA, resulting in thrombocytopenia, intravascular hemolysis, acute kidney injury, and, in many cases, multiorgan dysfunction, which often leads

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[13]Names of the 311 study group members are listed in the appendix

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to progressive hematologic abnormalities, kidney failure, or chronic kidney disease.[1–3]

Before the availability of eculizumab, the first terminal complement inhibitor approved for the treatment of aHUS in 2011,[4–11] therapeutic interventions were restricted to plasma exchange or plasma infusion, and clinical outcomes were generally poor.[12–14] Although transformative, eculizumab requires a standard treatment regimen of i.v. infusion every 2 weeks in patients with a body weight ≥10 kg.

Ravulizumab (Ultomiris, Alexion Pharmaceuticals, Inc., Boston, MA) is a long-acting, anticomplement C5 monoclonal antibody designed by targeted modifications of eculizumab that increase the affinity for the neonatal crystallizable fragment receptor at acidic pH levels and attenuate target-mediated drug disposition, leading to enhanced antibody recycling. This results in a molecule that targets the same epitope with similar affinity and rate as eculizumab, but with an extended half-life (∼52 days vs. ∼11 days).[15,16]

The efficacy and safety of ravulizumab in adults with aHUS naive to complement inhibitor treatment was revealed in the ALXN1210-aHUS-311 phase III trial. During the initial evaluation period of this trial, ravulizumab rapidly resolved complement-mediated TMA and provided immediate and complete terminal complement inhibition during 26 weeks of treatment, with no unexpected safety concerns.[16] On the basis of the positive results of this trial and the ALXN1210-aHUS-312 phase III trial conducted in pediatric patients with aHUS,[17] ravulizumab was recently approved by the European Medicines Agency, US Food and Drug Administration, and Japan for the treatment of adult and pediatric patients with aHUS.[18–20]

This study aims to reveal the efficacy and safety profile of ravulizumab when administered over a longer period of time than the initial 26-week evaluation period of the trial. Here, we present an interim analysis of the data from the extension period of the trial.

## METHODS

### Trial Oversight and Design

ALXN1210-aHUS-311 (NCT02949128; EudraCT 2016-002027-29) is a phase III, single-arm, global study evaluating the efficacy and safety of ravulizumab administered by i.v. infusion to adults (≥18 years of age) with aHUS who are naive to complement inhibitor treatment. The study methodology and results from the initial 26-week evaluation period have been previously reported.[16] This report details the results of all patients available for follow-up (median: 76.7 weeks; range: 0.6–118.3 weeks) from the currently ongoing 4.5-year extension period.

The dosing regimen for ravulizumab used in this study has been described previously.[16] Bodyweight-dependent maintenance doses (≥40 to <60 kg, 3000 mg; ≥60 to <100 kg, 3300 mg; ≥100 kg, 3600 mg) were repeated every 8 weeks in the extension period.

The protocol was approved by the institutional review board or independent ethics committee at each participating center, and the study was conducted in accordance with the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. All participants were required to give written informed consent, and the study was overseen by an external data monitoring committee.

### Key Inclusion and Exclusion Criteria

The complete inclusion and exclusion criteria have been published previously.[16] Briefly, to be included in the ALXN1210-aHUS-311 study, male or female patients ≥18 years of age and weighing ≥40 kg were required to present with evidence of active TMA, including the following: meeting the platelet and LDH criteria (<150 × $10^9$/l and ≥1.5 × upper limit of normal, respectively) and serum creatinine criteria (≥ upper limit of normal).[16]

Patients meeting any of the following criteria were excluded: having disintegrin and metalloproteinase with ADAMTS13 activity <5%; receiving immunosuppressive therapies except as part of a post-transplant regimen or if corticosteroids were being used for a different condition; or on chronic dialysis at screening. Plasma exchange or plasma infusion for a period of <28 days before screening was allowed but prohibited after the first dose of ravulizumab.

### Efficacy Endpoints

The primary efficacy endpoint, assessed in the 26-week initial evaluation period and throughout the extension period until the last available follow-up, was complete TMA response, defined as follows: platelet count normalization (≥150 × $10^9$/l), LDH normalization (≤246 U/l), and ≥25% improvement in serum creatinine from baseline to 183 days. Patients were required to meet all complete TMA response criteria simultaneously at 2 separate assessments, obtained at least 28 days apart, to meet the primary efficacy endpoint. All efficacy endpoints have been previously reported.[16]

The secondary endpoints of the study included the following: analysis of dialysis requirement status (patients were considered as being on dialysis at baseline if dialysis occurred within 5 days before ravulizumab initiation); time to complete TMA response; change in eGFR (calculated using the Modification of Diet In Renal Disease formula[21]); eGFR category, as evaluated by eGFR at select target days; change in hematologic variables (platelets, LDH, hemoglobin) from baseline;

and change in quality of life, as measured by The Functional Assessment of Chronic Illness Therapy—Fatigue version 4. Baseline was defined as the period from screening until the point of the first study drug infusion, including day 1.

### Safety Endpoints

The long-term safety and tolerability of ravulizumab were evaluated by physical examinations, vital signs, electrocardiograms, laboratory assessments, and by assessing the incidence of AEs and serious AEs. AEs were coded using MedDRA version 21.0, and the severity of AEs was graded using the Common Terminology Criteria for Adverse Events version 4.03. The proportion of patients who developed antidrug antibodies was also evaluated. In the previous report of the primary data from the initial 26-week evaluation period, safety analyses were performed on all safety data available at the time (median of 40 weeks).[16] In this study, safety analyses were conducted on all data until the last available follow-up and compared with safety data specifically from the initial 26 weeks.

### Genetic Analysis

For patients who provided informed consent for genetic analyses, complement genetic variant analysis was performed by whole-exome sequencing using the Novaseq 6000 platform with a 2 × 150-base pair paired-end module (Illumina, Inc., San Diego, CA), with pathogenesis determined as previously described.[16] For patients who provided consent to local centers, local site investigators were contacted and asked if they would agree to provide available data on complement gene variants. Variants were reviewed against previously reported variants in the literature and classified as pathogenic, likely pathogenic, nonpathogenic, or variant of uncertain significance. The known pathogenic and likely pathogenic variants are reported.

### Statistical Analyses

Demographics and baseline characteristics of all enrolled patients were summarized for the full analysis set and the safety set (patients who received ≥1 dose of the study drug, including those later excluded). Efficacy analyses were performed on the full analysis set. The primary efficacy analysis for complete TMA response was summarized by the number and proportion of responders with a 2-sided 95% confidence interval. Secondary analyses included the proportion of patients requiring dialysis over time and time to complete TMA; a Kaplan–Meier curve was generated for the time to complete TMA response. Kidney function was evaluated by eGFR using descriptive statistics, and eGFR category (as defined by Kidney Disease Improving Global Outcome chronic kidney disease criteria eGFR value parameters) was summarized over time.[22]

Hematologic laboratory variables were summarized using descriptive statistics. The proportion of patients achieving a hemoglobin response (an increase in hemoglobin from baseline [≥20 g/l] in at least 2 consecutive measurements ≥28 days apart) were summarized over time from baseline. The proportion of patients with at least a 3-point improvement for Functional Assessment of Chronic Illness Therapy—Fatigue was also summarized.

Pharmacokinetic and pharmacodynamic analysis was undertaken in all patients who had received at least 1 infusion of the study drug and had evaluable data. Safety analyses were performed on the safety set, and all AEs were summarized by system organ class and preferred term.

The data-cut for primary and secondary outcomes, and for all safety assessments, considered all available follow-up data. Data from day 351 onward were used for comparative purposes for secondary endpoints.

## RESULTS

### Patient Characteristics

This phase III trial included a total of 58 patients, 49 of whom completed the initial evaluation period and entered the extension period (Figure 1). During the extension period, 8 patients discontinued the study completely; 6 of these had achieved complete TMA response and were stable at the time of discontinuation.

An overview of the baseline demographics and disease characteristics of the overall 311 study population is found in Table 1; further demographics and disease characteristics of this patient population have been published previously.[16] Further information on patient clinical characteristics at the end of the 26-week initial evaluation period and at 52 weeks can be found in Supplementary Table S1. All available genetic and complement factor H (CFH) antibody testing results for the 56 patients in the trial can be found in Supplementary Table S2; results were not available for 11 patients, but among the 45 patients for whom information was available, a complement abnormality (pathogenic variant, likely pathogenic variant, or CFH autoantibodies) was detected in 14 (31%) whereas no pathogenic variant or CFH autoantibodies were detected in 31 (69%). In this analysis, 9 of 14 patients (64.2%) with a detected complement abnormality and 21 of 31 patients (67.7%) without a detected complement abnormality achieved complete TMA response.

### Complete TMA Response

Four additional patients achieved the primary efficacy endpoint of complete TMA response during the extension

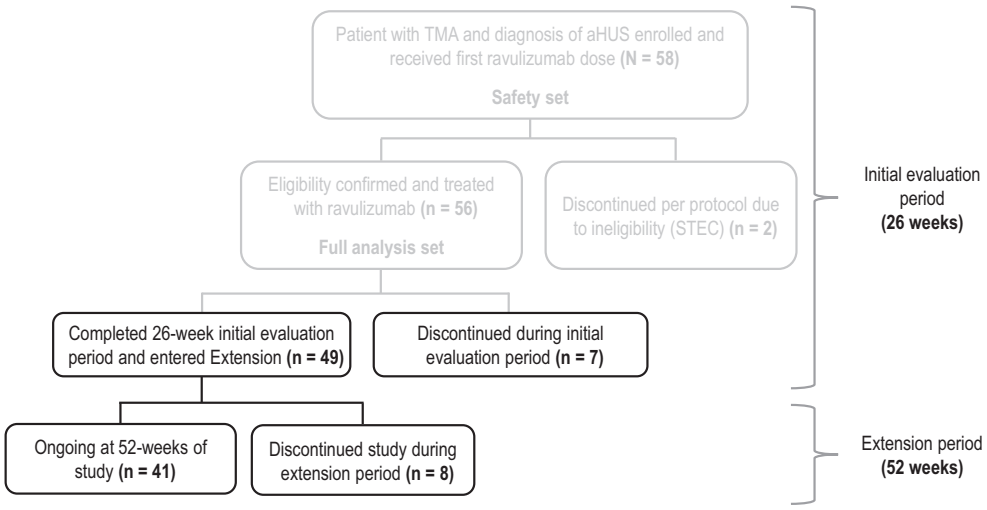


**Figure 1.** Patient disposition. Of the 8 patients who discontinued the study, 1 discontinued owing to protocol violation (the patient received frozen plasma, a prohibited procedure), 5 because of their own (patient) decision, and 2 because of the physician's decision. An additional 3 patients discontinued the study drug during the extension period but remained enrolled in the study. Of these 3 patients, 2 discontinued the drug owing to physician's decision and 1 because of their own (patient) decision. aHUS, atypical hemolytic uremic syndrome; STEC, Shiga toxin-producing *Escherichia coli*; TMA, thrombotic microangiopathy.

period, bringing the total to 34 of 56 (61%), an improvement from 30 of 56 (54%) at the end of the initial evaluation period. These 4 additional patients achieved complete TMA response at days 169, 295, 407, and 407. Furthermore, the needed parameters met to achieve the endpoint for each patient were LDH and platelet normalization, improvement in serum creatinine, LDH normalization, and LDH normalization, respectively.

Of the 4 patients who achieved complete TMA response during the extension period, 3 had a kidney transplant, 1 of whom achieved complete TMA response before week 26, but confirmatory measurements were performed after this week. The patient with a native kidney discontinued dialysis on day 140 and stopped treatment with the angiotensin-converting enzyme inhibitor on day 187, which was followed by increased blood pressure (173/105 mm Hg), thrombocytopenia ($114 \times 10^9$/l), nephrotic syndrome (proteinuria/creatinuria 5.43 g), and anemia (hemoglobin 9.3 g/dl); this was classified as a relapse by the principal investigator on day 187, which resolved on day 190 after restarting the antihypertensive medication. This patient had a pathogenic CFH deficiency mutation. No other genetic or complement autoantibodies were found in the other 3 patients who achieved complete TMA response during the extension period. The proportion of all patients who achieved complete TMA response in the current data-cut is found in Figure 2.

## Hematologic Endpoints

In the last follow-up, platelet count normalization was achieved in 48 patients (85.7%), LDH normalization was reached in 47 patients (83.9%), and hematologic normalization was found in 45 patients (80.4%); this was an improvement from the 47 (83.9%), 43 (76.8%), and 41 patients (73.2%) who achieved these endpoints, respectively, by the end of the initial evaluation period (Supplementary Figure S1). Platelet count, serum LDH, and hemoglobin level normalizations, which were observed by the end of the 183-day initial evaluation period, were sustained across all evaluated timepoints in the extension stage of this study (Figure 3). Changes from baseline and absolute values for platelet count, serum LDH, and hemoglobin levels at days 183 and 351 can be found in Supplementary Table S1.

## Kidney Endpoints

Kidney function (eGFR) substantially improved from baseline and remained stable through day 351 (median change, 23.00; minimum–maximum, −13 to 95 ml/min) (Figure 4, Supplementary Table S3). When compared with baseline, at day 351 the eGFR category stage had improved for 30 patients, remained consistent for 11,

**Table 1.** Baseline demographics and disease characteristics

| Variables | Overall (N = 56) |
|---|---|
| Women | 37 (66.1) |
| Median age at the time of the first aHUS symptoms, y (range) | 40.1 (9.3–76.6) |
| Median age at the time of the first infusion, y (range) | 41.1 (19.5–77.1) |
| Kidney transplant before entering the study, n (%) | 8 (14.3) |
| Dialysis within 5 days of the first dose, n (%) | 29 (51.8) |
| PE/PI before the first dose and related to the current TMA, n (%) | 48 (82.8)[a] |
| Postpartum, n (%) | 8 (14.3) |
| In ICU at screening (mean duration of 10.1 days), n (%) | 27 (50.9)[b] |

[a]Safety data set (N = 58).
[b]Based on the total number of patients who had any emergency room visits or hospitalizations due to aHUS prior to start of screening (n = 53).
aHUS, atypical hemolytic uremic syndrome; ICU, intensive care unit; PE, plasma exchange; PI, plasma infusion; TMA, thrombotic microangiopathy.

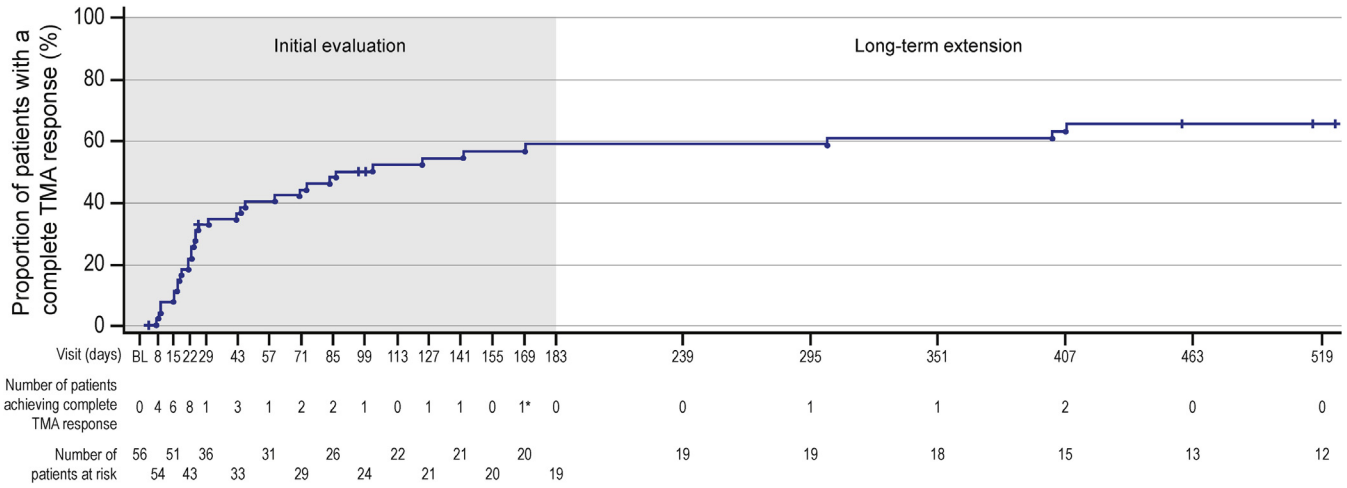


**Figure 2.** Kaplan–Meier graph depicting the time to complete TMA response. Patients who did not have a response were censored on the day of the last study visit or at study discontinuation. *Patient achieved initial complete TMA response measurement at day 169; however confirmatory measurement was not achieved until the extension period (day 239). BL, baseline; TMA, thrombotic microangiopathy.

and worsened for 2. At day 351, 7 patients (16.3%) were in category 1, 9 (20.9%) in category 2, 4 (9.3%) in category 3A, 6 (14.0%) in category 3B, 6 (14.0%) in category 4, and 11 (25.6%) in category 5.

At baseline, 29 of 56 patients (51.8%) were on dialysis. On day 183, 12 of the remaining 49 patients (24.5%) required dialysis, and 10 of the remaining 44 patients (22.7%) required dialysis by day 351. Of the 29 patients (58.6%) who were on dialysis at baseline, 17 discontinued dialysis during the initial evaluation period and did not restart dialysis during their follow-up in the extension period. All 5 patients who required dialysis initiation during this study did so during the initial evaluation period. The patient who discontinued participation in the study owing to a protocol violation received a plasma exchange before receiving a kidney transplant.

### Quality-of-Life Endpoints

Functional assessment of chronic illness therapy—fatigue scores improved from baseline in the initial 183-day evaluation period (median change, 20.00; minimum–maximum, −16 to 48), and the improvements were sustained through the extension period up to day 351 (median, 16.50; minimum–maximum, −17 to 50) (Figure 5).

### Pharmacodynamic Analyses

The levels of complement C5 inhibition observed in the initial evaluation period of this study[16] were maintained through the extension period (Supplementary Figure S2).

### Safety Analyses

A summary of AEs from days 1 to 183 and day 1 to the last available follow-up is given in Table 2. Overall, ravulizumab treatment resulted in no unexpected AEs in the 58 patients in the safety set through the study. At the last available follow-up, all patients experienced one or more AEs; 20 patients (34.5%) experienced treatment-related AEs, most often headache (22 of 58; 38%), diarrhea (19 of 58; 33%), and vomiting (18 of 58; 31%). A total of 33 patients (56.9%) experienced serious AEs, most often hypertension (3 of 58, 5.2%) and pneumonia (3 of 58, 5.2%). No meningococcal infections were reported during the study period. One patient had a treatment-emergent antidrug antibody-positive titer of <1:1 on day 68; however, there was no apparent impact on pharmacokinetics, pharmacodynamics, safety, or efficacy in this patient.

As reported previously, 4 patient deaths were recorded in the initial evaluation period, none of which was considered treatment-related by the study investigator after causality evaluation.[16] No further deaths were recorded until the last available follow-up in the extension period of this study.

## DISCUSSION

This study evaluated the long-term outcomes of treatment with ravulizumab in adult patients with aHUS who were previously naive to complement inhibitor treatment and confirms the findings of the primary analysis during the first 26 weeks,[16] with long-term data revealing sustained efficacy and safety. Ravulizumab maintained a positive benefit profile through a median follow-up of 76.7 weeks, as evidenced by sustained improvement in hematologic outcomes, eGFR, and patient-reported quality of life, alongside a reduction in the frequency of AEs from the end of the initial evaluation period to the extension period of this study.

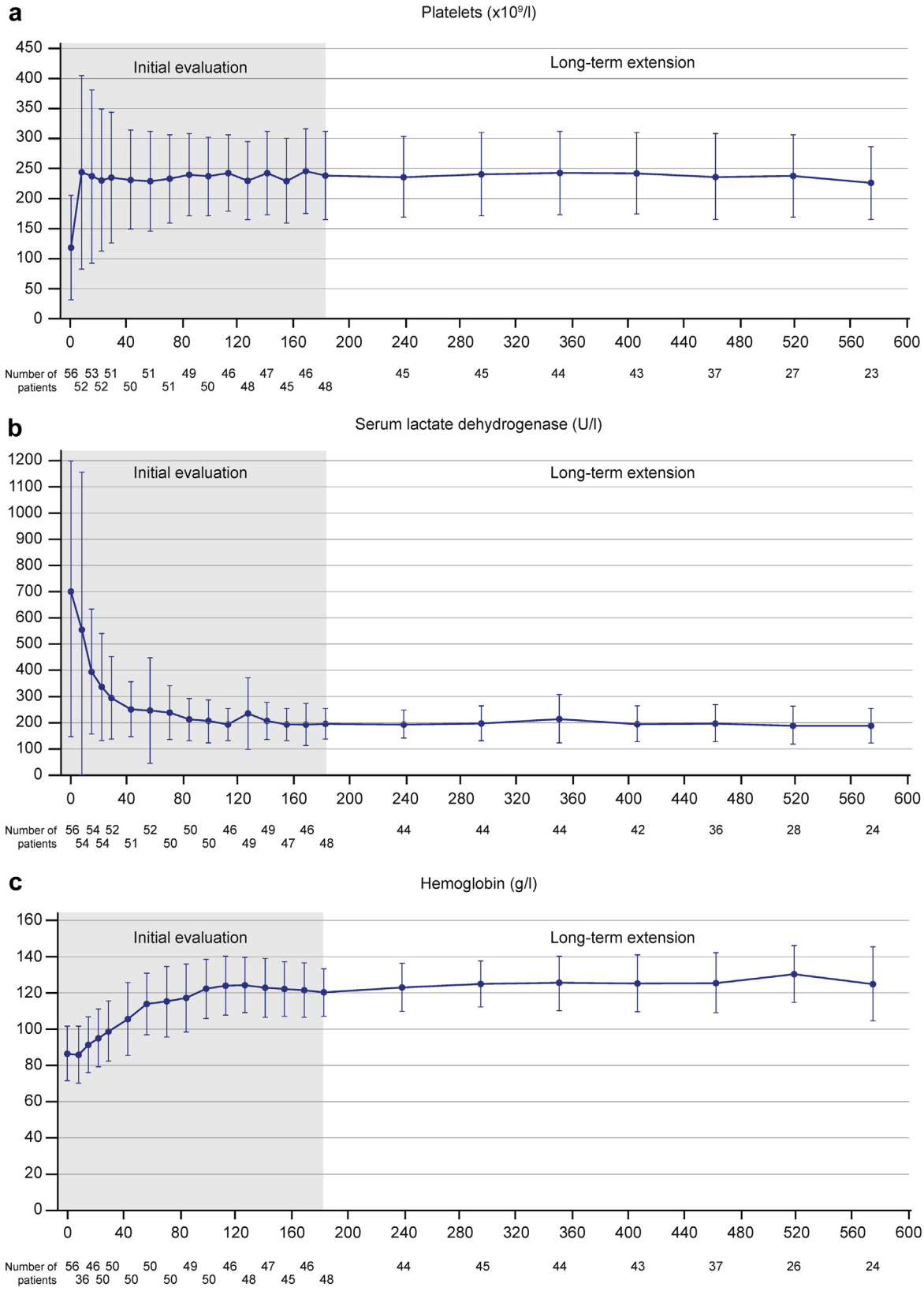


**Figure 3.** Observed laboratory values over time. (a) platelet count; (b) lactate dehydrogenase; (c) hemoglobin. Data are shown as mean (error bars, 95% confidence interval).

In the extension period of this study, an additional 4 patients achieved the primary endpoint of complete TMA response, increasing the overall proportion of patients achieving this endpoint to 61%. We observed that 3 of these 4 additional patients who achieved complete TMA response in the extension period had previously had fluctuating components of the complete TMA response outcome

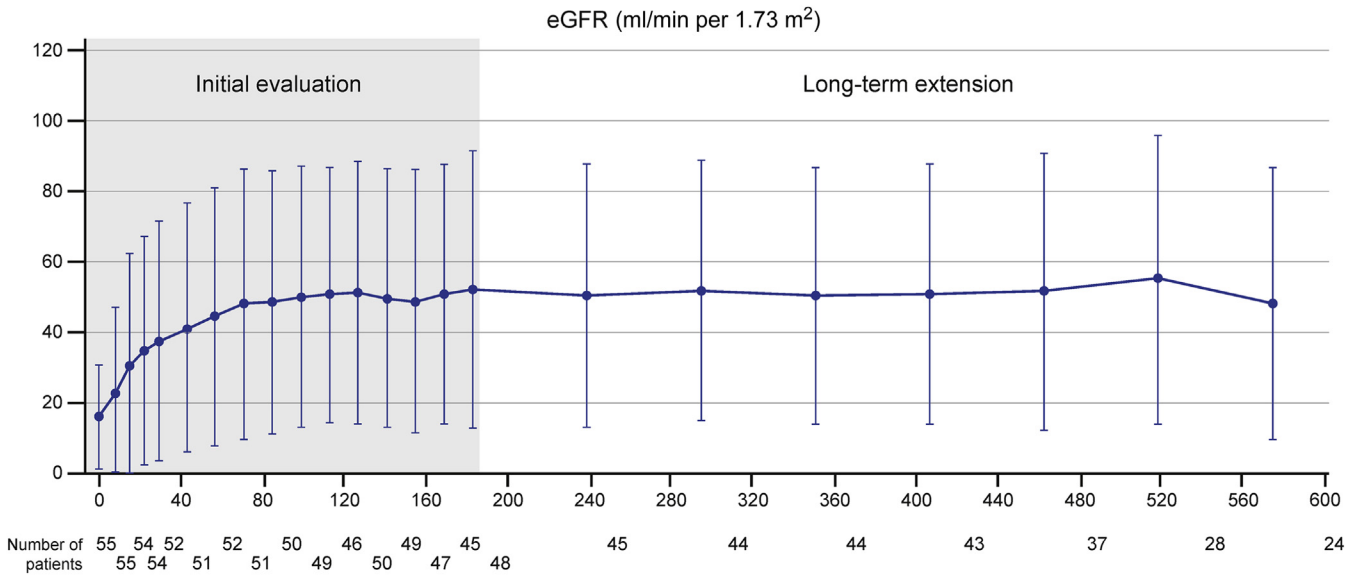


**Figure 4.** Observed eGFR values over time. eGFR, estimated glomerular filtration rate. Data are shown as mean (SD; error bars, 95% confidence interval).

but did not satisfy all criteria simultaneously in the initial evaluation period. This highlights the prospect that continued therapy beyond 6 months may be required to achieve maximum therapeutic response in some patients. Furthermore, the patients also maintained the clinically meaningful responses in hematologic, renal, and quality of life (as measured by Functional Assessment of Chronic Illness Therapy-Fatigue) outcomes observed during the initial evaluation period, suggesting some patients may continue to benefit beyond 6 months of treatment. Taken together, these data reveal that ravulizumab is effective in longer-term prevention of TMA.

In the current study, genetic testing by whole-exome sequencing was performed as an exploratory analysis in consenting patients, and the initial results have been published previously.[16] Although all patients included in the primary analysis had been diagnosed with aHUS on the basis of the laboratory criteria, the lack of data on complement pathogenic variants was deemed a notable limitation of the primary analysis,[23] and many of the included patients did not have a previous genetic test

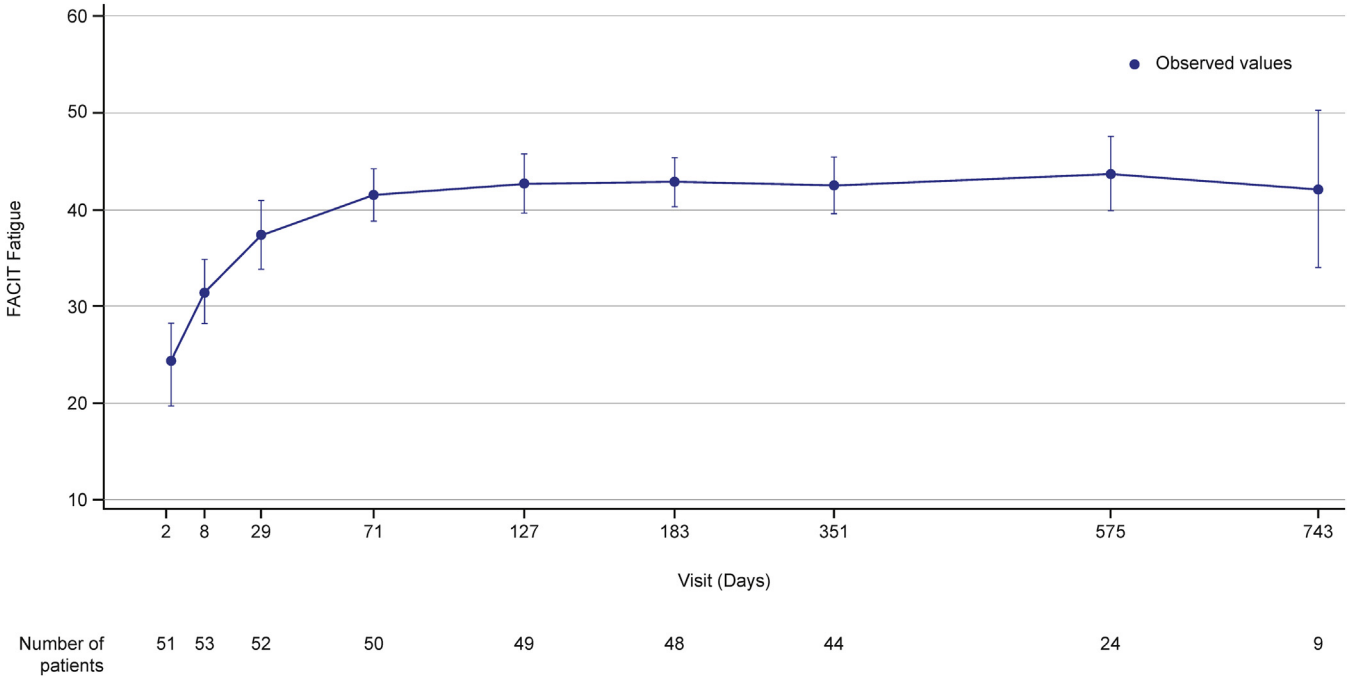


**Figure 5.** FACIT-Fatigue score over time. Data are shown as mean (error bars, 95% confidence interval). FACIT, Functional Assessment of Chronic Illness Therapy.

**Table 2.** Summary of AEs during the trial

| | Day 1–183 | | Day 1 until last available follow-up | |
|---|---|---|---|---|
| Event type | N = 58 | Events | N = 58 | Events |
| Any AE | 58 (100.0) | 696 | 58 (100.0) | 986 |
| Treatment related | 19 (32.8) | 50 | 20 (34.5) | 66 |
| Not treatment related | 58 (100.0) | 646 | 58 (100.0) | 920 |
| Any SAE | 28 (48.3) | 60 | 33 (56.9) | 84 |
| Fatal TEAEs | 3 (5.2) | 3 | 3 (5.2) | 3 |
| Study discontinuation owing to | | | | |
| TEAEs | 3 (5.2) | 3 | 3 (5.2) | 3 |
| TESAEs | 3 (5.2) | 3 | 3 (5.2) | 3 |
| Drug discontinuation owing to | | | | |
| TEAEs | 3 (5.2) | 3 | 3 (5.2) | 3 |
| TESAEs | 3 (5.2) | 3 | 3 (5.2) | 3 |
| SAEs during study drug infusion | 0 (0) | 0 | 0 (0) | 0 |
| Meningococcal infections | 0 (0) | 0 | 0 (0) | 0 |

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.
All values displayed as n (%).

result available. In the current analysis, we present all genetic testing and CFH autoantibody testing data currently available from patients enrolled in the trial; this includes both the whole-exome sequencing performed during the trial on the DNA of consenting patients and follow-up with individual investigators to obtain additional data collected from the individual centers (Supplementary Table S2).

Regarding treatment duration, the current length of the treatment recommended in the European Union and the United States is a minimum of 6 months.[19,20] However, data presented here suggest that patients may continue to benefit beyond this time frame. Long-term treatment with ravulizumab did not result in any unexpected safety signals in this study. Most AEs and serious AEs observed during all available follow-up occurred in the initial evaluation period, and the decrease in the total number of observed AEs in the extension period of the study suggests that long-term treatment with ravulizumab does not seem to pose any significant safety concerns. Indeed, if AEs were treatment related, initial signals would be expected to increase with increasing drug exposure. These findings also suggest against any selection bias, instead highlighting that the greater proportion of AEs observed in the initial evaluation period are likely representative of the disease severity of the patient population at baseline. Furthermore, no meningococcal infections were identified during the study, an important consideration when undertaking long-term inhibition of the terminal complement pathway.[24] The levels of complement C5 inhibition observed with ravulizumab during the initial evaluation period of this study[16] were maintained in the extension period, which was mirrored by the aforementioned improvements in hematologic and kidney parameters. This highlights the observation that ravulizumab has both robust pharmacodynamic and efficacy responses while minimizing the number of i.v. infusions required per year.

If untreated or incorrectly managed, the prognosis for patients with aHUS is poor.[25] One of the major benefits offered by ravulizumab therapy is the reduction in dosing frequency relative to eculizumab, which could improve patients' quality of life by requiring fewer hospital visits and venous punctures, and may have the added benefit of reducing the likelihood of exposure to infections. An expanded dosing interval could improve adherence to treatment, as patients would be taking less time out of education, work, or other commitments and would have much more personal time available for activities such as travel and vacations (an important component of the patients' quality of life). In the United States, a recent productivity analysis of patients with aHUS revealed that fewer infusions per year with ravulizumab substantially reduced the time spent in treatment, suggesting that impact on health systems and other costs are likely to be reduced and patients' quality of life is likely to improve.[26] Further studies will be needed to confirm the economic and humanistic impact of ravulizumab on patients with aHUS.

## CONCLUSIONS

This analysis of longer-term treatment with ravulizumab reveals that administration every 8 weeks is well tolerated and provides clinical improvement in kidney and hematologic parameters in adult patients with aHUS. Continued treatment with ravulizumab beyond the initial 26 weeks can provide further clinical improvements as evidenced by the 4 additional patients who achieved complete TMA response during the extension period (overall, 61%) and a substantial reduction in the number and severity of AEs observed. The long-term efficacy and safety of ravulizumab are important to improve outcomes under unpredictable conditions with a lifelong risk of TMA, such as aHUS. With reduced dosing frequency relative to eculizumab, ravulizumab treatment will lead to a reduction in treatment burden, improving the lives of patients with aHUS and their families.

## DISCLOSURE

This study was sponsored by Alexion Pharmaceuticals, Inc., Boston, Massachusetts, USA. Alexion Pharmaceuticals, Inc. contributed to data interpretation, preparation, review, and approval of the manuscript for submission. All authors had full access to all the data in the study and had the final responsibility for the decision to submit for publication. MS has received grant support from Shire and Novartis and has received speaker fees

and advisory board honoraria from Alexion Pharmaceuticals, Inc. GA has received consulting fees or advisory board honoraria from Alexion Pharmaceuticals, Inc., Chiesi, Advicenne, and Recordati Rare Diseases and has received lecture fees from Alexion Pharmaceuticals, Inc., Chiesi, Advicenne, Kyowa Kirin, and Recordati Rare Diseases. SC has received consulting fees or advisory board honoraria from Alexion Pharmaceuticals, Inc. KG is an employee of Alexion Pharmaceuticals Inc. NH has received consulting fees or advisory board honoraria from Alexion Pharmaceuticals, Inc., Baxter, Novartis, and Sanofi Genzyme; has received lecture fees from Alexion Pharmaceuticals, Inc., Astellas, Baxter, Chiesi, Hansa Biotech, and Novartis; has received travel support from Astellas; and has received research support from Chiesi. YM has received consulting fees or advisory board honoraria from Alexion Pharmaceuticals, Inc., Sanofi, Bioverative, Novo Nordisk, Zenyaku, Argenx, and UCB and has received lecture fees from Alexion Pharmaceuticals, Inc., Zenyaku, Chugai, Novartis, Kyowa Kirin, Bayer, Shire, and KM Biologics. YL has received travel grants from Novartis, Amgen, and Chiesi. JM has received consulting or lecture fees from Alexion Pharmaceuticals, Inc., Sanofi Genzyme, Ablynx, Boehringer Ingelheim, and AstraZeneca. DK has received fees from Alexion Pharmaceuticals, Inc., Gyroscope, Idorsia, Novartis, and Apellis; owns stock options in Gyroscope Therapeutics; and has received research support from Wellcome Trust, Medical Research Council, European Union, National Institute of Health Research Newcastle Biomedical Research Centre at Newcastle upon Tyne Hospitals NHS Foundation Trust, Kidney Research UK, Fight for Sight, Macular Disease Society, and The North Countries Kidney Research Fund. All the other authors declared no competing interests.

## APPENDIX

### List of Study Group Members

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## DATA SHARING

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

Link to Data Request Form (https://alexion.com/contact-alexion/medical-information)

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

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

**Figure S2.** Free complement C5 concentrations at each study visit after ravulizumab treatment.

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

**Table S2.** Patient genetic analysis.

**Table S3.** Observed median eGFR values at baseline, day 183, and day 351.

eGFR, estimated glomerular filtration rate.

**Plain Language Summary.**

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