Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome

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Atypical hemolytic uremic syndrome (aHUS) is caused by alternative complement pathway dysregulation, leading to systemic thrombotic microangiopathy (TMA) and severe end-organ damage. Based on 2 prospective studies in mostly adults and retrospective data in children, eculizumab, a terminal complement inhibitor, is approved for aHUS treatment. Here we prospectively evaluated efficacy and safety of weight-based dosing of eculizumab in eligible pediatric patients with aHUS in an open-label phase II study. The primary end point was complete TMA response by 26 weeks. Twenty-two patients (aged 5 months–17 years) were treated; 16 were newly diagnosed, 12 had no prior plasma exchange/infusion during current TMA symptomatology, 11 received baseline dialysis, and 2 had prior renal transplants. By week 26, 14 achieved a complete TMA response, 18 achieved hematologic normalization, and 16 had 25% or better improvement in serum creatinine. Plasma exchange/infusion was discontinued in all, and 9 of the 11 patients who required dialysis at baseline discontinued, whereas none initiated new dialysis. Eculizumab was well tolerated; no deaths or meningococcal infections occurred. Bone marrow failure, wrist fracture, and acute respiratory failure were reported as unrelated severe adverse events. Thus, our findings establish the efficacy and safety of eculizumab for pediatric patients with aHUS and are consistent with proposed immediate eculizumab initiation following diagnosis in children.

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Atypical hemolytic uremic syndrome (aHUS) is a progressive life-threatening thrombotic microangiopathy (TMA) associated with dysregulation of the complement alternative pathway.[1–3] Complement gene mutations (e.g., complement factor H [*CFH*], membrane cofactor protein [*MCP*], complement factor I [*CFI*], complement factor B [*CFB*], complement protein 3 [*C3*]), or factor H autoantibodies are identified in 50% to 60% of patients with aHUS.[4–6] Abnormalities in genes encoding thrombomodulin, plasminogen, and diacylglycerol kinase ε (DGKE)[7–9] occur in a small number of patients. Evidence of a genetic abnormality is not required for diagnosis.[4,10–13]

Although onset may occur at any age, 40% of patients develop aHUS by 18 years of age.[1,2,5] Clinical manifestations in children generally include anemia, thrombocytopenia, and acute kidney injury,[5] but peripheral gangrene,[14] arterial stenoses,[15] dilated cardiomyopathy, cardiorespiratory arrest,[16] and neurologic,[5,17] pulmonary,[11] and gastrointestinal complications[17] have been reported. Historically, aHUS was managed with plasma exchange/plasma infusion (PE/PI) and was associated with high morbidity and mortality rates,[1–3,5,18] with children having higher mortality than adults.[5] PE/PI may induce stabilization of hematologic parameters (but generally not significant renal function improvement),[19] is associated with complications, and impairs quality of life.[19,20]

The availability of eculizumab (Soliris, Alexion Pharmaceuticals, Inc., Cheshire, CT, USA)[21,22]— an anti-C5 monoclonal antibody and the first and only currently approved therapy for adult and pediatric patients—has profoundly changed aHUS management.[13,23] The efficacy and safety of

eculizumab was demonstrated in 2 prospective clinical trials of primarily adult patients with progressing TMA, long disease duration, and chronic kidney disease.[24,25] Use in children with aHUS is supported by case reports[13,16,26–37] and a retrospective study.[38,39] To further establish the efficacy and safety of eculizumab, a prospective clinical trial in patients with aHUS aged <18 years was conducted. Primary analysis results after 26 weeks of treatment are presented here.

RESULTS

Patients and treatment

Twenty-two patients were treated with eculizumab, and 19 (86%) completed the 26-week treatment period (Figure 1). Three patients discontinued treatment before week 26. Patients were exposed to eculizumab for a mean of 5.5 months (SD, 1.3 months).

Patients ranged in age from 5 months to 17 years (median age, 6.5 years) (Table 1). Median weight was 20 kg (range, 7−95 kg). Eleven (50%) had ≥1 identified complement gene abnormality or factor H autoantibody. One patient (5%) had a *DGKE* mutation. Six patients (27%; all <12 years of age) had a family history of aHUS. Sixteen patients (73%) were newly diagnosed. Ten patients (45%) received PE/PI at baseline. Overall, 18 patients (82%) had a baseline estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2, including 10 patients (64%) who had an eGFR <15 mL/min

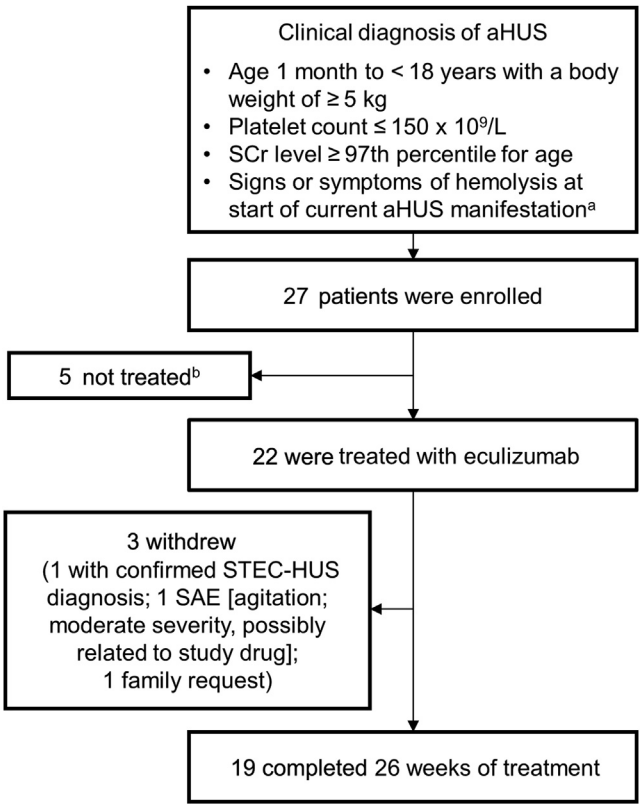

Figure 1 | Patient disposition. [a]LDH ≥ 1.5 × ULN; hemoglobin ≤ LLN; fragmented red blood cells with a negative Coombs test result. [b]One patient had a positive test for STEC infection, 1 had a normalized platelet count; 2 had a final diagnosis that was not aHUS, 1 had unspecified reasons. aHUS, atypical hemolytic uremic syndrome; LDH, lactate dehydrogenase; LLN, lower limit of normal; SAE, serious adverse event; SCr, serum creatinine; STEC, Shiga-like toxin-producing *Escherichia coli*; ULN, upper limit of normal.

Table 1 | Baseline demographics and disease characteristics

Variable	Intent-to-treat population (N = 22)
Median age at first infusion, yr (range)	6.5 (0.4–17)
Age range, n (%)	
1 mo to <23 mo (n = 5)	5 (23)
≥23 mo to <5 yr (n = 5)	5 (23)
≥5 to <12 yr (n = 8)	8 (36)
≥12 to <18 yr (n = 4)	4 (18)
Median weight, kg (range)	20 (7–95)
Female sex, n (%)	10 (45)
Race, n (%)	
Asian	2 (9)
Black or African American	0
White	18 (82)
Other	2 (9)
Patient-reported family history of aHUS, n (%)	6 (27)
Identified complement gene mutation, autoantibody, or polymorphism, n (%)	11 (50)
MCP[a]	3 (14)
CFH[b]	2 (9)
CFI[c]	2 (9)
CFH autoantibody	2 (9)
CFHR1/3 deletion (homozygous)	1 (5)
C3[d]	1 (5)
Identified *DGKE* mutation, n (%)[e]	1 (5)
Median duration from aHUS diagnosis until screening, mo (range)	0.6 (0–191)
Median duration of current manifestation to first dose, mo (range)	0.2 (0–4)
Newly diagnosed patients, n (%)	16 (73)
No PE/PI during current manifestation, n (%)	12 (55)
Dialysis at baseline, n (%)[f]	11 (50)
Previous renal transplant, n (%)	2 (9)
Mean platelet count, $\times 10^9$/l (SD)	88 (42)
Platelet count <150 $\times 10^9$/l, n (%)	22 (100)
Mean LDH level, U/l (SD)	1944 (1824)
LDH greater than ULN, n (%)	19 (86)
Mean hemoglobin concentration, g/dl (SD)	8.0 (1.5)
Mean serum creatinine level, mg/dl (SD)	1.7 (1.3)
Mean eGFR, ml/min per 1.73 m^2 (SD)	33 (30)
eGFR (ml/min per 1.73 m^2), n (%)	
<15	10 (46)
15–29	4 (18)
30–44	2 (9)
45–59	2 (9)
60–89	2 (9)
≥90	2 (9)

aHUS, atypical hemolytic uremic syndrome; *CFH*, complement factor H; *CFHR*, CFH-related protein; *CFI*, complement factor I; *DGKE*, diacylglycerol kinase ε; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; *MCP*, membrane cofactor protein; PE/PI, plasma exchange/infusion; ULN, upper limit of normal.
[a]*MCP* mutations: IVS3-2; p.Arg59Stop (c.175 C > T); p.Tyr189Asp (c.565 T > G).
[b]*CFH* mutations: p.Ser1191Leu and p.Val1197Ala; p.Ser1191Leu.
[c]*CFI* mutations: p.Ile340Thr (1019T > C) and p.Gly424Asp (1271G > A); p.Gly269Ser.
[d]*C3* mutation: p.Arg102Glyc (c.304C > G).
[e]After completion of the trial, patients with aHUS onset at <1 year of age and evidence of proteinuria (n = 3) were screened for *DGKE* mutations.
[f]Includes 1 patient who was receiving dialysis at baseline and discontinued dialysis during the baseline window before the first dose of eculizumab.

per 1.73 m^2. Eleven patients (50%) were receiving dialysis at baseline for a total median pretreatment duration of 13 days (range, 1−4826 days) and for 7 days (range, 1−36 days) during the current TMA manifestation (n = 10). Two patients (9%) had a history of renal transplantation for end-stage renal disease from aHUS.

Efficacy

Primary end point. Efficacy end points calculated for the intent-to-treat population are summarized in Table 2. By week 26, 14 patients (64%) achieved the primary end point of complete TMA response after a median of 8.6 weeks (range, 1–21.9 weeks).

TMA outcomes. TMA event-free status was achieved in 21 patients (95%) (Table 2). Between baseline and 26 weeks, the median TMA intervention rate was reduced from 0.4 to 0 events per patient per day, respectively ($P < 0.0001$). By study day 31, PE/PI was discontinued in all 10 patients who required it at baseline.

Hematologic outcomes. Hematologic normalization was achieved in 18 patients (82%) after a median of 55 days (range, 1–153 days). Twenty-one patients (95%) achieved platelet count normalization after a median of 7 days (range, 1–80 days) (Table 2). The 1 patient who did not achieve platelet count normalization withdrew after a single dose of eculizumab because of a diagnosis of Shiga-like toxin-producing *Escherichia coli* hemolytic uremic syndrome (Figure 1).

Table 2 | Summary of efficacy results after 26 weeks of eculizumab therapy

Study end point	Total (N = 22)
Primary end point	
Complete TMA response	
n (%)	14 (64)
95% CI	41–83
TMA outcome	
TMA event-free status	
n (%)	21 (95)
95% CI	77–100
Hematologic outcomes	
Hematologic normalization	
n (%)	18 (82)
95% CI	60–95
Platelet count normalization	
n (%)	21 (95)
95% CI	77–99
LDH normalization	
n (%)	18 (82)
95% CI	60–95
Hemoglobin improvement ≥2 g/dl	
n (%)	15 (68)
95% CI	45–86
Renal outcomes	
Serum creatinine level decrease by ≥25%, n (%)	16 (73)
eGFR improvement by ≥15 ml/min per 1.73 m^2, n (%)	19 (86)
CKD improvement by ≥1 stage, n (%)	17 (77)

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy.

Eculizumab was associated with a rapid and sustained increase in platelet count from baseline to 27 weeks ($P \leq 0.0001$) (Figures 2 and 3). The mean improvement in platelet count at 27 weeks was 164 × 10^9/L (SD, 76 × 10^9/L). Lactate dehydrogenase (LDH) normalization was achieved in 18 patients (82%) after a median of 48 days (range, 1–153 days). Fifteen patients (68%) had an improvement in hemoglobin of ≥2 g/dL.

Renal outcomes. A decrease in serum creatinine level by ≥25% occurred in 16 patients (73%) (Table 2) after a median of 21 days (range, 2–140 days). Nineteen (86%) patients had eGFR improvement of ≥15 ml/min per 1.73 m^2. The mean improvement from baseline to week 27 in eGFR was 64 ml/min per 1.73 m^2 ($P < 0.0001$) (Figures 4 and 5). Among 20 patients with chronic kidney disease (CKD) stage >2, 17 (85%) had improvement of ≥1 stage. Nine of 11 patients (82%) receiving dialysis at baseline discontinued dialysis during the study after a median of 7 days (range, 4−15 days; n = 8); of these, 1 discontinued dialysis before eculizumab initiation. All 11 patients not receiving baseline dialysis remained dialysis free. Two patients (9%) were receiving dialysis at week 26.

Efficacy by mutational status. The efficacy of eculizumab was observed in patients with (n = 11) and those without (n = 11) identified complement abnormalities (complement gene mutations or polymorphisms or factor H autoantibodies, or both). Complete TMA response was achieved in 8 patients (73%) with and 6 patients (55%) without abnormalities. TMA event-free status was achieved by 11 patients (100%) and 10 patients (91%) with and without abnormalities, respectively. Ten patients (90%) with and 8 patients (73%) without complement abnormalities met criteria for hematologic normalization. eGFR improvement ≥15 ml/min per 1.73 m^2 occurred in 11 patients (100%) and 8 patients (73%) with and without abnormalities, respectively.

The patient with the identified *DGKE* mutation discontinued dialysis at initiation of eculizumab treatment and did not require dialysis during the study. This patient achieved complete TMA response, TMA event-free status, and hematologic normalization by week 26.

Post hoc analysis of patient characteristics by criteria for the primary end point. Table 3 shows the baseline demographic characteristics of patients who did (n = 14) and those who did not (n = 8) meet criteria for the primary end point at 26 weeks. The subgroup of patients who did not achieve complete TMA response had a lower frequency of identified complement abnormalities (38% compared with 57%) as well as worse renal function at baseline. Sixty-three percent of patients with baseline eGFR <15 ml/min per 1.73 m^2 did not achieve complete TMA response.

Patients who did and those who did not achieve complete TMA response had a similar duration of exposure to eculizumab (mean, 5.7 months [SD, 0.7 months] and 5.0 months [SD, 2.0 months], respectively). These subgroups received a mean of 14.3 eculizumab infusions (SD, 2.2) and 11.5 eculizumab infusions (SD, 4.9), respectively.

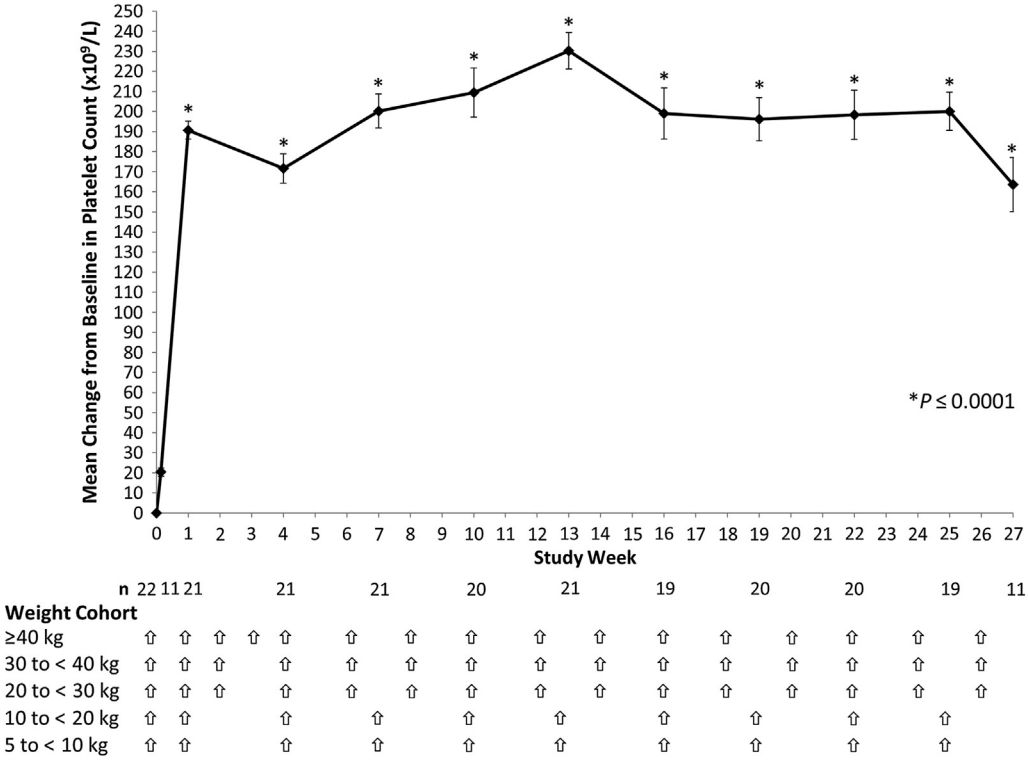

Figure 2 | Improvement in platelet count over 27 weeks of eculizumab treatment. N values <5 were not included. Bars represent standard error of the mean. Arrows denote administration of eculizumab.

Health-related quality of life

The pediatric Functional Assessment of Chronic Illness Therapy—Fatigue least squares mean change from baseline to week 27 was 19.7 (range, 15.6–23.7; $P < 0.0001$; n = 5).

Pharmacokinetics and pharmacodynamics

Clearance and volume of distribution of the central compartment values were 0.0104 l/h and 5.23 l, respectively; between-subject variability was low and consistent with

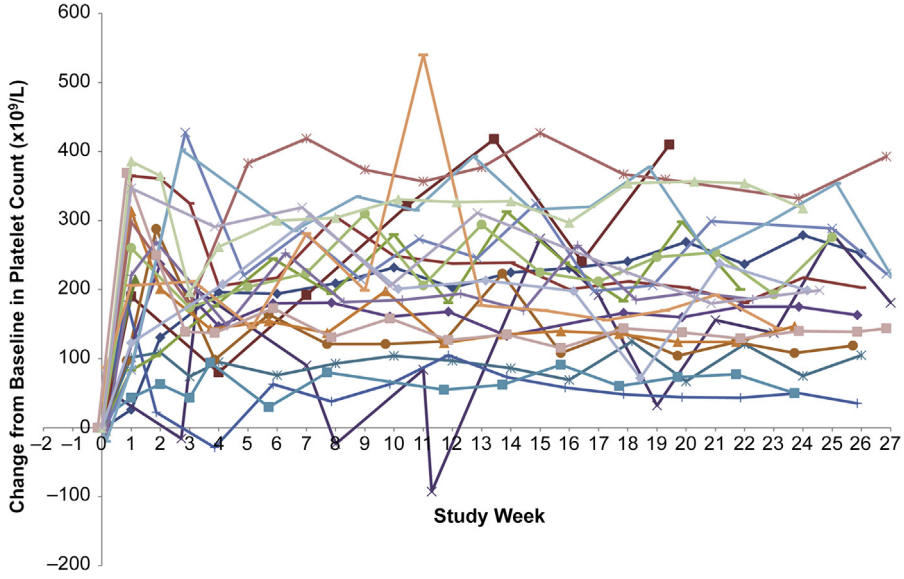

Figure 3 | Improvement in platelet count over 27 weeks of eculizumab treatment in individual patients.

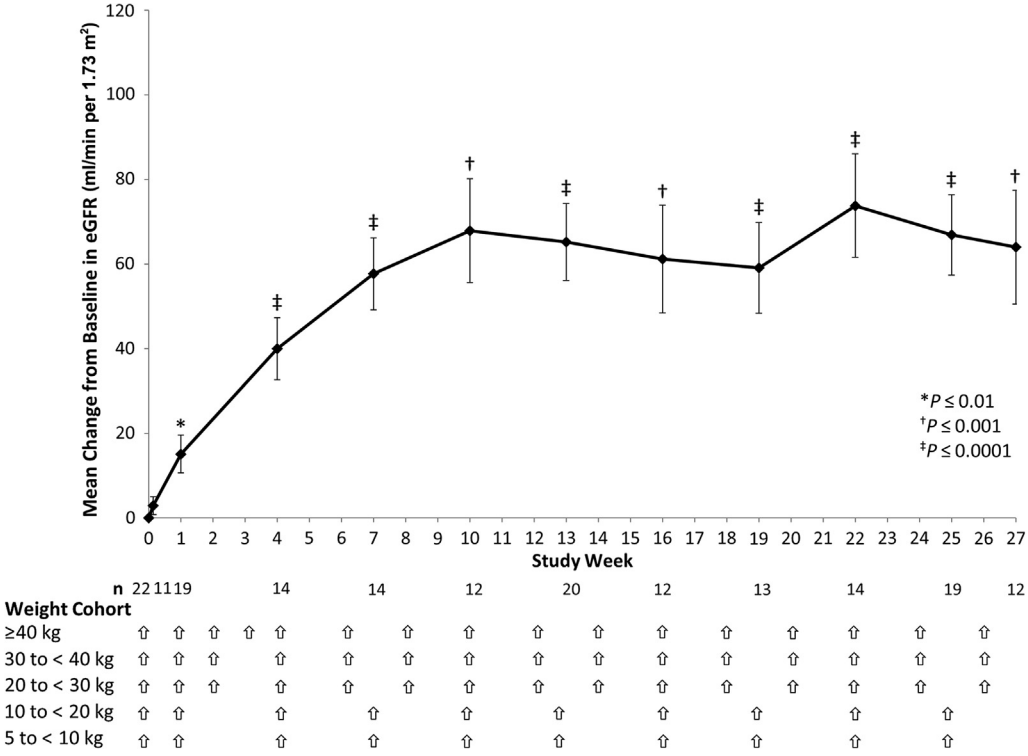

Figure 4 | Improvement in estimated glomerular filtration rate (eGFR) over 27 weeks of eculizumab treatment. N values <5 were not included. Bars represent SEM. Arrows denote administration of eculizumab.

previous studies.[24] The elimination half-life of eculizumab was 14.5 days. Overall, individual minimum concentration (C_{min}) values were generally >50 μg/ml, and maximum concentration (C_{max}) values were <700 μg/ml in each age cohort (Table 4). Mean area under the concentration time curve (AUC) values decreased with increasing age during induction. After 24 hours, all 18 patients with evaluable data had evidence of complete terminal complement inhibition. One patient (30 months old), who tested positive for human antihuman antibodies (HAHAs), had a C_{min} <50 μg/ml on study days 36 and 91. On day 121, the patient had confirmed evidence of HAHAs, an eculizumab trough concentration of 17.1 μg/ml, and decreased inhibition of hemolytic activity. The patient did not have pharmacokinetic (PK) samples out of the target range or incomplete inhibition of hemolysis at any other time point

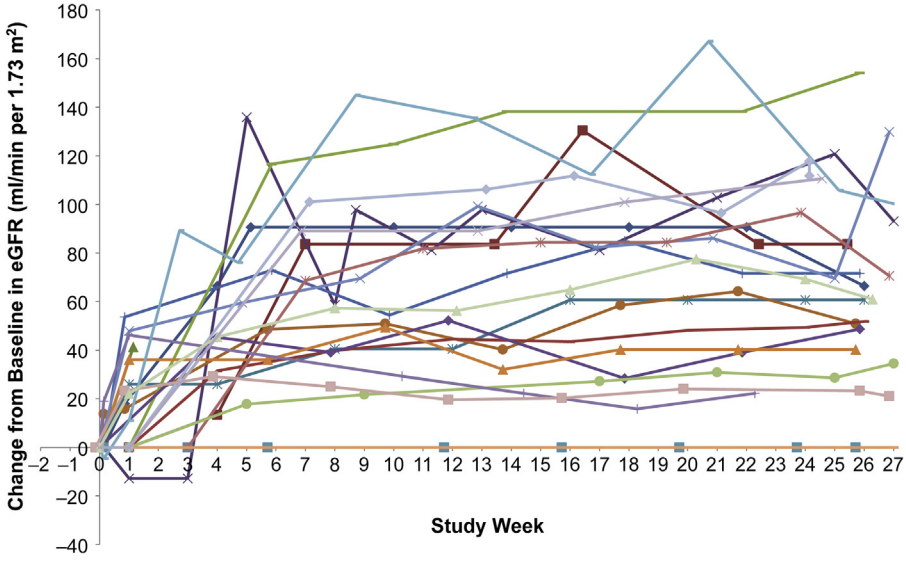

Figure 5 | Improvement in estimated glomerular filtration rate (eGFR) over 27 weeks of eculizumab treatment in individual patients.

Table 3 | Baseline demographics and disease characteristics of patients who did and those who did not meet criteria for the primary end point (post hoc analysis)

Variable	Achieved complete TMA response (n = 14)	Did not achieve complete TMA response (n = 8)
Median age at first infusion, yr (range)	7.5 (0.0–17.0)	2.0 (0.0–17.0)
Age range, n (%)		
1 mo to <23 mo (n = 5)	3 (21)	2 (25)
≥23 mo to <5 yr (n = 5)	2 (14)	3 (38)
≥5 to <12 yr (n = 8)	6 (43)	2 (25)
≥12 to <18 yr (n = 4)	3 (21)	1 (13)
Median weight, kg (range)	22 (7–68)	14 (8–95)
Female sex, n (%)	7 (50)	3 (38)
Race, n (%)		
Asian	1 (7)	1 (13)
Black or African American	0 (0)	0 (0)
White	11 (79)	7 (88)
Other	2 (14)	0 (0)
Patient-reported family history of aHUS, n (%)	3 (21)	3 (38)
Identified complement gene mutation, autoantibody, or polymorphism, n (%)	8 (57)	3 (38)
MCP	3 (21)	0 (0)
CFH	1 (7)	1 (13)
CFI	1 (7)	1 (13)
CFH autoantibody	2 (14)	0 (0)
CFHR1/3 deletion (homozygous)	1 (7)	0 (0)
C3	0 (0)	1 (13)
No identified complement gene mutation, autoantibody, or polymorphism, n (%)	6 (43)	5 (63)
Median duration from aHUS diagnosis until screening, mo (range)	0 (0–191)	0 (0–58)
Median duration of current manifestation to first dose, mo (range)	0.2 (0–4)	0.2 (0–1)
Newly diagnosed patients, n (%)	10 (71)	6 (75)
No PE/PI during current manifestation, n (%)	NA	NA
Dialysis at baseline, n (%)	6 (43)	5 (63)
Previous renal transplant, n (%)	2 (14)	0 (0)
Mean platelet count, $\times 10^9$/l (SD)	85 (44)	91 (41)
Platelet count <150 $\times 10^9$/l, n (%)	14 (100)	8 (100)
Mean LDH level, U/l (SD)	1923 (1670)	1979 (2192)
LDH greater than the ULN, n (%)	14 (100)	5 (63)
Mean hemoglobin concentration, g/dl (SD)	8 (1.3)	8 (2.0)
Mean serum creatinine level, mg/dl (SD)	2.0 (1.5)	1.2 (0.8)
Mean eGFR, ml/min per 1.73 m^2 (SD)	NA	NA
eGFR (ml/min per 1.73 m^2), n (%)		
<15	5 (36)	5 (63)
15–29	2 (14)	2 (25)
30–44	2 (14)	0 (0)
45–59	2 (14)	0 (0)
60–89	2 (14)	0 (0)
≥90	1 (7)	1 (13)

aHUS, atypical hemolytic uremic syndrome; *CFH*, complement factor H; *CFHR*, CHF-related protein; *CFI*, complement factor I; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; *MCP*, membrane cofactor protein; PE/PI, plasma exchange/infusion; ULN, upper limit of normal.

during the maintenance phase. The patient did not achieve complete TMA response, achieved hematologic normalization after the first eculizumab dose, did not have improvement in eGFR or serum creatinine level, and was receiving dialysis at baseline and 26 weeks.

Safety

Treatment-emergent adverse events (TEAEs) occurred in 20 patients (Table 5); most were mild or moderate in severity, and the most common were fever, cough, abdominal pain, diarrhea, and upper respiratory tract infection. Of these events, 3 (occurring in 2 patients who were 1 month to <23 months of age and in 1 patient who was 5 to <12 years of age) were judged to be severe: bone marrow failure, wrist fracture, and acute respiratory failure. Bone marrow failure was diagnosed after laboratory results showed anemia, thrombocytopenia, mild hemolysis, and low white blood cell count; the severity of the anemia and associated neutropenia and thrombocytopenia were attributed to both aHUS and effects of a viral infection. The investigator reported the bone marrow failure as viral-induced bone marrow suppression; the patient had a parainfluenza type 3 infection during the same period. A bone marrow biopsy was not performed. The patient was treated with packed red blood cells and recovered. The event of acute respiratory failure occurred in a patient with choking and vomiting followed by a sudden onset of respiratory distress that required intubation. Both patients recovered and remained on study medication; neither severe TEAE was judged to be related to eculizumab. Thirteen patients (59%) reported ≥1 serious TEAE (Table 5), 1 of which (agitation of moderate severity) led to treatment discontinuation. The patient with HAHAs remained on eculizumab without safety concerns. No deaths or meningococcal infections occurred.

Elevated levels of alanine transaminase and aspartate aminotransferase were noted in some patients before and after receiving eculizumab. More patients had elevated levels before baseline and at day 0 compared with after baseline, and most patients had enzyme level normalization by week 26. This trend was consistently observed for patients with elevations >3 times the upper limit of normal (ULN).

The patient who discontinued the study because of the serious TEAE of agitation had no identified complement abnormality and did not have TMA complications after 1 year of follow-up. One additional patient who withdrew from the study because of a family request was not followed after consent was withdrawn.

DISCUSSION

We are reporting the first prospective trial conducted exclusively in patients with aHUS <18 years of age. Eculizumab treatment led to complete TMA response in 64% of patients after 26 weeks, and the majority met criteria for

Table 4 | Eculizumab descriptive statistics of AUC, Cmax, and Cmin values by age group

Population	Parameter[a]	Induction period		Maintenance period	
		Mean (CV%)	Median (range)	Mean (CV%)	Median (range)
≥1 to <23 mo (n = 5)	AUC (μg/hr/ml)	58,600.6 (35.3)	50,908.0 (40,748.5 – 88,516.6)	147,276.8 (18.1)	152,045.0 (104,500.5 – 177,946.5)
	C_{max} (μg/ml)	421.5 (40.1)	372.0 (282.4 – 686.2)	519.1 (8.0)	513.7 (467.6 – 583.5)
	C_{min} (μg/ml)	287.2 (31.0)	244.4 (207.8 – 396.2)	215.0 (36.1)	185.6 (146.0 – 342.7)
≥23 mo to <5 yr (n = 5)	AUC (μg/hr/ml)	52,814.9 (14.9)	49,476.6 (44,561.5 – 64,680.8)	106,864.6 (36.5)	115,749.7 (43,652.9 – 139,521.9)
	C_{max} (μg/ml)	377 (17.1)	386.2 (290.3 – 439)	424.0 (24.2)	449.7 (267.4 – 534.3)
	C_{min} (μg/ml)	262.8 (21.2)	252.4 (188.9 – 337.5)	235.9 (48.3)	257.1 (50.2 – 338)
≥5 to <12 yr (n = 8)	AUC (μg/hr/ml)	35,380.9 (11.7)	35,354.7 (29,667.2–39,716.4)	160,471 (28.1)	151,654.5 (117,194.4 – 261,814.4)
	C_{max} (μg/ml)	244 (11.3)	240.2 (205.0 – 282.2)	636.1 (30.6)	580.9 (461.0 – 1094.4)
	C_{min} (μg/ml)	181.4 (12.6)	184.2 (143.8 – 205.7)	348.5 (25.9)	344.4 (231.1 – 531.1)
≥12 to 18 yr (n = 4)	AUC (μg/hr/ml)	24,308.7 (24.2)	24,155.5 (17,556.7 – 31,367.3)	110,279.1 (21.6)	103,362.9 (90,429.5 – 143,960.8)
	C_{max} (μg/ml)	172.4 (25.5)	173.6 (121.2 – 221)	456.4 (21.5)	437.8 (357.7 – 592.1)
	C_{min} (μg/ml)	120.9 (23.2)	118.3 (89.9 – 157)	227.0 (23.1)	215.2 (179.8 – 298.1)
Overall (n = 22)	AUC (μg/hr/ml)	42,607.2 (38.8)	39,700.1 (17,556.7 – 88,516.6)	136,163.2 (30.9)	141,741.4 (43,652.9 – 261,814.4)
	C_{max} (μg/ml)	301.5 (41.9)	276.6 (121.2 – 686.2)	528.6 (29.5)	515.4 (267.4 – 1094.4)
	C_{min} (μg/ml)	213.0 (37.2)	201.1 (89.9 – 396.2)	270.5 (37.8)	256.7 (50.2 – 531.1)

[a]AUC, area under the concentration time curve from day 0 to week 1 for the induction period and area under the concentration time curve under steady-state conditions; C_{max}, maximum concentration; C_{min}, minimum concentration; CV(%), coefficient of variation.

improvements in all hematologic and renal parameters. Clinical benefits were demonstrated by the discontinuation of PE/PI in all patients and discontinuation of dialysis in 82% of patients who required it at baseline. Patients who did not require baseline dialysis did not progress to end-stage renal disease or require dialysis during treatment. Benefits were observed in patients with or without identified genetic abnormalities, including 1 patient with an identified *DGKE* mutation. Health-related quality of life significantly improved after 26 weeks of therapy. The safety profile of eculizumab was consistent with previous studies in aHUS,[24] and no new safety concerns were noted. Overall, findings are consistent with prospective clinical trials of eculizumab in adults with aHUS and progressing TMA, in adolescent and adult patients with a long disease history and CKD,[24,25] and in a retrospective study of pediatric patients with aHUS.[21]

Significantly greater recovery of renal function is achieved when eculizumab is instituted as soon as possible after aHUS presentation.[24,40,41] In the current study, patients received eculizumab approximately 2.5 weeks after diagnosis. Although most had eGFR <30 ml/min per 1.73 m^2 and half were receiving dialysis at baseline, significant eGFR increases were observed as early as 1 week after initiation of therapy and were maintained throughout the study. The observed early and ongoing recovery of renal function, including CKD improvement and discontinuation of dialysis, is compelling considering that 29% of children with aHUS progress to end-stage renal disease or die within 1 year when managed with PE/PI.[5] Overall, these findings are consistent with results from a companion prospective study of eculizumab in adult patients with aHUS.[42]

A post hoc analysis was performed to evaluate potential baseline factors that may affect recovery of hematologic and renal function as defined by the primary end point of complete TMA response. Although the small patient number is limiting, patients who did not achieve complete TMA response had a trend toward not having an identified complement gene mutation and having worse renal function at baseline. Additional studies are necessary to evaluate these potential effects more rigorously.

In the current study, 55% of patients did not receive previous PE/PI. Thus, this population differed from those in

Table 5 | Treatment-emergent adverse events

Parameter	Intent-to-treat population(N = 22)
TEAEs (frequency ≥20%), n (%)	
Fever	11 (50)
Cough	8 (36)
Abdominal pain	7 (32)
Diarrhea	7 (32)
Upper respiratory tract infection	7 (32)
Nasopharyngitis	6 (27)
Vomiting	6 (27)
Patients with TEAEs related to eculizumab, n (%)	
Unrelated	11 (50)
Possibly[a]	8 (36)
Probably[b]	1 (5)
Definite	0 (0)
Patients with any SAE, n (%)	13 (59)
Severity, n (%)	
Mild	3 (14)
Moderate	7 (32)
Severe	3 (14)
SAEs occurring in 2 or more patients, n (%)	
Fever	2 (9)
Gastroenteritis, viral	2 (9)
Hypertension	2 (9)
Upper respiratory tract infection	2 (9)

SAEs, serious adverse events; TEAEs, treatment-emergent adverse events.
[a]Includes abdominal discomfort, agitation, alopecia, diaper dermatitis, diarrhea, dyspepsia, ear infection, eye discharge, eczema, fungal infection, headache, injection site rash, muscle spasms, nasopharyngitis, pain, rash, respiratory syncytial virus infection, viral respiratory tract infection, viral upper respiratory tract infection (n = 1 each).
[b]Includes rash (n = 1).

pivotal clinical trials[24] and exclusively adult patients,[42] in which 85% to 100% received PE/PI before starting eculizumab. A recent report described an infant with aHUS who received first-line eculizumab, which was well tolerated and led to hematologic and renal function improvement.[43] Our findings support recent recommendations to initiate eculizumab after ruling out other potential causes of TMA and on clinical diagnosis of aHUS in pediatric patients to achieve optimal outcomes and to avoid potential complications associated with PE/PI.[13,44,45]

This report includes the first PK analyses of eculizumab in a prospective clinical trial in children. Overall, the approved pediatric dosing regimen resulted in eculizumab concentrations of 50 to 700 μg/ml for all age cohorts, consistent with those reported in the pivotal trials.[24] One patient had evidence of HAHAs, relatively low eculizumab concentrations, decreased inhibition of hemolytic activity at 1 time point during the maintenance phase, and remained on dialysis but continued in the study without safety concerns. In pivotal studies of eculizumab, neutralizing HAHAs were not detected in patients with aHUS and were detected in about 1% of patients with paroxysmal nocturnal hemoglobinuria without correlations with clinical responses or AEs.[21] In clinical practice, HAHA testing can be reserved for rare scenarios in which complement activity is suspected during ongoing therapy.[13]

Recently, there was a report of liver toxicity associated with eculizumab in a few patients with aHUS.[46] In the current study, elevated liver enzymes were noted in some patients before and after receiving eculizumab. Overall, there was a strong trend toward normalization of hepatic enzyme levels after eculizumab initiation. Our findings suggest that the increased alanine transaminase and aspartate aminotransferase levels seen in some patients after eculizumab initiation may be related to pre-existing ongoing TMA that developed before treatment initiation. In addition, these elevations were transient and not associated with clinical AEs. Importantly, no patient discontinued eculizumab because of elevated liver enzyme levels or hepatic AEs.

Because this was an open-label study, interpretation of these results may be limited by the lack of a control group. Additionally, the definition of the primary end point of complete TMA response required improvement in serum creatinine levels. This definition excluded patients who had hematologic normalization but irreversible kidney failure.

The availability of eculizumab has fundamentally improved the outlook for patients with aHUS. This prospective study confirms that eculizumab inhibits complement-mediated TMA and is well tolerated in children. Prevention of hemolysis and improvement of renal function during eculizumab therapy, without the need for PE/PI, represents an important clinical benefit. The ongoing extension treatment phase and a global aHUS registry study will provide further insights regarding long-term use of eculizumab in children with aHUS.

METHODS

Patients

From September 2010 through March 2012, patients aged 1 month to 18 years with an aHUS diagnosis who weighed ≥5 kg were enrolled at 17 clinical sites across North America, Europe, and Australia. At screening, eligible patients had a platelet count less than the lower limit of normal, LDH level ≥1.5 times the ULN, hemoglobin less than or equal to the lower limit of normal, fragmented red blood cells with a negative Coombs test result, and serum creatinine level ≥97th percentile for age. Patients with or without an identified complement gene mutation, autoantibody, or polymorphism (or all of these) were included; mutation testing (for *CFB*, *CFH*, *CFI*, *MCP*, *C3* mutations, *CFHR1-CFHR3* polymorphisms, and CFH and CFI antibody titers) was performed at regional laboratories if mutation status was unknown or negative before study entry. Screening for *DGKE* mutations occurred in patients with onset at <1 year of age and evidence of proteinuria after completion of the trial. Exclusion criteria included HUS of other causes (ie, Shiga-like toxin-producing *E coli*) or severe a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency (<5%), PE/PI for >5 weeks before enrollment, chronic dialysis for end-stage renal disease, and previous use of eculizumab or hypersensitivity to its components.

All patients were vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* 14 days or more before initiation of treatment or received prophylactic antibiotics until 2 weeks after meningococcal vaccination to avoid delaying therapy initiation. Patients ≤2 years old received antibiotic prophylaxis throughout treatment, because at the time there was no vaccine for individuals of this age group.

Study design

This was an open-label nonrandomized single-arm multicenter phase II clinical trial of eculizumab in patients <18 years of age with aHUS (ClinicalTrials.gov Identifier: NCT01193348; registration August 31, 2010), including a 7-day screening period, a 26-week treatment period, an extension treatment period of up to 2 years, and a 12-week safety follow-up period after eculizumab discontinuation. Patients who discontinued treatment were followed at 3-month intervals for 1 year to assess aHUS status and outcomes.

Eculizumab was administered at doses prespecified by body weight (Table 6) based on previous experience with patients with paroxysmal nocturnal hemoglobinuria and PK data to ensure that ≥95% of patients had complete and sustained terminal complement inhibition (including at times of increased complement activity, e.g., infection or surgery) and to provide peak concentrations (50–700 μg/ml) within the target range. Doses were administered by intravenous infusion over approximately 1 to 4 hours at the

Table 6 | Schedule of eculizumab dose administration based on patient weight

Weight cohort	Induction	Maintenance
≥40 kg	900 mg weekly ×4	1200 mg wk 5; 1200 mg q2 wk
30 to <40 kg	600 mg weekly ×2	900 mg wk 3; 900 mg q2 wk
20 to <30 kg	600 mg weekly ×2	600 mg wk 3; 600 mg q2 wk
10 to <20 kg	600 mg weekly ×1	300 mg wk 2; 300 mg q2 wk
5 to <10 kg	300 mg weekly ×1	300 mg wk 2; 300 mg q3 wk

q2 weeks, every 2 weeks.
Patients who required plasmapheresis or plasma infusion received a supplemental dose of eculizumab 300 mg (if previous eculizumab dose was 300 mg) or 600 mg (if previous dose was ≥600 mg).

investigator's discretion. If PE/PI was required, an additional eculizumab dose was administered within 1 hour of treatment completion.

The primary objective was to assess the efficacy and safety of eculizumab in patients with aHUS <18 years of age to inhibit complement-mediated TMA, characterized by thrombocytopenia, hemolysis, and renal impairment. The study protocol was approved by the institutional review board at each center or by an independent ethics committee and was conducted in accordance with the International Conference on Harmonisation Tripartite Guideline and the Declaration of Helsinki. All patients or parents/guardians, or both, provided written informed consent and assent if applicable.

Efficacy end points

The primary end point was the proportion of patients who achieved complete TMA response, defined as hematologic normalization (platelet count $\geq 150 \times 10^9$/L, LDH levels less than the ULN) and improvement in renal function (≥25% decrease in serum creatinine level from baseline) on 2 consecutive measurements obtained ≥4 weeks apart. Time to complete TMA response was calculated from the first eculizumab dose to the day that the first measurement was obtained.

Secondary end points included TMA event-free status (no decrease in platelet count >25% from baseline, no PE/PI, and no new dialysis); the TMA intervention rate (the number of PE/PI and new dialysis events per patient per day); hematologic normalization (platelet count $\geq 150 \times 10^9$/L and LDH level less than the ULN); hemoglobin increase ≥2 g/dL; ≥25% decrease in serum creatinine levels; improvement in eGFR by ≥15 ml/min per 1.73 m^2, and improvement in CKD by ≥1 stage. eGFR was calculated using the Schwartz formula—0.41 × height (cm)/serum creatinine (mg/dL)[47]—and defined as 10 ml/min per 1.73 m^2 while receiving dialysis. Categorical end points were required to be sustained for ≥2 consecutive measurements obtained ≥4 weeks apart. The change in health-related quality of life from baseline was measured using the pediatric Functional Assessment of Chronic Illness Therapy—Fatigue questionnaire, designed for children 7 to 17 years of age who could complete the questionnaire without help[48] and scored using standard algorithms.[49] Mean changes from baseline in platelet count, eGFR, and Functional Assessment of Chronic Illness Therapy—Fatigue score were assessed at week 27 because of lack of analysis points at week 26.

Baseline demographic and clinical characteristics of subgroups of patients who did and those who did not meet criteria for the primary end point were evaluated in a post hoc analysis.

Pharmacokinetic and pharmacodynamic assessments

Baseline and trough PK and pharmacodynamic blood samples for determination of eculizumab concentrations and percent inhibition of hemolysis[50] were drawn after 24 hours and according to schedules specific to each dosing weight cohort (Table 7). Samples were collected before (trough) and 60 minutes after infusion (peak). Serum concentrations were measured using a validated enzyme-linked immunosorbent assay.[51]

Plasma eculizumab concentrations were fitted to a 1-compartment model, used to support weight-based dosing of eculizumab,[52] to estimate PK parameters (AUC, C_{max}, and C_{min}).

Table 7 | Pharmacokinetic and pharmacodynamic blood sampling collection schedule by weight cohort

Weight cohort	Peak	Peak and trough	Trough
≥40 kg	Wk 4	Wk 16	Wk 26
30 to <40 kg	Wk 2	Wk 18	Wk 28
20 to <30 kg	Wk 2	Wk 18	Wk 28
10 to <20 kg	Wk 1	Wk 17	Wk 27
5 to <10 kg	Wk 4	Wk 16	Wk 25

Safety assessments

Safety assessments included TEAEs. The presence of HAHAs was assessed at weight cohort–specified time points (5 to <10 kg: weeks 0, 7, 13, and 15; 10 to <20 kg: weeks 0, 5, and 13; 20 to <30 kg and 30 to <40 kg: weeks 0, 6, and 14; ≥40 kg: weeks 0, 12, and 26) and study termination. An electrochemiluminescence bridging assay used eculizumab conjugated to biotin and to SULFO-TAG (Meso Scale Diagnostics, LLC, Rockville, MD). Equimolar quantities of the 2 conjugated eculizumab structures were added to the serum-containing samples (2% [volume/volume]) and incubated overnight. Samples were transferred to a blocked assay plate and incubated at room temperature in the dark for 3 hours, followed by washing and measurement of electrochemiluminescence with the Sector Imager 2400 (Meso Scale Diagnostics, LLC; normalized against a standard curve).

Statistical analysis

All analyses were performed in the intent-to-treat population, defined as all patients who received ≥1 eculizumab dose. Baseline was defined as the last value collected before the first eculizumab infusion. The baseline period for dialysis was defined as 7 days before until 14 days after the first eculizumab dose. Complete TMA response at week 26 was assessed using the Clopper-Pearson method. For composite end points, patients were censored at the last follow-up day if component data were missing. Patients without valid values were treated as failures regarding end points. The proportion of patients with eGFR improvement ≥15 ml/min per 1.73 m^2 was calculated similarly to the primary end point. Platelet count, LDH level, hemoglobin value, serum creatinine level, and eGFR values were summarized using descriptive statistics. All statistical tests for efficacy end points (including the primary end point) were assessed at the 2-sided $\alpha = 5\%$ level without adjusting for multiplicity. Descriptive statistics of PK parameters were provided during the induction (i.e., after the first dose) and maintenance phase (i.e., at steady state) by age and weight cohorts.

The planned number of patients to be enrolled was 20, based on a postmarketing requirement to enroll ≥5 patients in each of the following age cohorts: 1 month to <23 months, 24 months to <5 years, and 5 to <12 years.

DISCLOSURE

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AUTHOR DISCLOSURE

LAG is a consultant and receives honoraria and research funding from Alexion Pharmaceuticals. GA is a formal advisor and receives honoraria from Alexion Pharmaceuticals. SIA receives honoraria and research funding from Alexion Pharmaceuticals. PH receives grant support and research funding from Alexion Pharmaceuticals. LP receives grant support, honoraria, and research funding and is a member of the Speakers Bureaus of Novartis Pharmaceuticals and Alexion Pharmaceuticals. NCAJvdK is a member of the aHUS International Advisory Board and the Speakers Bureau, and receives honoraria from Alexion Pharmaceuticals. JVW is a member of the Ferring Safety Board, Astellas Safety and Investigator Board for

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