



Terminal Complement Inhibitor Eculizumab in Adult Patients With Atypical Hemolytic Uremic Syndrome: A Single-Arm, Open-Label Trial

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Background: Atypical hemolytic uremic syndrome (aHUS) is a rare genetic life-threatening disease of chronic uncontrolled complement activation leading to thrombotic microangiopathy (TMA) and severe end-organ damage. Eculizumab, a terminal complement inhibitor approved for aHUS treatment, was reported to improve hematologic and renal parameters in 2 prior prospective phase 2 studies. This is the largest prospective study of eculizumab in aHUS to date, conducted in an adult population.

Study Design: Open-label single-arm phase 2 trial.

Setting & Participants: Patients 18 years or older with aHUS (platelet count $<150 \times 10^3/\mu\text{L}$, hemoglobin \leq lower limit of normal, lactate dehydrogenase $\geq 1.5 \times$ upper limit of normal [ULN], and serum creatinine \geq ULN) were included in this multicenter multinational study.

Intervention: Intravenous eculizumab (900 mg/wk for 4 weeks, 1,200 mg at week 5 and then every 2 weeks) for 26 weeks.

Outcomes & Measurements: Primary end point was complete TMA response within 26 weeks, defined as hematologic normalization (platelet count $\geq 150 \times 10^3/\mu\text{L}$, LDH \leq ULN), and preservation of kidney function ($<25\%$ serum creatinine increase from baseline), confirmed by 2 or more consecutive measurements obtained 4 or more weeks apart.

Results: 41 patients were treated; 38 (93%) completed 26 weeks of treatment. 30 (73%) were included during their first TMA manifestation. 30 (73%) had complete TMA response. Platelet counts and estimated glomerular filtration rates increased from baseline ($P < 0.001$). All 35 patients on baseline plasma exchange/plasma infusion discontinued by week 26. Of 24 patients requiring baseline dialysis, 5 recovered kidney function before eculizumab initiation and 15 of the remaining 19 (79%) discontinued dialysis during eculizumab treatment. No patients lost existing transplants. Quality-of-life measures were significantly improved. Two patients developed meningococcal infections; both recovered, and 1 remained on eculizumab treatment.

Limitations: Single-arm open-label design.

Conclusions: Results highlight the benefits of eculizumab in adult patients with aHUS: improvement in hematologic, renal, and quality-of-life parameters; dialysis discontinuation; and transplant protection.

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INDEX WORDS: Eculizumab; Soliris; terminal complement inhibitor; atypical hemolytic uremic syndrome (aHUS); thrombotic microangiopathy (TMA); kidney disease; platelet count; hemoglobin; lactate dehydrogenase (LDH); renal function; hematologic normalization; TMA response; adults; clinical trial.

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A typical hemolytic uremic syndrome (aHUS) is a rare, often progressive, and life-threatening cause of systemic thrombotic microangiopathy (TMA) resulting from long-term uncontrolled alternative complement activation.¹⁻³ Complement gene mutations or factor H autoantibodies have been identified in up to 70% of patients with aHUS,⁴⁻⁶ but are not required for diagnosis. Although frequently diagnosed during childhood, the majority (58%) of aHUS cases occur in patients older than 18 years.⁵

The underlying pathophysiology associated with aHUS involves endothelial cell activation, platelet activation and aggregation, leukocyte recruitment, and a systemic procoagulant state, leading to TMA.^{3,4,6-8} Decreased kidney function and end-stage renal disease (ESRD) are recognized as severe complications of aHUS. Forty-six percent of patients have already reached ESRD by the time aHUS is diagnosed,⁵ and the risk for kidney failure and death increases with disease duration.^{4,5} More rarely, TMA in aHUS also leads to significant morbidity in other vital organ systems, including neurologic, cardiovascular, pulmonary, and gastrointestinal.^{1,9}

Historically, management of aHUS has included plasma exchange/plasma infusion (PE/PI), yet outcomes for adults with aHUS receiving PE/PI are poor; up to 56% progress to ESRD or die within 1 year of diagnosis.⁵ The longer term outlook is equally dire because up to 79% of patients have permanently decreased kidney function or ESRD or die within 3 years.⁴ Kidney transplantation in patients with aHUS historically also has been unsuccessful because approximately 50% to 71% of patients with aHUS have transplant failure within 1 year as a result of a subsequent TMA manifestation.^{4,10}

Eculizumab (Soliris; Alexion Pharmaceuticals, Inc) is a humanized monoclonal antibody that blocks cleavage of the terminal complement protein C5 into the proinflammatory C5a and lytic C5b-9.^{6,11} In 2011, eculizumab became the first and only approved treatment for aHUS.^{12,13} The efficacy and safety of eculizumab in aHUS were first demonstrated in 2 prospective clinical trials of primarily adult patients, either with evidence of progressing TMA or with long disease duration and chronic kidney disease (CKD).^{14,15} Both pivotal trials included patients with native kidneys and kidney transplants.¹⁴ The current study is the first and largest study of eculizumab in an exclusively adult population with severe aHUS and was conducted to satisfy requirements for full approval in the United States. This report presents results of the primary analysis based on a 26-week eculizumab treatment period.

METHODS

Study Design and Approval

This was an open-label, single-arm, multicenter, phase 2 trial in adult patients with aHUS to assess the efficacy of eculizumab in inhibiting complement-mediated TMA. The study consisted of a

7-day screening period, 26-week treatment period, and an extension period in which patients could receive eculizumab for up to 2 years. Patients 18 years or older with aHUS, platelet counts $<150 \times 10^3/\mu\text{L}$, hemoglobin levels at or less than the lower limit of normal range, lactate dehydrogenase (LDH) levels ≥ 1.5 times the upper limit of normal range, and serum creatinine levels at or greater than the upper limit of normal range at screening were enrolled at 23 centers in North America and Europe from August 2010 through September 2011. An identified complement abnormality was not required for enrollment, although complement mutation analysis was performed in all patients upon study entry. Use of PE/PI was not a prerequisite for inclusion. Patients must have been vaccinated against *Neisseria meningitidis*; if vaccination occurred fewer than 14 days prior to receiving the first eculizumab dose, patients received prophylactic antibiotics until at least 14 days after vaccination. Key exclusion criteria were described previously.¹⁴

The protocol was approved by the institutional review board at each participating center or by an independent ethics committee (Table S1, available as online supplementary material) and was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guidelines and the Declaration of Helsinki. All patients provided written informed consent before entry into the study.

Dosages

Eculizumab dosages were based on previous clinical studies¹⁴ and were administered intravenously at 900 mg once a week for 4 weeks, 1,200 mg at week 5, and then 1,200 mg every 2 weeks. Patients who discontinued eculizumab therapy were followed up for 8 weeks to assess safety parameters and for 1 year to assess aHUS disease status and outcomes.

End Points

Efficacy end points were within 26 weeks of the treatment (primary analysis) and were defined elsewhere¹⁴ unless specified here. The primary end point was proportion of patients who achieved complete TMA response, defined as hematologic normalization (platelet count $\geq 150 \times 10^3/\mu\text{L}$ and LDH \leq upper limit of normal range) and preservation of kidney function ($<25\%$ increase in serum creatinine from baseline), confirmed by 2 or more consecutive measurements obtained 4 or more weeks apart. Secondary end points included modified complete TMA response, defined as hematologic normalization (platelets and LDH) and improvement in kidney function (ie, $\geq 25\%$ decrease in serum creatinine level from baseline), TMA event-free status (absence of platelet count decrease $> 25\%$ from baseline, PE/PI, and new dialysis for ≥ 12 weeks), TMA intervention rate (number of PE/PI and/or new dialysis events per patient-days), hematologic normalization, and improvements in hematologic parameters (platelet count, LDH, and hemoglobin levels) and kidney function measures (estimated glomerular filtration rate [eGFR]¹⁶ and CKD improvement by ≥ 1 stage). Categorical end points were required to be sustained for 2 or more consecutive measurements obtained 4 or more weeks apart. All enrolled patients were included in analyses of response variable end points (eg, complete TMA response, modified complete TMA response, TMA event-free status, platelet count normalization, LDH normalization, hematologic normalization, improvement in hemoglobin level by ≥ 2 g/dL, eGFR improvement by ≥ 15 mL/min/ 1.73 m², and CKD improvement by ≥ 1 stage). If a patient did not have sufficient data to meet the achievement criteria for a response variable end point and sustain achievement for 28 days, the patient could not achieve the end point. Data may be missing if patients did not attend the week 26 visit or no measurement was recorded for the following continuous variables: mean change from baseline in platelet count and eGFR, mean eGFR and serum creatinine level, and CKD stage. Health-related quality of life was assessed by the

EQ-5D (EuroQol Group) US time trade-off¹⁷ as described previously,¹⁴ the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F),¹⁸ and the 36-Item Short Form Health Survey (SF-36)¹⁹ questionnaires. The safety and tolerability of eculizumab was assessed by reported adverse events (AEs), reviewed by an independent data monitoring committee. The presence of neutralizing human anti-human antibodies was assessed at study days 0 and 28 and at the end of study with an electrochemiluminescence bridging assay, which conjugated eculizumab to biotin and to SulfoTag (Meso Scale Diagnostics, LLC).

Statistical Analyses

All analyses were performed for the intention-to-treat population, defined as all patients who received 1 or more dose of eculizumab, using the SAS System (version 9.2; SAS Institute Inc). Statistical tests were assessed at the 2-sided $\alpha = 5\%$ level without adjustment for multiplicity. Complete TMA response, modified complete TMA response, and proportion of patients with a ≥ 15 mL/min/1.73 m² change in eGFR were assessed using the Clopper-Pearson method for responder rate at the 1-sided $\alpha = 5\%$ level. For all composite end points, patients were censored at the last follow-up day if baseline or postbaseline values were missing for any component; patients unable to be assessed for all components were considered treatment failures. Effect size for the EQ-5D was calculated as Cohen d standardized mean change from baseline. Baseline demographic and clinical characteristics and efficacy outcomes of subgroups of patients who did and did not require dialysis at study baseline were analyzed post hoc.

RESULTS

Patients

Forty-four adult patients were enrolled, 41 were treated, and 38 (93%) completed the 26-week study period (Fig 1). Patient demographics, disease characteristics, and baseline laboratory values in the intention-to-treat population and for patients who did (n = 24) and did not (n = 17) require dialysis use at baseline are summarized in Table 1. The study population was mainly white (93%) and female (68%), with a mean age of 40 years. Twenty-one (51%) patients had 1 or more identified complement genetic mutation, autoantibody, or deletion. Thirty (73%) patients had aHUS newly diagnosed and were enrolled in the study during their first clinical TMA manifestation. Thirty-five (85%) patients received eculizumab after undergoing PE/PI during the current manifestation; 6 (15%) received first-line eculizumab without prior PE/PI. Twenty-four (59%) patients were on dialysis at baseline for a median pre-treatment duration of 13 (range, 2-2,376) days (measured in 20 patients; the other 4 initiated dialysis between days 0 and 14), including 13 (range, 2-26) days during the current manifestation (n = 18). Nine (22%) patients had a history of prior kidney transplantation.

Efficacy

Primary End Point

There was complete TMA response in 30 patients (73%; 95% confidence interval [CI], 57%-86%; N = 41) by 26 weeks (Table 2). Criteria for the primary end point were met by 17 of 24 (71%) patients requiring dialysis

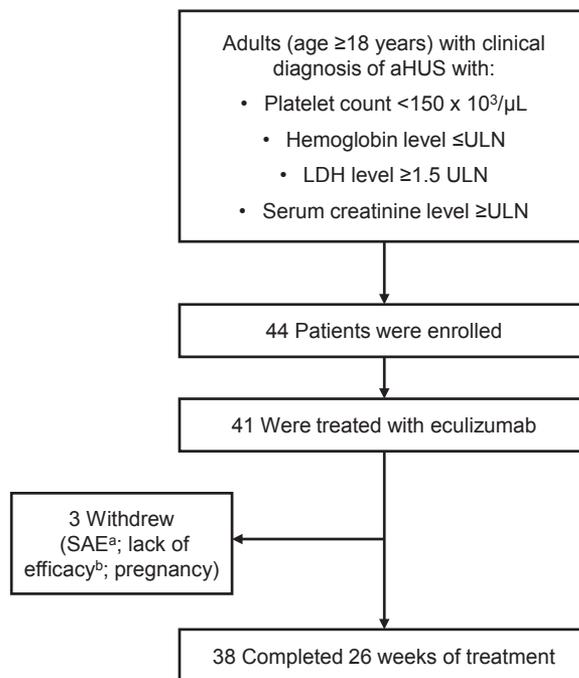


Figure 1. Patient disposition. ^aPatient with meningococcal meningitis who recovered but permanently discontinued the study. ^bEighty-year-old patient who had complete thrombotic microangiopathy response (ie, normalization of platelets, lactate dehydrogenase [LDH], and preservation of kidney function with <25% increase in serum creatinine from baseline) on eculizumab therapy. However, the patient's serum creatinine level did not decrease and hemoglobin level did not normalize. The patient was withdrawn from the study on day 104. Abbreviations: aHUS, atypical hemolytic uremic syndrome; SAE, serious adverse event; ULN, upper limit of the normal range.

and 13 of 17 (77%) who did not require dialysis at baseline. Overall, median time to complete TMA response was 56 (range, 2-147) days.

Other TMA Outcomes

By 26 weeks, modified complete TMA response was achieved by 23 patients (56%; 95% CI, 40%-72%; N = 41) at a median of 57 (range, 2-147) days. TMA event-free status was reached by 37 patients (90%; 95% CI, 77%-97%; N = 41; Table 2) after a mean of 6.1 ± 14.3 (standard deviation) days. The median TMA intervention rate significantly decreased from 0.6 (range, 0-1.4) per patient before treatment to 0 (range, 0-0.6) per patient while on eculizumab therapy ($P < 0.001$). Of 35 patients on PE/PI at baseline, all (100%) discontinued PE/PI during the study period (range, day 0-163). Four of the 6 patients not receiving PE/PI at baseline initiated PE/PI during the study period. However, no patients who remained on eculizumab treatment at week 26 were receiving PE/PI.

Hematologic Outcomes

Forty patients (98%; 95% CI, 87%-100%; N = 41) had platelet count normalization (Table 2) at a median

Table 1. Patient Demographics and Baseline Clinical Characteristics

Variable	ITT Population (N = 41)	Dialysis ^a (n = 24)	No Dialysis ^a (n = 17)
Age, y			
Mean	40 ± 15	35 ± 13	48 ± 15
Range	18-80	18-65	27-80
Age category			
18-44 y	27 (66)	19 (79)	8 (47)
45-65 y	12 (29)	5 (21)	7 (41)
>65 y	2 (5)	0 (0)	2 (12)
Female sex	28 (68)	17 (71)	11 (65)
Race/ethnicity			
White	38 (93)	NA	NA
Black or African American	2 (5)	NA	NA
Asian	1 (2)	NA	NA
Patient-reported family history of aHUS	6 (15)	4 (17)	2 (12)
Identified complement gene mutation or autoantibody	20 (49)	13 (54)	7 (41)
CFH	10 (24)	9 (38)	1 (6)
C3 gain-of-function	4 (10)	1 (4)	3 (18)
CFI	2 (5)	0 (0)	2 (12)
MCP	2 (5)	2 (8)	0 (0)
CFH and MCP	1 (2)	0 (0)	1 (6)
CFH autoantibody	1 (2)	1 (4)	0 (0)
Identified CFHR3-CFHR1 deletion	1 (2)	1 (4)	0 (0)
Time from aHUS diagnosis until screening, mo	0.8 (0-311)	0.5 (0-136)	19 (0-311)
Duration of current clinical manifestation of aHUS, mo	0.5 (0-19)	0.4 (0-1)	1 (0-19)
Newly diagnosed	30 (73)	23 (96)	7 (41)
PE/PI during current manifestation	35 (85)	22 (92)	13 (76)
Dialysis at baseline ^a	24 (59)	24 (100)	0 (0)
Duration of prebaseline dialysis, d	13 (2-2,376) ^b	13 (2-2,376) ^b	—
Prior kidney transplant	9 (22)	3 (13)	6 (35)
Platelet count (×10 ³ /μL)	119 ± 66	108 ± 75	135 ± 50
Platelet count < 150 × 10 ³ /μL	27 (66)	18 (75)	9 (53)
LDH, U/L	493 ± 501	572 ± 628	381 ± 194
LDH > ULN	32 (78)	19 (79)	13 (77)
Hemoglobin, g/dL, n = 38	8.7 ± 2.1	8.2 ± 1.4	9.7 ± 1.7
Serum creatinine, mg/dL, n = 40	4.6 ± 3.0	6.0 ± 3.2	2.9 ± 1.5
eGFR, mL/min/1.73 m ²	17 ± 12	10 ± 3	27 ± 13
eGFR category			
<15 mL/min/1.73 m ²	27 (66)	23 (96)	4 (24)
15-29 mL/min/1.73 m ²	6 (15)	1 (4)	5 (29)
30-44 mL/min/1.73 m ²	6 (15)	0 (0)	6 (35)
45-59 mL/min/1.73 m ²	2 (5)	0 (0)	2 (12)

Note: Unless otherwise indicated, values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median (range). Conversion factors for hemoglobin in g/dL to g/L, ×10; serum creatinine in mg/dL to μmol/L, ×88.4.

Abbreviations: aHUS, atypical hemolytic uremic syndrome; CFH, complement factor H; CFHR, CFH-related protein; CFI, complement factor I; eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; LDH, lactate dehydrogenase; MCP, membrane cofactor protein; NA, not available; PE/PI, plasma exchange/plasma infusion; ULN, upper limit of the normal range.

^aPatients were grouped by dialysis use at study baseline. Baseline dialysis was defined as any occurring within 7 days prior to and up to 14 days after the first eculizumab dose.

^bIn the 20 patients who discontinued dialysis during the study.

of 8 (range, 0-84) days. Improvement in platelet counts from baseline was significant at 1 week (mean change, 104 ± 115 × 10³/μL) and was maintained to 26 weeks (mean change from baseline, 135 ± 114 × 10³/μL; n = 27; P ≤ 0.001 at all time points; Fig 2). There was LDH level normalization in 37 patients (90%; 95% CI, 77%-97%; N = 41) at a median of 54 (range, 2-146) days. At 26 weeks, mean change from baseline in LDH levels

was -323 ± 590 U/L (P = 0.008; n = 28). There was hematologic normalization in 36 patients (88%; 95% CI, 74%-96%; N = 41) by 26 weeks, at a median of 55 (range, 2-146) days. A total of 25 patients (61%; 95% CI, 45%-76%; N = 41) had an improvement in hemoglobin level of at least 2 g/dL by week 26, at a median of 25 (range, 7-113) days. Mean change from baseline in hemoglobin level after 26 weeks was 3.3 ± 3.2 g/dL (P < 0.001; n = 25).

Table 2. TMA, Hematologic, and Kidney Disease Outcomes for Eculizumab in Adult Patients With aHUS, by 26 Weeks of Treatment

Primary and Secondary End Points	ITT Population (N = 41)	Dialysis ^a (n = 24)	No Dialysis ^a (n = 17)
Primary end point			
Complete TMA response ^b	30 (73%)	17 (71%)	13 (77%)
95% CI	57%-86%	49%-87%	50%-93%
TMA outcomes			
Modified complete TMA response ^b	23 (56%)	15 (63%)	8 (47%)
95% CI	40%-72%	41%-81%	23%-72%
TMA event-free status ^b	37 (90%)	22 (92%)	15 (88%)
95% CI	77%-97%	73%-99%	64%-99%
Hematologic outcomes			
Platelet count normalization ^b	40 (98%)	23 (96%)	17 (100%)
95% CI	87%-100%	79%-100%	81%-100%
Change from baseline in platelet count, $\times 10^3/\mu\text{L}$ (n = 27) ^c	135 \pm 114	163 \pm 120	87 \pm 88
	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> = 0.01
LDH normalization ^b	37 (90%)	23 (96%)	14 (82%)
95% CI	77%-97%	79%-100%	57%-96%
Hematologic normalization ^b	36 (88%)	22 (92%)	14 (82%)
95% CI	74%-96%	73%-99%	57%-96%
Improvement in hemoglobin by ≥ 2 g/dL ^b	25 (61%)	16 (67%)	9 (53%)
95% CI	45%-76%	45%-84%	28%-77%
Kidney disease outcomes			
eGFR improvement by ≥ 15 mL/min/1.73 m ^{2b}	22 (54%)	15 (63%)	7 (41%)
95% CI	37%-69%	41%-81%	18%-67%
Change from baseline in eGFR, mL/min/1.73 m ² (n = 29) ^d	29 \pm 24	35 \pm 22	20 \pm 24
	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> = 0.02
eGFR, mL/min/1.73 m ² (n = 29) ^d	47 \pm 24	46 \pm 23	51 \pm 28
Serum creatinine, mg/dL (n = 29) ^d	1.7 \pm 0.8	NA	NA
Patients on dialysis at baseline who discontinued it	20/24 (83%)	20/24 (83%)	—
Discontinued before the initial eculizumab dose, but within the baseline period	5/24 (21%)	5/24 (21%)	—
Discontinued during the study period	15/19 (79%)	15/19 (79%)	—
Patients not on dialysis at baseline who initiated in study period	4/17 (24%)	—	4/17 (24%)
CKD stage ^d			
1	2 (5%)	0 (0%)	2 (12%)
2	6 (15%)	5 (21%)	1 (6%)
3a	8 (20%)	6 (25%)	2 (12%)
3b	6 (15%)	2 (8%)	4 (24%)
4	2 (5%)	1 (4%)	1 (6%)
5	5 (12%)	4 (17%)	1 (6%)
Unknown	12 (29%)	6 (25%)	6 (35%)

Note: Unless otherwise indicated, values for categorical variables are given as number (percentage) or n/N (percentage); values for continuous variables are given as mean \pm standard deviation. Complete TMA response was defined as platelet count $\geq 150 \times 10^3/\mu\text{L}$, LDH at ULN or less, and <25% increase in serum creatinine from baseline (ie, preservation of kidney function) and was confirmed by 2 or more consecutive measurements obtained 4 or more weeks apart. Modified complete TMA response was defined as platelet count $\geq 150 \times 10^3/\mu\text{L}$, LDH at ULN or less, and $\geq 25\%$ improvement in serum creatinine level from baseline (ie, improvement in kidney function). TMA event-free status was defined as the absence of the following for 12 or more weeks: >25% decrease from baseline in platelet count, PE/PI while receiving eculizumab, and new dialysis. Categorical end points were required to be sustained for 2 or more consecutive measurements obtained 4 or more weeks apart. Conversion factors for hemoglobin in g/dL to g/L, $\times 10$; for serum creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$.

Abbreviations: aHUS, atypical hemolytic uremic syndrome; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; LDH, lactate dehydrogenase; NA, not available; PE/PI, plasma exchange/plasma infusion; TMA, thrombotic microangiopathy; ULN, upper limit of normal range.

^aPatients were grouped by dialysis use at study baseline. Baseline dialysis was defined as any occurring within 7 days prior to and up to 14 days after the first eculizumab dose.

^bN = 41. All enrolled patients were included in the analysis. If a patient did not have sufficient data to meet the achievement criteria for a response variable end point and sustain achievement for 28 days, the patient could not achieve the end point.

^cData for 14 of 41 (34%) patients were not available at week 26. Data were missing if the patient did not attend the week 26 visit or no measurement was recorded.

^dData for 12 of 41 (29%) patients were not available at week 26. Data were missing if the patient did not attend the week 26 visit or no measurement was recorded.

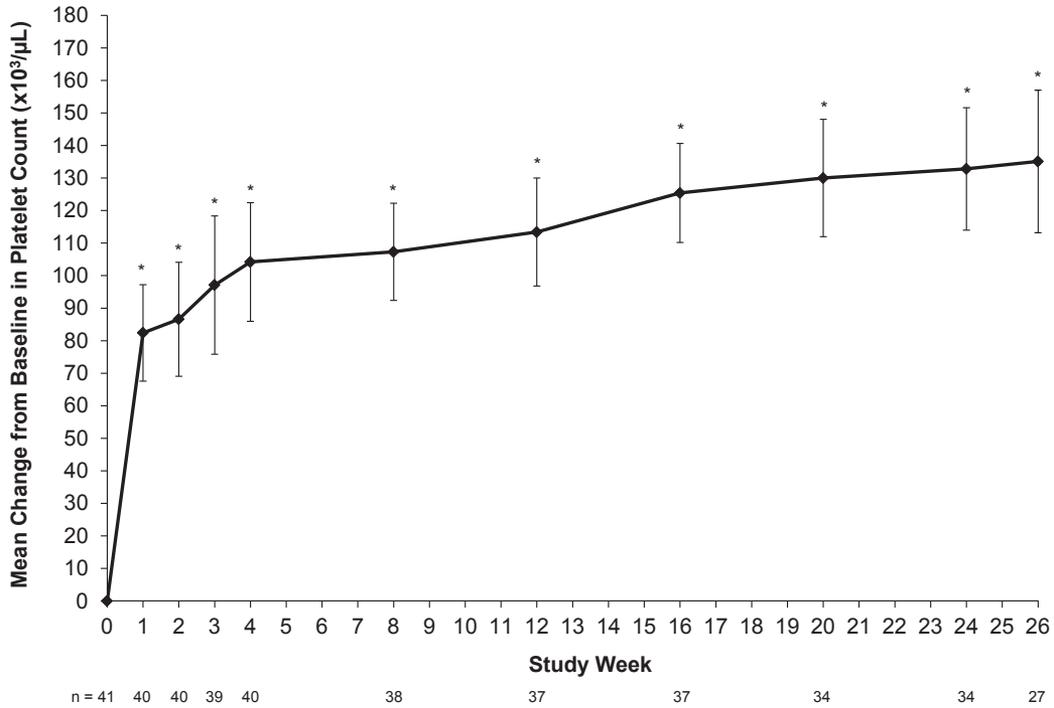


Figure 2. Improvement in platelet count over 26 weeks of eculizumab treatment. Bars represent standard error. * $P \leq 0.001$. Only $n > 5$ are shown.

Kidney Disease Outcomes

Twenty-two patients (54%; 95% CI, 37%-69%; $N = 41$) had eGFR improvement of ≥ 15 mL/min/1.73 m² by week 26 (Table 2). Significant improvements in eGFRs from baseline were achieved by

week 1 ($P < 0.05$) and were maintained over 26 weeks of treatment (Fig 3). Mean change from baseline in eGFRs at 26 weeks was 29 ± 24 mL/min/1.73 m² ($P < 0.001$; $n = 29$). Improvements in eGFRs were greater for patients on dialysis at baseline compared with those who did

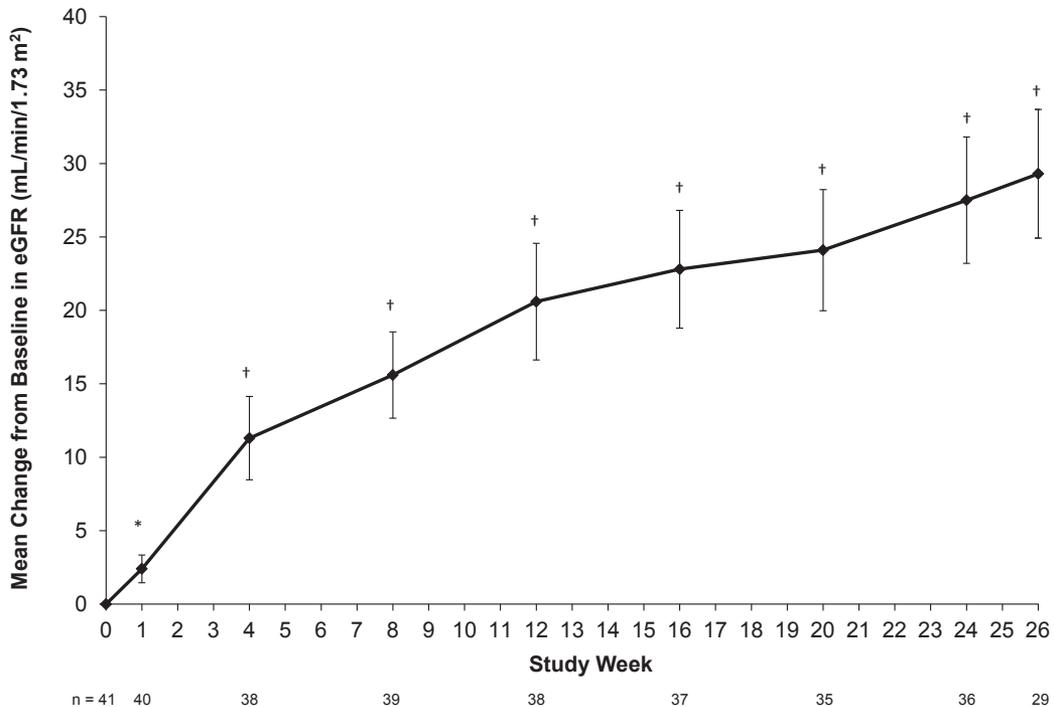


Figure 3. Improvement in estimated glomerular filtration rate (eGFR) over 26 weeks of eculizumab treatment. Bars represent standard error. * $P \leq 0.05$; † $P \leq 0.01$. Only $n > 5$ are shown.

not require baseline dialysis (Table 2). At week 26, mean serum creatinine level was 1.7 ± 0.8 mg/dL ($n = 29$). During the 26-week study period, 26 patients (63%; $N = 41$) improved by 1 or more stage of CKD. Of the 24 patients on dialysis at baseline, 20 (83%) discontinued dialysis. Of these, 5 discontinued dialysis before receiving the initial dose of eculizumab. Of the other 19 patients, 15 (79%) discontinued before week 26, after a posttreatment median of 29 (range, 1-180) days. Four of the 19 patients continued dialysis at week 26 (Fig 4). No patient who discontinued dialysis needed to resume dialysis during the 26-week study period. Of the 17 patients not on dialysis at baseline, 4 (24%) initiated new dialysis during the study (on days 36, 62, 120, and 160), including 2 who discontinued prior to and 2 who remained on dialysis at week 26. Thus, at week 26, a total of 6 patients (15%) were receiving dialysis, compared with 19 (46%) at the start of eculizumab therapy.

Health-Related Quality of Life

Patient health-related quality of life was also improved after 26 weeks of eculizumab therapy (Fig 5). Thirteen of 23 (57%) evaluable patients met criteria for clinically important improvements (≥ 0.06)²⁰ on the US time trade-off index in the EQ-5D questionnaire by 26 weeks, and mean change from baseline was significant ($P < 0.001$). FACIT-F and SF-36 score changes from baseline after 26 weeks are presented in Item S1.

Pharmacokinetics and Pharmacodynamics

Pharmacokinetic and pharmacodynamic data are presented in Item S2.

Safety

All patients in the study reported at least 1 treatment-emergent AE (Table S2). Serious treatment-emergent AEs were reported by 18 patients (44%; Table S3), 1 of which (meningococcal meningitis; serogroup unknown) led to a permanent eculizumab therapy discontinuation at day 98. A serious treatment-emergent AE of meningococcal sepsis (serogroup B) was reported in 1 patient, who was hospitalized and recovered without sequelae; eculizumab treatment was not interrupted. In both cases of meningococcal infection, the patients had been immunized against serogroups A, C, W, and Y, but had not received long-term antibiotic prophylaxis (see additional details in Table S4). No deaths or unexpected safety concerns occurred during the study.

Prior to receiving the first dose of eculizumab, elevated alanine transaminase and aspartate aminotransferase levels were noted in 14 (34%) and 19 (46%) of 41 patients, respectively. In addition, transient liver enzyme level elevations were observed during the study. Most patients had normalization of enzyme levels during eculizumab treatment; at week 26, 3 of 38 (8%) patients had elevated alanine transaminase levels and 1 of 38 (3%) had elevated aspartate aminotransferase levels.

DISCUSSION

This study, which to our knowledge is the largest prospective trial of eculizumab in aHUS to date, demonstrates the efficacy of eculizumab in an exclusively adult population with severe aHUS and predominantly native kidneys, including patients who

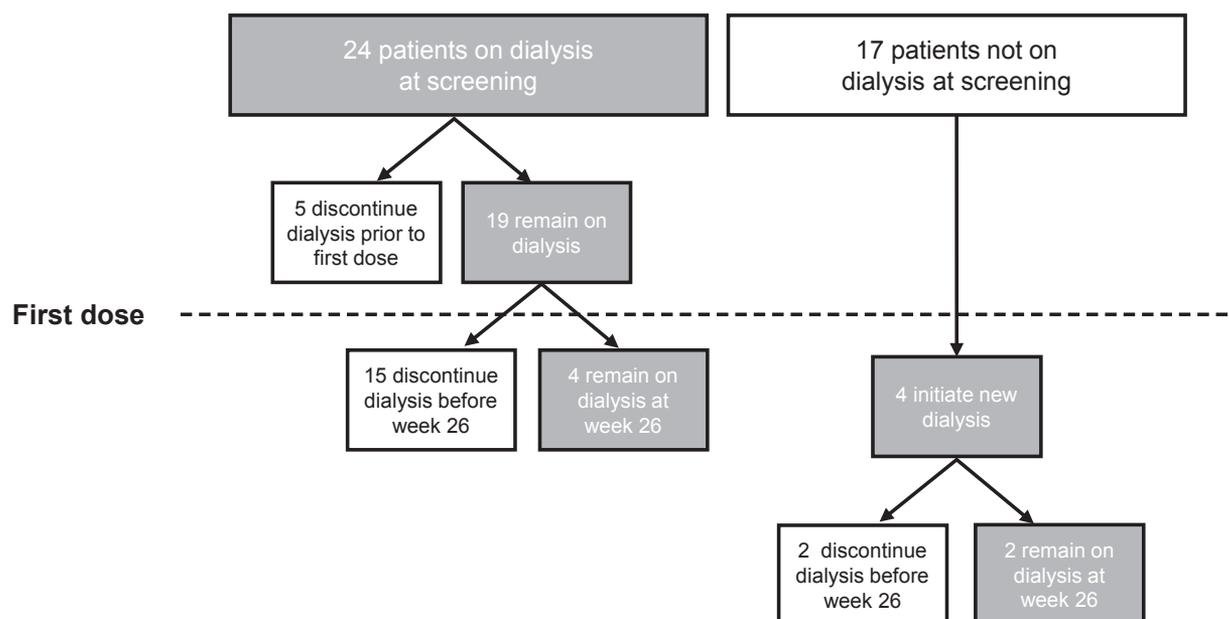


Figure 4. Dialysis use at baseline and during the study.

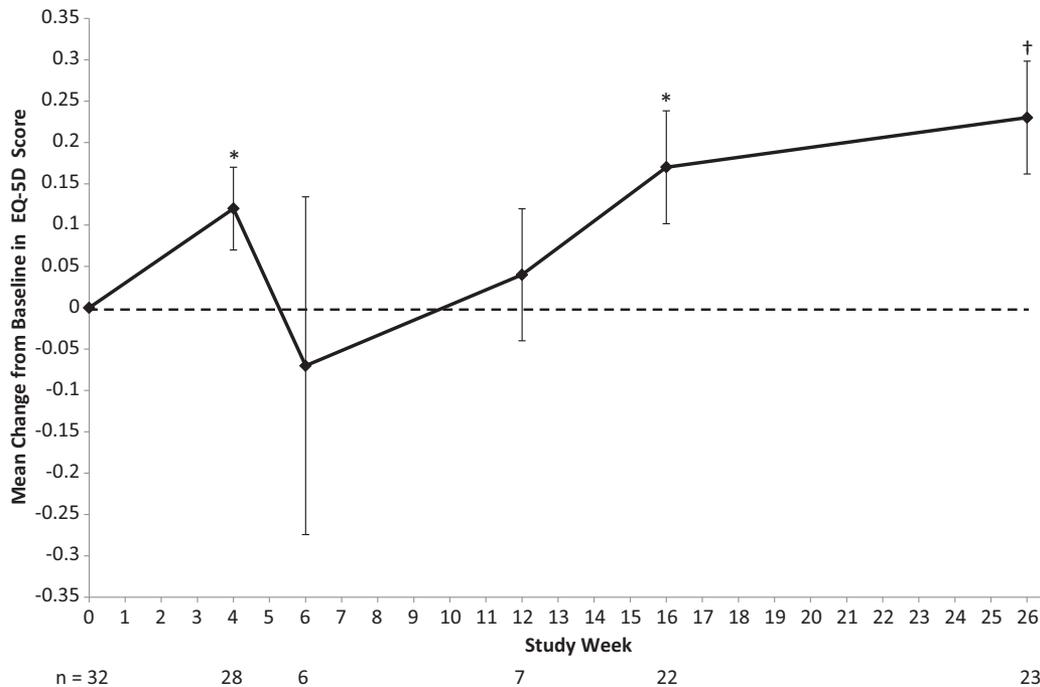


Figure 5. Mean change from baseline in patient EQ-5D United States time trade-off score over 26 weeks of eculizumab treatment. Bars represent standard error. A change from baseline of 0.06 in EQ-5D score is considered clinically meaningful.²⁰ * $P \leq 0.05$; † $P \leq 0.01$. Only $n > 5$ are shown.

had not received PE/PI prior to enrollment. The primary end point of complete TMA response was reached by the majority of patients (73%) after 26 weeks, and high proportions of patients saw improvements in key hematologic and kidney disease outcomes. These benefits were observed in patients who did and did not require dialysis at study baseline. Importantly, 79% of patients requiring dialysis at baseline discontinued dialysis after the initiation of eculizumab therapy.

In addition, improvements in other outcomes related to the overall well-being of patients with aHUS, including discontinuation of PE/PI, contribute to the important clinical benefits of eculizumab. It should be noted that 4 patients with no history of PE/PI at baseline initiated new PE/PI during the study and received it concomitantly with eculizumab therapy for a median duration of 28 (range, 6-81) days. No patients were on PE/PI at week 26. Due to the single-arm open-label study design, it was not possible to evaluate the effects of supportive care in these particular patients.

The recovery of kidney function and other clinical benefits shown in the current trial stand in sharp contrast to the natural history of aHUS. In a large case series of patients with aHUS before the availability of eculizumab, 81% of adult patients required dialysis at onset and 56% could be expected to progress to ESRD or die in the first year after diagnosis despite the use of PE/PI in a large proportion of these

patients.⁵ In the current study, platelet count normalization occurred more rapidly than improvements in hemoglobin levels or kidney function (ie, serum creatinine level in modified complete TMA response), although significant improvements in eGFRs were seen as early as 1 week after eculizumab therapy initiation and continued to occur over 26 weeks of therapy. Although transplantation historically has been contraindicated in patients with aHUS, no patient who entered the study with a kidney transplant lost the transplant after 26 weeks. Together, these findings confirm the disease-modifying effects of eculizumab, including maintenance or improvement of existing kidney function and protection of kidney transplants.

In the current trial, eculizumab treatment was initiated approximately 1 month after diagnosis, a substantially shorter duration than in the 2 pivotal trials (which had median intervals prior to treatment of 9.7 months in patients with aHUS with progressing TMA and 48.3 months in those with long disease duration and CKD).¹⁴ Evidence from these pivotal trials¹⁴ and case studies of patients with aHUS^{6,9} demonstrate that earlier initiation of eculizumab therapy is associated with significantly greater improvements in kidney disease outcomes. A larger proportion (54%) of patients in the current study met criteria for improvement in eGFR by ≥ 15 mL/min/1.73 m² compared to the pivotal trial of patients with long disease duration and CKD (5%). The proportion of patients having this eGFR improvement and overall change from baseline in eGFR were similar in the

current study and the pivotal study of patients with progressing TMA.¹⁴ Thus, data from the current study provide further evidence for the recommendation to diagnose aHUS accurately and quickly and initiate early treatment with eculizumab in order to prevent rapid progression and potentially life-threatening consequences of TMA.⁹

In the current study, benefits of eculizumab were demonstrated in an adult patient population including 34% with normal platelet counts and 20% with only moderately reduced kidney function (ie, eGFRs of 30-59 mL/min/1.73 m²) at baseline. Diagnosis of aHUS can be particularly complex in adult patients.⁶ ADAMTS-13 (von Willebrand factor protease) activity can be evaluated to inform differential diagnosis with thrombotic thrombocytopenic purpura.²¹ It has been recommended⁶ that relatively higher serum creatinine levels (ie, >3.2 mg/dL) or platelet counts (ie, >30 × 10³/μL) at the time of TMA may be predictive of sufficient ADAMTS-13 levels and lower likelihood of thrombotic thrombocytopenic purpura diagnosis²²; overall, the relative risk that patients presenting with TMA and values exceeding these thresholds do not have severely deficient ADAMTS-13 activity is 21.8 (P. Coppo, personal communication, May 2015). One should suspect aHUS in all patients with TMA,^{9,23} even without the most common presenting signs.

Overall, eculizumab was well tolerated in the study population and no unexpected safety signals or deaths were noted. The C5b-9 complex confers protection against encapsulated bacteria, particularly *N meningitidis*, and its formation is blocked by eculizumab.¹ Two cases of meningococcal infection were reported in the current trial; both patients recovered, and 1 remained on eculizumab therapy. In 1 case, the meningococcal serogroup was not identified and thus it is possible that the vaccine could not have protected the patient. A vaccine against serogroup B was recently approved for use in the European Union²⁴ and may provide increased protection against meningococcal infection for patients with aHUS treated with eculizumab in the future. No reports of meningococcal disease have occurred in previous studies of eculizumab in aHUS, including in the 2-year follow-up of the pivotal trials¹⁵ and the concurrent pediatric trial.²⁵ Based on an analysis of exposure to eculizumab in a real-world setting, meningococcal infection may be classified as an uncommon event (0.6 event/100 patient-years on eculizumab therapy in a 10-year study of patients with paroxysmal nocturnal hemoglobinuria²⁶). However, these cases highlight the necessity of vaccination against *N meningitidis* before eculizumab therapy initiation and/or prophylactic antibiotic therapy and for continued vigilance for symptoms of meningococcal infection during therapy.

Elevated liver enzyme levels were noted in some patients prior to receiving the first dose of eculizumab and also in the postbaseline period in a smaller number of patients. Overall, there was a strong trend toward normalization of hepatic enzyme levels after initiation of eculizumab therapy. These findings suggest that the increases in alanine transaminase and aspartate aminotransferase levels that are present after eculizumab therapy initiation in some patients are most likely related to the pre-existing TMA. Importantly, these elevations were not associated with clinical AEs, and no patient discontinued eculizumab due to elevated liver enzyme levels or hepatic AEs.

The availability of eculizumab has profoundly changed the management of aHUS.²⁷ This current study demonstrates that eculizumab effectively inhibits complement-mediated TMA, provides significant clinical benefits for adults with aHUS, and has a safety profile consistent with that reported from other clinical studies.¹⁴ Results from continued follow-up in this study and a separate long-term prospective trial are expected to provide further insights regarding eculizumab for the treatment of aHUS.

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SUPPLEMENTARY MATERIAL

Table S1: Ethics committee approvals at centers enrolling patients.

Table S2: Treatment-emergent AEs occurring in $\geq 15\%$ of patients.

Table S3: Serious treatment-emergent AEs.

Table S4: Patients with meningococcal infections.

Item S1: Health-related quality-of-life measures.

Item S2: Pharmacokinetics and pharmacodynamics.

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