SA-PO546

Safety and Efficacy of Eculizumab in Pediatric Patients With aHUS, With or Without Baseline Dialysis

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INTRODUCTION

- Atypical hemolytic uremic syndrome (aHUS) is a disease characterized by chronic, uncontrolled complement activation and thrombotic microangiopathy (TMA), leading to renal and other end organ damage[1,2]
- Plasma exchange/plasma infusion (PE/PI) provides uncertain benefit to children with aHUS, as 16% progressed to end-stage renal disease or death at first manifestation, and 29% progress within the first year of diagnosis.[2,3] In addition, complications of central venous catheters inserted for PE/PI occur in one third of children with aHUS[4]
- Eculizumab (Soliris®; Alexion Pharmaceuticals, Inc., Cheshire, CT, USA), a terminal complement inhibitor, is a humanized monoclonal antibody that binds with high affinity to the human C5 complement protein, blocking the generation of pro-inflammatory C5a and C5b-9.[5] It is the first and only approved treatment for aHUS in pediatric and adult patients[6,7]
- In a previous prospective trial of adults with aHUS and clinical evidence of progressing TMA treated with eculizumab (C08-002), 80% of patients who were receiving dialysis at the beginning of the study were able to discontinue dialysis during the treatment period[8]
  - Results from a subanalysis of patients with and without a history of dialysis at baseline showed that at 2-year follow-up, eculizumab was well tolerated, inhibited TMA, and significantly increased estimated glomerular filtration rate (eGFR) in all patients[8]
- In the current study (C10-003)—the first-ever prospective study of pediatric patients with aHUS—eculizumab inhibited complement-mediated TMA[9]
  - Notably, 81.8% of patients with dialysis at baseline were able to discontinue dialysis during the study period after receiving sustained treatment with eculizumab[9]

STUDY OBJECTIVE

- Here, we report the results of a post hoc subanalysis of study C10-003 (US National Institutes of Health www.ClinicalTrials.gov Identifier NCT01193348), which was undertaken to characterize the efficacy and safety of eculizumab in pediatric aHUS patients with and without dialysis at baseline

METHODS

Study Design

- Open-label, single-arm, multicenter, multinational, interventional clinical trial
- Pediatric patients with aHUS aged 1 month to <18 years with a body weight ≥5 kg
- No PE/PI for >5 weeks prior to enrollment
- Thrombocytopenic: platelet count at screening and baseline visit <150 x 10^9/L
- Exhibited signs or symptoms of hemolysis at start of current aHUS episode:
  - Lactate dehydrogenase (LDH) ≥1.5 x upper limit of the normal range (ULN)
  - Hemoglobin concentration ≤ lower limit of normal range (LLN)
  - Fragmented red blood cells with a negative Coombs test
- Serum creatinine (SCr) ≥97th percentile for age at screening
- No requirement for identified complement mutation or antibody
- Patients must have been vaccinated against *Neisseria meningitidis*, pneumococcus, and haemophilus (as per the vaccine label) ≥14 days prior to study drug initiation or otherwise be protected by prophylactic antibiotics for 14 days after meningococcus vaccination. Due to lack of availability of a vaccine for patients less than 2 years of age, patients in this age group received antibiotic prophylaxis throughout the treatment period

Efficacy Endpoints

- Primary endpoint
  - Proportion of patients who achieved complete TMA response at 26 weeks, defined as:
    - Platelet count normalization (≥150 x 10^9/L)
    - Normalization of LDH (LDH < ULN)
    - Improvement of renal function (≥25% decrease in SCr from baseline)
    - Confirmed by 2 consecutive measurements obtained ≥4 weeks apart
- Secondary endpoints included:
  - Hematologic normalization (platelet count normalization [≥150 x 10^9/L] and LDH normalization [LDH ≤ ULN]) sustained for ≥2 consecutive measurements obtained ≥4 weeks apart)
  - TMA event-free status:
    No decrease in platelet count >25% from baseline, no PE/PI, and no new dialysis
  - ≥25% decrease in SCr from baseline (sustained for ≥2 consecutive measurements obtained ≥4 weeks apart)
  - Change from baseline in eGFR
  - eGFR improvement ≥15 mL/min/1.73 m^2 from baseline sustained for ≥2 consecutive measurements obtained ≥4 weeks apart
  - Change in health-related quality of life (as measured by the Pediatric Functional Assessment of Chronic Illness Therapy–Fatigue [FACIT-F] questionnaire)

Dosing

- Fixed doses of eculizumab were administered intravenously based on pre-specified body weight cohorts (**Table 1**)

Table 1. Schedule of Eculizumab Dose Administration Based on Weight

Weight Cohort	Induction	Maintenance
≥40 kg	900 mg weekly x 4	1200 mg week 5; 1200 mg q2 weeks
30 to <40 kg	600 mg weekly x 2	900 mg week 3; 900 mg q2 weeks
20 to <30 kg	600 mg weekly x 2	600 mg week 3; 600 mg q2 weeks
10 to <20 kg	600 mg weekly x 1	300 mg week 2; 300 mg q2 weeks
5 to <10 kg	300 mg weekly x 1	300 mg week 2; 300 mg q3 weeks

RESULTS

Patient Disposition

- A total of 27 pediatric patients were enrolled and 22 were treated with eculizumab
  - Of the 22 patients treated, 11 patients required dialysis at baseline and 11 patients did not

Patient Subgroup Demographics and Baseline Laboratory Values

- Patient subgroup (with or without dialysis) demographics and laboratory values at baseline are summarized in **Table 2**

Table 2. Trial C10-003: Subgroup Demographics and Baseline Laboratory Values

Category	Dialysis (n=11)	No Dialysis (n=11)	*P* Value
Age at first infusion, mean (range), years	5.5 (0.0–17.0)	7.7 (1.0–17.0)	0.2465
Age, n (%)			0.2796
1 month to <23 months	4 (36.4)	1 (9.1)	
≥23 months to <5 years	3 (27.3)	2 (18.2)	
≥5 to <12 years	2 (18.2)	6 (54.5)	
≥12 to <18 years	2 (18.2)	2 (18.2)	
Female gender, n (%)	4 (36.4)	6 (54.6)	0.6699
Patient-reported family history of aHUS, n (%)	3 (27.3)	3 (27.3)	NE
Identified complement abnormalities, n (%)			1.0000
Factor H autoantibody (+)	1 (9.1)	1 (9.1)	
C3 (gain-of-function mutation)	1 (9.1)	0	
Factor H mutation	2 (18.2)	0	
Factor I mutation	1 (9.1)	1 (9.1)	
Membrane cofactor protein (*MCP*)	0	3 (27.3)	
Identified *DGKE* mutation, n (%)	NE	NE	
No identified mutation, n (%)	6 (54.5)	5 (45.5)	NE
Duration from aHUS diagnosis until screening, median (range), days	6.9 (3.9–5740.2)	62.1 (0.9–1738.5)	0.2237
Duration of aHUS clinical manifestation to baseline, median (range), days	6 (0.9–40.2)	5.4 (0.9–127.8)	0.5007
First clinical TMA manifestation, n (%)	10 (90.9)	6 (54.6)	0.1486
No PE/PI during current manifestation, n (%)	6 (54.6)	6 (54.6)	1.0000
Prior renal transplant, n (%)	1 (9.1)	1 (9.1)	1.0000
Platelet count x 10^9/L, mean (SD)	105.6 (34.2)	69.4 (43.3)	0.0878
Patients with platelet count <150 x 10^9/L, n (%)	11 (100.0)	11 (100.0)	1.0000
LDH (U/L), mean (SD)	1357.2 (1138.3)	2530.2 (2222.1)	0.1486
LDH >ULN, n (%)	8 (72.7)	11 (100.0)	0.6497
Hemoglobin concentration (g/L), mean (SD)	77.6 (17.5)	83.1 (13.0)	0.5960
Serum creatinine (µmol/L), mean (SD)	212.0 (146.1)	107.4 (57.2)	0.0946
eGFR[a] mL/min/1.73 m^2, mean (SD)	11.2 (3.9)	54.2 (30.0)	<0.0001
eGFR (mL/min/1.73 m^2), n (%)			<0.0001
<15	10 (90.9)	0	
15–29	1 (9.1)	3 (27.3)	
30–44	0	2 (18.2)	
45–59	0	2 (18.2)	
60–89	0	2 (18.2)	
≥90	0	2 (18.2)	
Duration of dialysis during current manifestation prior to first eculizumab dose, median (range), days	7 (1.0–36.0)[b]	N/A	

aHUS, atypical hemolytic uremic syndrome; *DGKE*, diacylglycerol kinase ε; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; N/A, not applicable; NE, not evaluated; PE/PI, plasma exchange/plasma infusion; SD, standard deviation; TMA, thrombotic microangiopathy; ULN, upper limit of the normal range.
[a]The eGFR was calculated using the Schwartz formula: eGFR (mL/min/1.73 m^2) = [0.4136 x height (cm)] / SCr (mg/dL)].
[b]n=10. One patient receiving dialysis at baseline was not included in the calculation of pretreatment dialysis duration due to receipt of dialysis outside of the specified range from Day -7 to Day 14.

Efficacy Outcomes

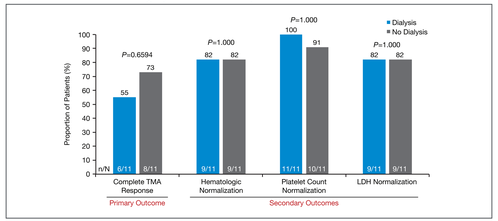
Primary Outcome: Complete TMA Response at 26 Weeks

- Complete TMA response was achieved in 6 of 11 (54.5%; 95% confidence interval [CI]: 23.4–83.3) patients with, and 8 of 11 (72.7%; 95% CI: 39.0–94.0) patients without baseline dialysis (*P*=0.6594) (**Figure 1**)
  - Median (range) time to complete TMA response was 103.0 (35.0–153.0) and 36.5 (7.0–83.0) days, respectively (*P*=0.0141)

TMA and Hematologic Outcomes at 26 Weeks

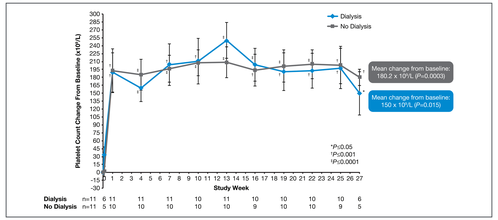
- Eleven of 11 (100.0%) and 10 of 11 patients (90.9%) with and without baseline dialysis, respectively, achieved TMA event-free status
- Hematologic normalization was observed in 9 of 11 patients (81.8%; 95% CI: 48.2–97.7) (**Figure 1**) with and without baseline dialysis, respectively (*P*=1.000)
- Platelet count normalization was achieved in all 11 (100.0%; 95% CI: 71.5–100.0) and 10 of 11 (90.9%; 95% CI: 58.7–99.8) patients with and without baseline dialysis (*P*=1.000) (**Figure 1**)
- Eculizumab significantly improved mean (SD) platelet count (x 10^9/L) change from baseline in patients with (149.8 [101.0]) and without (180.2 [34.9]) baseline dialysis (*P*=0.0150 and *P*=0.0003, respectively) (**Figure 2**)
- Nine of 11 (81.8%; 95% CI: 48.2–97.7) patients with and without baseline dialysis, respectively, achieved LDH normalization from baseline to 26 weeks of eculizumab treatment (*P*=1.00) (**Figure 1**)
- Of 10 patients on PE/PI at baseline (5 in each subgroup), all (100.0%) discontinued by the end of the 26-week study

Figure 1. Proportion of Patients in Each Subgroup Achieving Complete TMA Response and Hematologic, Platelet Count, and LDH Normalization at 26 Weeks



LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy.

Figure 2. Mean Platelet Count Improvement Over 26 Weeks



Endpoint assessment occurred at Week 27.
P values were generated by statistical comparisons between values at 27 weeks and at baseline.

Renal Outcomes at 26 Weeks

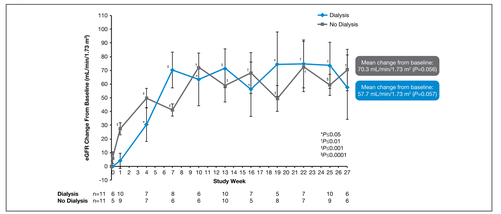
- Nine of 11 (81.8%) and 10 of 11 patients (90.9%) with and without baseline dialysis had eGFR improvement ≥15 mL/min/1.73 m^2 from baseline to Week 26 (**Table 3, Figure 3**)
- Of the 11 patients on dialysis at baseline, 9 (81.8%) discontinued during the 26-week study period (**Table 3**)
  - Mean (range) time to discontinuation of dialysis after eculizumab initiation was 7 (4.0–15.0) days
  - Two of 11 patients were on dialysis at Week 26
- Of the 11 patients not on dialysis at baseline, all 11 (100.0%) remained dialysis-free during 26 weeks
- Thus, 2/22 (9%) of pediatric patients were on dialysis at 26 weeks
  - These patients received dialysis for 7 and 36 days before initiation of eculizumab

Table 3. Summary of Renal Outcomes

Parameter	Dialysis (n=11)	No Dialysis (n=11)	*P* Value
eGFR change from baseline (mL/min/1.73 m^2), mean (SD)[a]	+57.7 (57.3) *P*=0.0568[c]	+70.3 (37.1) *P*=0.0056[c]	0.0759[b]
eGFR (mL/min/1.73 m^2), mean (SD)	69.8 (59.1)	124.6 (24.6)	NE
eGFR improvement from baseline ≥15 mL/min/1.73 m^2, n (%)	9 (81.8)	10 (90.9)	1.0000[b]
Serum creatinine decrease ≥25%, n (%)	7 (63.6)	9 (81.8)	0.6351[b]
CKD improvement ≥1 stage from baseline, n (%)	9 (81.8)	8 (88.9)	1.0000[b]
Patients on dialysis at baseline who discontinued dialysis during the study, n (%)	9 (81.8)	N/A	
Time to discontinuation of dialysis after eculizumab initiation, mean (range), days	7 (4.0–15.0)[d]	N/A	

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; N/A, not applicable; NE, not evaluated; SD, standard deviation.
[a]Endpoint assessment occurred at Week 27.
[b]*P* values were generated by statistical comparisons between subgroups.
[c]*P* values were generated by statistical comparisons between values at 27 weeks and baseline.
[d]n=8. One patient discontinued dialysis before the first dose of eculizumab and received no new dialysis. Two additional patients were still on dialysis at Week 26.

Figure 3. Mean Improvement in eGFR Over 26 Weeks



eGFR, estimated glomerular filtration rate.
P values were generated by statistical comparisons between values at 27 weeks and at baseline.

Improvement in Health-Related Quality of Life

- The Pediatric FACIT-F mean change from baseline to 27 weeks was 28.66 (range, 16.91–45.00) for patients with baseline dialysis and 20.50 (range, 2.00–32.00) for patients without a history of dialysis (*P*=0.2394)

Eculizumab Was Safe and Well Tolerated Over the 26-Week Study Period

- There were no deaths or meningococcal infections reported during the study period
- Most treatment-emergent adverse events (TEAEs) were mild or moderate in severity (**Table 4**)
  - The most common TEAEs (frequency ≥20%) were abdominal pain, catheter site infection, cough, diarrhea, headache, hypertension, muscle spasms, nasopharyngitis, oropharyngeal pain, pyrexia, upper respiratory tract infection, urinary tract infection, and vomiting
- Thirteen of 22 patients (59%) reported at least 1 serious TEAE, including 9 patients (82%) with baseline dialysis and 4 patients (36%) without dialysis (**Table 5**)
  - One patient (on baseline dialysis) discontinued due to agitation, a serious TEAE
  - One patient (on baseline dialysis) had a human anti-human antibody response, and continued eculizumab treatment without apparent adverse effect and with no apparent impact on clinical response to eculizumab treatment

Table 4. Safety of Eculizumab Treatment and Summary of TEAEs

Category	Dialysis (n=11)	No Dialysis (n=11)
TEAEs (frequency ≥15%), n (%)		
Abdominal pain	3 (27.3)	4 (36.4)
Acute tonsillitis	—	2 (18.2)
Catheter site infection	3 (27.3)	—
Cough	4 (36.4)	4 (36.4)
Dermatitis diaper	2 (18.2)	—
Diarrhea	3 (27.3)	4 (36.4)
Dyspepsia	2 (18.2)	—
Headache	3 (27.3)	—
Hypertension	3 (27.3)	—
Lymphadenopathy	—	2 (18.2)
Muscle spasms	—	3 (27.3)
Nasopharyngitis	2 (18.2)	4 (36.4)
Neck pain	—	2 (18.2)
Oropharyngeal pain	—	3 (27.3)
Pleural effusion	2 (18.2)	—
Pyrexia	6 (54.5)	5 (45.5)
Rash	2 (18.2)	—
Upper respiratory tract infection	4 (36.4)	3 (27.3)
Urinary tract infection	3 (27.3)	—
Vomiting	3 (27.3)	3 (27.3)

TEAEs, treatment-emergent adverse events.

Table 5. Serious TEAEs During Eculizumab Treatment

Category	Dialysis (n=11)	No Dialysis (n=11)
Patients with any serious TEAE, n (%)	9 (81.8)	4 (36.4)
Relationship to eculizumab treatment, n (%)		
Unrelated	6 (54.5)	4 (36.4)
Possible	3 (27.3)	0
SAEs occurring in 2 or more patients, n (%)		
Fever	2 (18.2)	0
Gastroenteritis viral	1 (9.1)	1 (9.1)
Upper respiratory tract infection	2 (18.2)	0
Hypertension	2 (18.2)	0

SAEs, serious adverse events; TEAEs, treatment-emergent adverse events.

CONCLUSIONS

- In this post hoc analysis, eculizumab produced significant and clinically meaningful improvements in hematologic and renal parameters in patients with and without dialysis at baseline
- No patients not on dialysis at baseline required dialysis after eculizumab initiation, and 82% of those on dialysis at baseline were free of dialysis during eculizumab therapy
- There were no meningococcal infections or new safety concerns reported
- Together, these data provide additional support that sustained treatment is effective and well tolerated in pediatric patients with aHUS, regardless of dialysis status at baseline

REFERENCES

1. Noris M, et al. *Clin J Am Soc Nephrol*. 2010;5:1844–1859.
2. Fremeaux-Bacchi V, et al. *Clin J Am Soc Nephrol*. 2013;8:554–562.
3. Loirat C, et al. *Semin Thromb Hemost*. 2010;36:673–681.
4. Johnson S, et al. *Pediatr Nephrol*. 2014;29;1967–1978.
5. Legendre C, et al. *N Engl J Med*. 2013;368:2169–2181.
6. US Food and Drug Administration. Soliris® (eculizumab) [prescribing information]. Cheshire, CT: Alexion Pharmaceuticals, Inc.; 2014.
7. European Medicines Agency. Soliris® (eculizumab) [summary of product characteristics]. Paris, France: Alexion Europe SAS; 2014.
8. Legendre C, et al. Presented at: the 50th ERA-EDTA Congress; May 18–21, 2013; Istanbul, Turkey.
9. Greenbaum LA, et al. *J Am Soc Nephrol*. 2013;24: Abstract SA-PO849.

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Presented at the American Society of Nephrology (ASN) Kidney Week 2014 Annual Meeting, November 11–16, 2014, Philadelphia, Pennsylvania.

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≥5 to <12 years	2 (18.2)	6 (54.5)	
≥12 to <18 years	2 (18.2)	2 (18.2)	
Female gender, n (%)	4 (36.4)	6 (54.6)	0.6699
Patient-reported family history of aHUS, n (%)	3 (27.3)	3 (27.3)	NE
Identified complement abnormalities, n (%)			1.0000
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15–29	1 (9.1)	3 (27.3)	
30–44	0	2 (18.2)	
45–59	0	2 (18.2)	
60–89	0	2 (18.2)	
≥90	0	2 (18.2)	
Duration of dialysis during current manifestation prior to first eculizumab dose, median (range), days	7 (1.0–36.0)[b]	N/A	

aHUS, atypical hemolytic uremic syndrome; *DGKE*, diacylglycerol kinase ε; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; N/A, not applicable; NE, not evaluated; PE/PI, plasma exchange/plasma infusion; SD, standard deviation; TMA, thrombotic microangiopathy; ULN, upper limit of the normal range.

[a]The eGFR was calculated using the Schwartz formula: eGFR (mL/min/1.73 m^2) = [0.4136 x height (cm)] / SCr (mg/dL)].

[b]n=10. One patient receiving dialysis at baseline was not included in the calculation of pretreatment dialysis duration due to receipt of dialysis outside of the specified range from Day -7 to Day 14.

Efficacy Outcomes

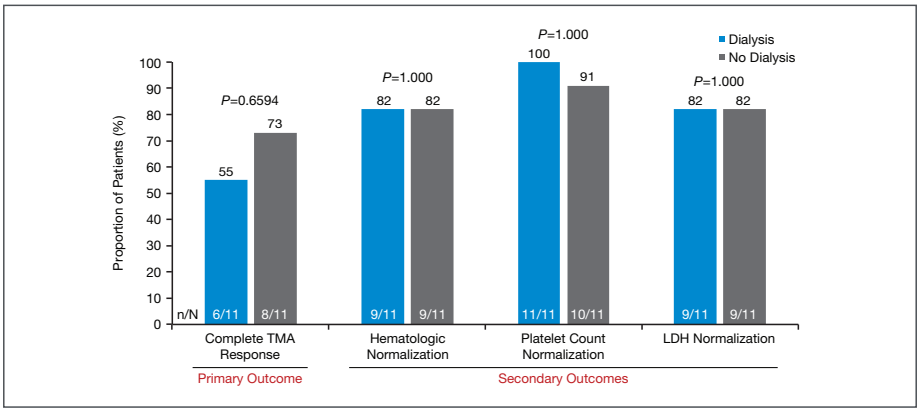
Primary Outcome: Complete TMA Response at 26 Weeks

- Complete TMA response was achieved in 6 of 11 (54.5%; 95% confidence interval [CI]: 23.4–83.3) patients with, and 8 of 11 (72.7%; 95% CI: 39.0–94.0) patients without baseline dialysis (*P*=0.6594) (**Figure 1**)
  - Median (range) time to complete TMA response was 103.0 (35.0–153.0) and 36.5 (7.0–83.0) days, respectively (*P*=0.0141)

TMA and Hematologic Outcomes at 26 Weeks

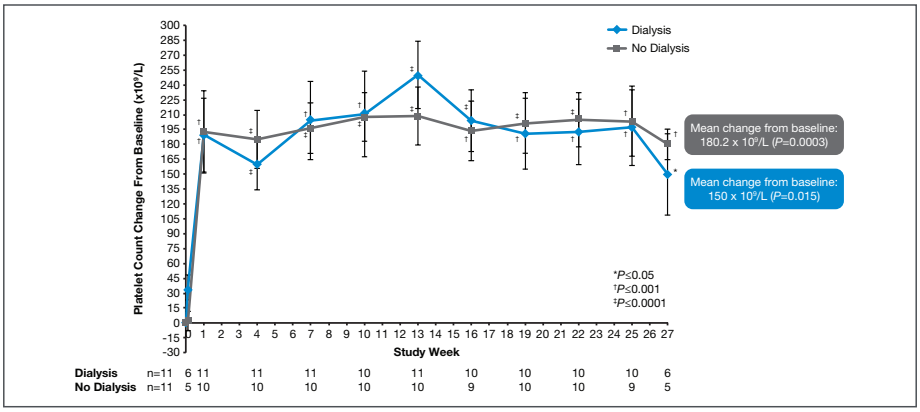
- Eleven of 11 (100.0%) and 10 of 11 patients (90.9%) with and without baseline dialysis, respectively, achieved TMA event-free status
- Hematologic normalization was observed in 9 of 11 patients (81.8%; 95% CI: 48.2–97.7) (**Figure 1**) with and without baseline dialysis, respectively (*P*=1.000)
- Platelet count normalization was achieved in all 11 (100.0%; 95% CI: 71.5–100.0) and 10 of 11 (90.9%; 95% CI: 58.7–99.8) patients with and without baseline dialysis (*P*=1.000) (**Figure 1**)
- Eculizumab significantly improved mean (SD) platelet count (x 10^9/L) change from baseline in patients with (149.8 [101.0]) and without (180.2 [34.9]) baseline dialysis (*P*=0.0150 and *P*=0.0003, respectively) (**Figure 2**)
- Nine of 11 (81.8%; 95% CI: 48.2–97.7) patients with and without baseline dialysis, respectively, achieved LDH normalization from baseline to 26 weeks of eculizumab treatment (*P*=1.00) (**Figure 1**)
- Of 10 patients on PE/PI at baseline (5 in each subgroup), all (100.0%) discontinued by the end of the 26-week study

Figure 1. Proportion of Patients in Each Subgroup Achieving Complete TMA Response and Hematologic, Platelet Count, and LDH Normalization at 26 Weeks



LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy.

Figure 2. Mean Platelet Count Improvement Over 26 Weeks



Endpoint assessment occurred at Week 27.
P values were generated by statistical comparisons between values at 27 weeks and at baseline.

Renal Outcomes at 26 Weeks

- Nine of 11 (81.8%) and 10 of 11 patients (90.9%) with and without baseline dialysis had eGFR improvement ≥15 mL/min/1.73 m^2 from baseline to Week 26 (**Table 3, Figure 3**)

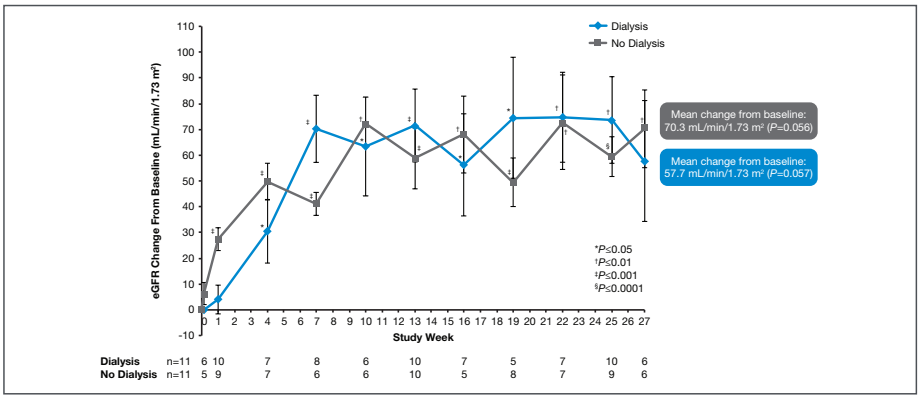
- Of the 11 patients on dialysis at baseline, 9 (81.8%) discontinued during the 26-week study period (**Table 3**)
  - Mean (range) time to discontinuation of dialysis after eculizumab initiation was 7 (4.0–15.0) days
  - Two of 11 patients were on dialysis at Week 26
- Of the 11 patients not on dialysis at baseline, all 11 (100.0%) remained dialysis-free during 26 weeks
- Thus, 2/22 (9%) of pediatric patients were on dialysis at 26 weeks
  - These patients received dialysis for 7 and 36 days before initiation of eculizumab

Table 3. Summary of Renal Outcomes

Parameter	Dialysis (n=11)	No Dialysis (n=11)	*P* Value
eGFR change from baseline (mL/min/1.73 m^2), mean (SD)[a]	+57.7 (57.3) *P*=0.0568[c]	+70.3 (37.1) *P*=0.0056[c]	0.0759[b]
eGFR (mL/min/1.73 m^2), mean (SD)	69.8 (59.1)	124.6 (24.6)	NE
eGFR improvement from baseline ≥15 mL/min/1.73 m^2, n (%)	9 (81.8)	10 (90.9)	1.0000[b]
Serum creatinine decrease ≥25%, n (%)	7 (63.6)	9 (81.8)	0.6351[b]
CKD improvement ≥1 stage from baseline, n (%)	9 (81.8)	8 (88.9)	1.0000[b]
Patients on dialysis at baseline who discontinued dialysis during the study, n (%)	9 (81.8)	N/A	
Time to discontinuation of dialysis after eculizumab initiation, mean (range), days	7 (4.0–15.0)[d]	N/A	

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; N/A, not applicable; NE, not evaluated; SD, standard deviation.
[a]Endpoint assessment occurred at Week 27.
[b]*P* values were generated by statistical comparisons between subgroups.
[c]*P* values were generated by statistical comparisons between values at 27 weeks and baseline.
[d]n=8. One patient discontinued dialysis before the first dose of eculizumab and received no new dialysis. Two additional patients were still on dialysis at Week 26.

Figure 3. Mean Improvement in eGFR Over 26 Weeks



eGFR, estimated glomerular filtration rate.
P values were generated by statistical comparisons between values at 27 weeks and at baseline.

Improvement in Health-Related Quality of Life

- The Pediatric FACIT-F mean change from baseline to 27 weeks was 28.66 (range, 16.91–45.00) for patients with baseline dialysis and 20.50 (range, 2.00–32.00) for patients without a history of dialysis (*P*=0.2394)

Eculizumab Was Safe and Well Tolerated Over the 26-Week Study Period

- There were no deaths or meningococcal infections reported during the study period
- Most treatment-emergent adverse events (TEAEs) were mild or moderate in severity (**Table 4**)
  - The most common TEAEs (frequency ≥20%) were abdominal pain, catheter site infection, cough, diarrhea, headache, hypertension, muscle spasms, nasopharyngitis, oropharyngeal pain, pyrexia, upper respiratory tract infection, urinary tract infection, and vomiting
- Thirteen of 22 patients (59%) reported at least 1 serious TEAE, including 9 patients (82%) with baseline dialysis and 4 patients (36%) without dialysis (**Table 5**)
  - One patient (on baseline dialysis) discontinued due to agitation, a serious TEAE
  - One patient (on baseline dialysis) had a human anti-human antibody response, and continued eculizumab treatment without apparent adverse effect and with no apparent impact on clinical response to eculizumab treatment

Table 4. Safety of Eculizumab Treatment and Summary of TEAEs

Category	Dialysis (n=11)	No Dialysis (n=11)
TEAEs (frequency ≥15%), n (%)		
Abdominal pain	3 (27.3)	4 (36.4)
Acute tonsillitis	—	2 (18.2)
Catheter site infection	3 (27.3)	—
Cough	4 (36.4)	4 (36.4)
Dermatitis diaper	2 (18.2)	—
Diarrhea	3 (27.3)	4 (36.4)
Dyspepsia	2 (18.2)	—
Headache	3 (27.3)	—
Hypertension	3 (27.3)	—
Lymphadenopathy	—	2 (18.2)
Muscle spasms	—	3 (27.3)
Nasopharyngitis	2 (18.2)	4 (36.4)
Neck pain	—	2 (18.2)
Oropharyngeal pain	—	3 (27.3)
Pleural effusion	2 (18.2)	—
Pyrexia	6 (54.5)	5 (45.5)
Rash	2 (18.2)	—
Upper respiratory tract infection	4 (36.4)	3 (27.3)
Urinary tract infection	3 (27.3)	—
Vomiting	3 (27.3)	3 (27.3)

TEAEs, treatment-emergent adverse events.

Table 5. Serious TEAEs During Eculizumab Treatment

Category	Dialysis (n=11)	No Dialysis (n=11)
Patients with any serious TEAE, n (%)	9 (81.8)	4 (36.4)
Relationship to eculizumab treatment, n (%)		
Unrelated	6 (54.5)	4 (36.4)
Possible	3 (27.3)	0
SAEs occurring in 2 or more patients, n (%)		
Fever	2 (18.2)	0
Gastroenteritis viral	1 (9.1)	1 (9.1)
Upper respiratory tract infection	2 (18.2)	0
Hypertension	2 (18.2)	0

SAEs, serious adverse events; TEAEs, treatment-emergent adverse events.

CONCLUSIONS

- In this post hoc analysis, eculizumab produced significant and clinically meaningful improvements in hematologic and renal parameters in patients with and without dialysis at baseline
- No patients not on dialysis at baseline required dialysis after eculizumab initiation, and 82% of those on dialysis at baseline were free of dialysis during eculizumab therapy
- There were no meningococcal infections or new safety concerns reported
- Together, these data provide additional support that sustained treatment is effective and well tolerated in pediatric patients with aHUS, regardless of dialysis status at baseline

REFERENCES

1. Noris M, et al. *Clin J Am Soc Nephrol*. 2010;5:1844–1859.
2. Fremeaux-Bacchi V, et al. *Clin J Am Soc Nephrol*. 2013;8:554–562.
3. Loirat C, et al. *Semin Thromb Hemost*. 2010;36:673–681.
4. Johnson S, et al. *Pediatr Nephrol*. 2014:29;1967–1978.
5. Legendre C, et al. *N Engl J Med*. 2013;368:2169–2181.
6. US Food and Drug Administration. Soliris® (eculizumab) [prescribing information]. Cheshire, CT: Alexion Pharmaceuticals, Inc.; 2014.
7. European Medicines Agency. Soliris® (eculizumab) [summary of product characteristics]. Paris, France: Alexion Europe SAS; 2014.
8. Legendre C, et al. Presented at: the 50th ERA-EDTA Congress; May 18–21, 2013; Istanbul, Turkey.
9. Greenbaum LA, et al. *J Am Soc Nephrol*. 2013;24: Abstract SA-PO849.

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