SP281

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

Johan Vande Walle,[1] Larry A. Greenbaum,[2] Camille L. Bedrosian,[3] Masayo Ogawa,[3] John F. Kincaid,[3] Chantal Loirat[4]

[1]UZ Gent Dienst Nefrologie, Ghent, Belgium; [2]Emory University, Atlanta, GA, USA; [3]Alexion Pharmaceuticals, Inc., Cheshire, CT, USA; [4]Assistance Publique–Hôpitaux de Paris, Hôpital Robert-Debré, Paris, France

## 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
- Plasma exchange/plasma infusion (PE/PI) provides limited clinical benefit to children with aHUS—29% progress to end-stage renal disease or die within the first year of diagnosis.[1,2] PE/PI is also associated with a higher frequency of complications and quality of life impairment in children with aHUS[3]
- 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.[4] It is the first and only approved treatment for aHUS in pediatric and adult patients[5,6]
- A prior retrospective study of pediatric patients with aHUS showed that eculizumab reduced TMA and improved kidney function (including elimination of dialysis in 50% of patients)[7]
- In a previous prospective trial of patients 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[4]
  - To further characterize the safety and efficacy of eculizumab in patients with and without a history of dialysis at baseline, a subanalysis of this trial was conducted in these patients[8]
  - Results from this subanalysis 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 and improved eGFR in pediatric patients with aHUS. Notably, 82% of patients with dialysis at baseline were able to discontinue dialysis during the study period after receiving 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 designed to characterize the safety and efficacy of eculizumab in pediatric aHUS patients with and without a history of 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
- 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 were to receive antibiotic prophylaxis throughout the treatment period

### Efficacy End Points

- Primary end point
  - 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)
    - Complete TMA response confirmed by 2 consecutive measurements obtained ≥4 weeks apart
- Secondary end points 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
- Eculizumab induction and maintenance dosing regimens are described in **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 had a history of dialysis at baseline and 11 patients did not
- Nineteen of 22 patients (86.4%) completed the 26-week study period
  - Ten of 19 patients (52.6%) had a history of dialysis at baseline and 9 of 19 patients (47.4%) did not
  - Of the 3 patients who discontinued before completing the 26-week study period, 1 patient had a history of dialysis at baseline and 2 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 (54.5) | 0.6699 |
| Race, n (%) | | | |
| Asian | 0 | 2 (18.2) | |
| White | 10 (90.0) | 8 (72.7) | |
| Other | 1 (9.1) | 1 (9.1) | |
| Patient-reported family history of aHUS, n (%) | 3 (27.3) | 3 (27.3) | NE |
| Identified complement abnormalities, n (%) | | | 1.0000 |
| Anti-complement factor antibody: | | | |
| Factor H autoantibody (+) | 1 (9.1) | 0 | |
| Factor H autoantibody (+) and CFHR1/3 polymorphism | 0 | 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) | |
| 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 (54.5) | 0.1486 |
| No PE/PI during current manifestation, n (%) | 6 (54.5) | 6 (54.5) | 1.0000 |
| Prior renal transplant, n (%) | 1 (9.1) | 1 (9.1) | 1.0000 |
| Platelet count x $10^9$/L, mean (SD) | 105.5 (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, mean (range), days | 137 (1.0–1252.0) | N/A | |

aHUS, atypical hemolytic uremic syndrome; CFHR, complement factor H-related; 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)].

### Efficacy Outcomes

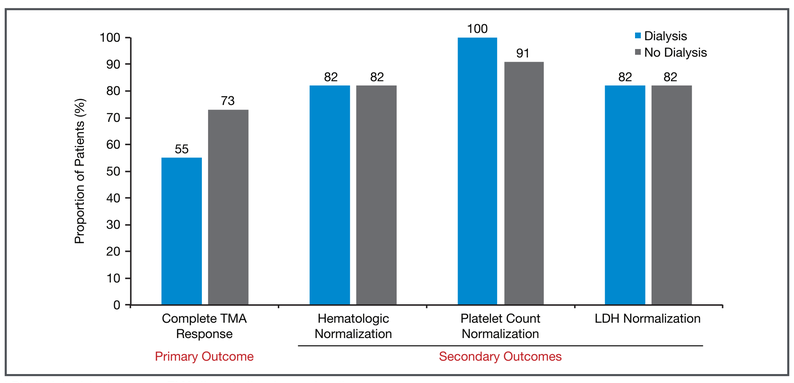
**Primary Outcome: Complete TMA Response at 26 Weeks**

- 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 a history of dialysis (**Figure 1**)
  - The number of patients in the dialysis and non-dialysis groups who achieved a complete TMA response was not statistically significant between subgroups (*P*=0.6594)
  - Median (range) time to complete TMA response was 103.0 (35.0–153.0) and 36.5 (7.0–83.0) days, respectively
    - Median time to complete TMA response observed for the dialysis and non-dialysis groups was statistically significant between subgroups (*P*=0.0141)

**TMA and Hematologic Outcomes at 26 Weeks**

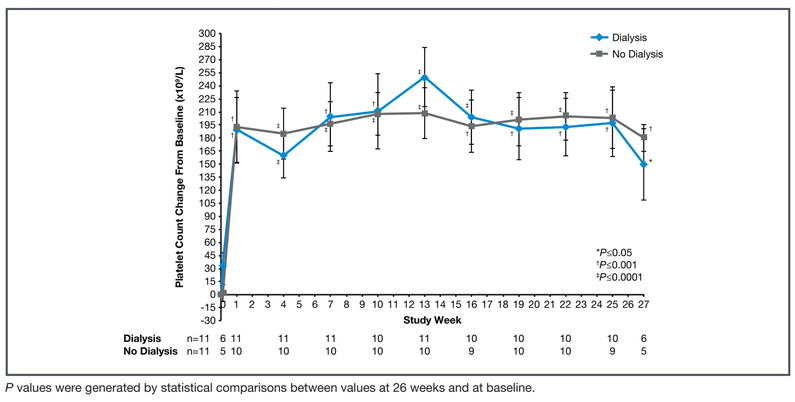
- Eleven of 11 (100.0%) and 10 of 11 patients (90.9%) with and without a history of dialysis, respectively, achieved TMA event-free status
- Hematologic normalization was observed in 9 of 11 patients (81.8%; 95% CI: 48.2–97.7) (**Figure 1**) with and without a history of dialysis, respectively
- Platelet 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 a history of dialysis (**Figure 1**)
  - Median (range) time to platelet count normalization was 8.0 days in patients with (2.0–92.0) and without (7.0–21.0) a history of dialysis, respectively
- Eculizumab significantly improved mean (SD) platelet count (x $10^9$/L) change from baseline in patients with (149.8 [101.0], *P*=0.0150) and without (180.2 [34.9], *P*=0.0003) a history of dialysis (**Figure 2**)
  - End point assessment occurred at Week 27
- Nine of 11 (81.8%; 95% CI: 48.2–97.7) patients with and without a history of dialysis, respectively, achieved LDH normalization from baseline to 26 weeks of eculizumab treatment (**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**




*P* values were generated by statistical comparisons between values at 26 weeks and at baseline.

**Renal Outcomes at 26 Weeks**

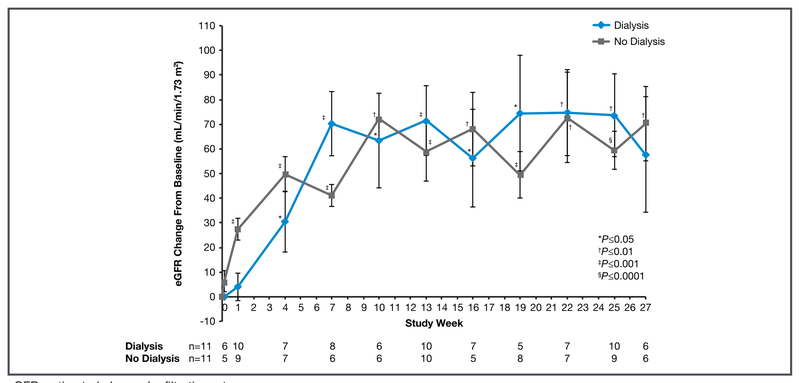
- Nine of 11 (81.8%) and 10 of 11 patients (90.9%) with and without a history of dialysis had eGFR improvement ≥15 mL/min/1.73 $m^2$ from baseline through 26 weeks (**Table 3, Figure 3**)
- Of the 11 patients on dialysis at baseline, 9 (81.8%) discontinued during the 26-week study period (**Table 3**)
  - Mean (range) time to discontinuation of dialysis after eculizumab initiation was 74 (4.0–460.0) 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

**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 improvement from baseline ≥15 mL/min/1.73 $m^2$, n (%) | 9 (81.8) | 10 (90.9) | 1.0000[b] |
| eGFR (mL/min/1.73 $m^2$) at 27 weeks, mean (SD) | 69.8 (59.1) | 124.6 (24.6) | NE |
| 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] |
| Time to discontinuation of dialysis after eculizumab initiation, mean (range), days | 74 (4.0–460.0) | N/A | |
| Patients with a history of dialysis at baseline who discontinued dialysis during the study, n (%) | 9 (81.8) | N/A | |

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; N/A, not applicable; NE, not evaluated; SD, standard deviation.
[a]End point 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 26 weeks and baseline.

**Figure 3. Mean Improvement in eGFR Over 26 Weeks**




eGFR, estimated glomerular filtration rate.
*P* values were generated by statistical comparisons between values at 26 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 a history of dialysis and 20.50 (range, 2.00–32.00) for patients without a history of dialysis

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

- There were no deaths or meningococcal infections reported during the 26-week 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—9 patients (82%) with a history of dialysis and 4 patients (36%) without a history of dialysis (**Table 4**)
  - One patient (with a history of dialysis) discontinued due to agitation, a serious TEAE
  - One patient (with a history of 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 (27.0) | 4 (36.0) |
| Acute tonsillitis | — | 2 (18.0) |
| Catheter site infection | 3 (27.0) | — |
| Cough | 4 (36.0) | 4 (36.0) |
| Dermatitis diaper | 2 (18.0) | — |
| Diarrhea | 3 (27.0) | 4 (36.0) |
| Dyspepsia | 2 (18.0) | — |
| Headache | 3 (27.0) | — |
| Hypertension | 3 (27.0) | — |
| Lymphadenopathy | — | 2 (18.0) |
| Muscle spasms | — | 3 (27.0) |
| Nasopharyngitis | 2 (18.0) | 4 (36.0) |
| Neck pain | — | 2 (18.0) |
| Oropharyngeal pain | — | 3 (27.0) |
| Pleural effusion | 2 (18.0) | — |
| Pyrexia | 6 (55.0) | 5 (46.0) |
| Rash | 2 (18.0) | — |
| Upper respiratory tract infection | 4 (36.0) | 3 (27.0) |
| Urinary tract infection | 3 (27.0) | — |
| Vomiting | 3 (27.0) | 3 (27.0) |
| Patients with any serious TEAE, n (%) | **9 (82.0)** | **4 (36.0)** |
| Severity, n (%) | | |
| Mild | TBD | TBD |
| Moderate | TBD | TBD |
| Severe | TBD | TBD |
| Relationship to eculizumab treatment, n (%) | | |
| Unrelated | 6 (55.0) | 4 (36.0) |
| Possible | 3 (27.0) | 0 |
| SAEs occurring in 2 or more patients, n (%) | | |
| Fever | 2 (18.0) | 0 |
| Gastroenteritis viral | 1 (9.0) | 1 (9.0) |
| Upper respiratory tract infection | 2 (18.0) | 0 |
| Hypertension | 2 (18.0) | 0 |

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

## CONCLUSIONS

- In this post hoc subanalysis, designed to characterize the safety and efficacy of eculizumab in aHUS pediatric patients with and without a history of dialysis at baseline, treatment with eculizumab resulted in clinically meaningful improvements in hematologic and renal parameters in both groups
- Further analysis of hematologic and renal parameters showed that, in general, outcomes were similar between patients with and without a history of dialysis, and that statistically significant efficacy could be achieved regardless of dialysis history
  - Notably, 4 of 11 patients with a history of dialysis presented with severe genetic mutations at baseline (CFH or C3), while 3 of 11 patients without a history of dialysis presented with a less severe mutation (MCP)
  - These baseline characteristics could account for the apparent differences in the actual and final eGFR gains observed between subgroups
- These data are consistent with what has been previously reported in a subanalysis of patients with clinical evidence of progressing TMA who did and did not have a history of dialysis at the time of eculizumab initiation[8]
  - In both subanalyses, eculizumab improved hematologic and renal outcomes irrespective of baseline dialysis status
  - Importantly, in both subanalyses, a similar proportion of patients on dialysis at baseline were able to discontinue dialysis by data cutoff
- In addition, patients with no history of dialysis at baseline did not require new dialysis during eculizumab treatment, which is consistent with previously reported data from a retrospective eculizumab trial in 19 pediatric patients (aged 2 months to 17 years)[7]
- There were no meningococcal infections or new safety concerns reported
- Together, these data provide additional support that eculizumab is a proven, effective, and safe treatment in all pediatric patients with aHUS, regardless of dialysis history

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## ACKNOWLEDGMENTS

The authors would like to acknowledge Kenyon Ogburn of Alexion Pharmaceuticals, Inc., and Peloton Advantage, LLC, for providing editorial support with funding from Alexion Pharmaceuticals, Inc.

**Disclosures:** [To come upon finalization].

**Presented at the 51st European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Congress, May 31–June 3, 2014, Amsterdam, The Netherlands.**

SP281

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- Serum creatinine (SCr) ≥97th percentile for age at screening
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    - Normalization of LDH (LDH < ULN)
    - Improvement of renal function (≥25% decrease in SCr from baseline)
    - Complete TMA response confirmed by 2 consecutive measurements obtained ≥4 weeks apart
- Secondary end points 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
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  - 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)

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# RESULTS

## Patient Disposition

- A total of 27 pediatric patients were enrolled and 22 were treated with eculizumab
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## 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 (54.5) | 0.6699 |
| Race, n (%) | | | |
| Asian | 0 | 2 (18.2) | |
| White | 10 (90.0) | 8 (72.7) | |
| Other | 1 (9.1) | 1 (9.1) | |
| Patient-reported family history of aHUS, n (%) | 3 (27.3) | 3 (27.3) | NE |
| Identified complement abnormalities, n (%) | | | 1.0000 |
| Anti-complement factor antibody: | | | |
| Factor H autoantibody (+) | 1 (9.1) | 0 | |
| Factor H autoantibody (+) and CFHR1/3 polymorphism | 0 | 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) | |

**Table 2. Trial C10-003: Subgroup Demographics and Baseline Laboratory Values (cont'd)**

| Category | Dialysis (n=11) | No Dialysis (n=11) | *P* Value |
|---|---|---|---|
| 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 (54.5) | 0.1486 |
| No PE/PI during current manifestation, n (%) | 6 (54.5) | 6 (54.5) | 1.0000 |
| Prior renal transplant, n (%) | 1 (9.1) | 1 (9.1) | 1.0000 |
| Platelet count x $10^9$/L, mean (SD) | 105.5 (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, mean (range), days | 137 (1.0–1252.0) | N/A | |

aHUS, atypical hemolytic uremic syndrome; CFHR, complement factor H-related; 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)].

## Efficacy Outcomes

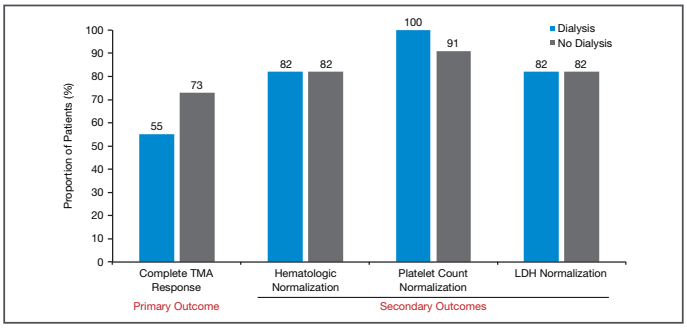
**Primary Outcome: Complete TMA Response at 26 Weeks**

- 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 a history of dialysis (**Figure 1**)
  - The number of patients in the dialysis and non-dialysis groups who achieved a complete TMA response was not statistically significant between subgroups (*P*=0.6594)
  - Median (range) time to complete TMA response was 103.0 (35.0–153.0) and 36.5 (7.0–83.0) days, respectively
    - Median time to complete TMA response observed for the dialysis and non-dialysis groups was statistically significant between subgroups (*P*=0.0141)

**TMA and Hematologic Outcomes at 26 Weeks**

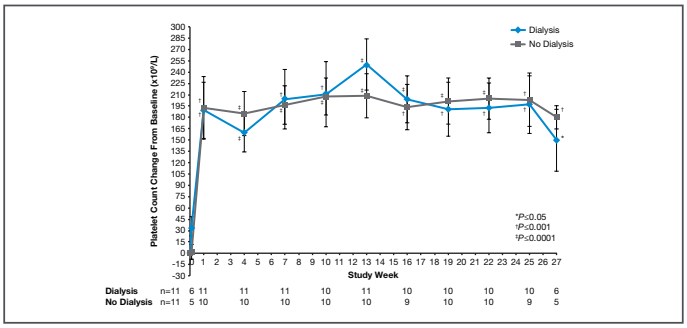
- Eleven of 11 (100.0%) and 10 of 11 patients (90.9%) with and without a history of dialysis, respectively, achieved TMA event-free status
- Hematologic normalization was observed in 9 of 11 patients (81.8%; 95% CI: 48.2–97.7) (**Figure 1**) with and without a history of dialysis, respectively
- Platelet 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 a history of dialysis (**Figure 1**)
  - Median (range) time to platelet count normalization was 8.0 days in patients with (2.0–92.0) and without (7.0–21.0) a history of dialysis, respectively
- Eculizumab significantly improved mean (SD) platelet count (x $10^9$/L) change from baseline in patients with (149.8 [101.0], *P*=0.0150) and without (180.2 [34.9], *P*=0.0003) a history of dialysis (**Figure 2**)
  - End point assessment occurred at Week 27
- Nine of 11 (81.8%; 95% CI: 48.2–97.7) patients with and without a history of dialysis, respectively, achieved LDH normalization from baseline to 26 weeks of eculizumab treatment (**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**




*P* values were generated by statistical comparisons between values at 26 weeks and at baseline.

**Renal Outcomes at 26 Weeks**

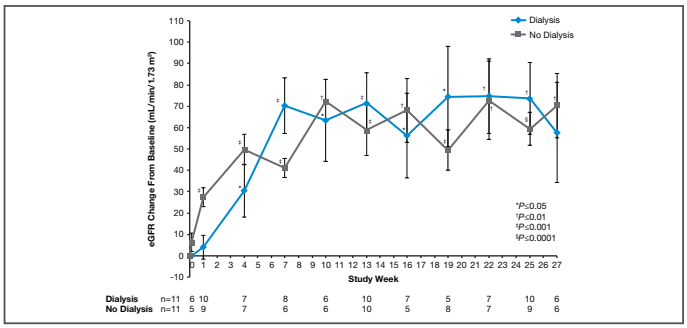
- Nine of 11 (81.8%) and 10 of 11 patients (90.9%) with and without a history of dialysis had eGFR improvement ≥15 mL/min/1.73 $m^2$ from baseline through 26 weeks (**Table 3, Figure 3**)
- Of the 11 patients on dialysis at baseline, 9 (81.8%) discontinued during the 26-week study period (**Table 3**)
  - Mean (range) time to discontinuation of dialysis after eculizumab initiation was 74 (4.0–460.0) 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

**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)<br>*P*=0.0568[c] | +70.3 (37.1)<br>*P*=0.0056[c] | 0.0759[b] |
| eGFR improvement from baseline ≥15 mL/min/1.73 $m^2$, n (%) | 9 (81.8) | 10 (90.9) | 1.0000[b] |
| eGFR (mL/min/1.73 $m^2$) at 27 weeks, mean (SD) | 69.8 (59.1) | 124.6 (24.6) | NE |
| 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] |
| Time to discontinuation of dialysis after eculizumab initiation, mean (range), days | 74 (4.0–460.0) | N/A | |
| Patients with a history of dialysis at baseline who discontinued dialysis during the study, n (%) | 9 (81.8) | N/A | |

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; N/A, not applicable; NE, not evaluated; SD, standard deviation.
[a]End point 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 26 weeks and baseline.

**Figure 3. Mean Improvement in eGFR Over 26 Weeks**




eGFR, estimated glomerular filtration rate.
*P* values were generated by statistical comparisons between values at 26 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 a history of dialysis and 20.50 (range, 2.00–32.00) for patients without a history of dialysis

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

- There were no deaths or meningococcal infections reported during the 26-week 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—9 patients (82%) with a history of dialysis and 4 patients (36%) without a history of dialysis (**Table 4**)
  - One patient (with a history of dialysis) discontinued due to agitation, a serious TEAE
  - One patient (with a history of 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 (27.0) | 4 (36.0) |
| Acute tonsillitis | — | 2 (18.0) |
| Catheter site infection | 3 (27.0) | — |
| Cough | 4 (36.0) | 4 (36.0) |
| Dermatitis diaper | 2 (18.0) | — |
| Diarrhea | 3 (27.0) | 4 (36.0) |
| Dyspepsia | 2 (18.0) | — |
| Headache | 3 (27.0) | — |
| Hypertension | 3 (27.0) | — |
| Lymphadenopathy | — | 2 (18.0) |
| Muscle spasms | — | 3 (27.0) |
| Nasopharyngitis | 2 (18.0) | 4 (36.0) |
| Neck pain | — | 2 (18.0) |
| Oropharyngeal pain | — | 3 (27.0) |
| Pleural effusion | 2 (18.0) | — |
| Pyrexia | 6 (55.0) | 5 (46.0) |
| Rash | 2 (18.0) | — |
| Upper respiratory tract infection | 4 (36.0) | 3 (27.0) |
| Urinary tract infection | 3 (27.0) | — |
| Vomiting | 3 (27.0) | 3 (27.0) |
| Patients with any serious TEAE, n (%) | **9 (82.0)** | **4 (36.0)** |
| Severity, n (%) | | |
| Mild | TBD | TBD |
| Moderate | TBD | TBD |
| Severe | TBD | TBD |
| Relationship to eculizumab treatment, n (%) | | |
| Unrelated | 6 (55.0) | 4 (36.0) |
| Possible | 3 (27.0) | 0 |
| SAEs occurring in 2 or more patients, n (%) | | |
| Fever | 2 (18.0) | 0 |
| Gastroenteritis viral | 1 (9.0) | 1 (9.0) |
| Upper respiratory tract infection | 2 (18.0) | 0 |
| Hypertension | 2 (18.0) | 0 |

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

## CONCLUSIONS

- In this post hoc subanalysis, designed to characterize the safety and efficacy of eculizumab in aHUS pediatric patients with and without a history of dialysis at baseline, treatment with eculizumab resulted in clinically meaningful improvements in hematologic and renal parameters in both groups
- Further analysis of hematologic and renal parameters showed that, in general, outcomes were similar between patients with and without a history of dialysis, and that statistically significant efficacy could be achieved regardless of dialysis history
  - Notably, 4 of 11 patients with a history of dialysis presented with severe genetic mutations at baseline (CFH or C3), while 3 of 11 patients without a history of dialysis presented with a less severe mutation (MCP)
  - These baseline characteristics could account for the apparent differences in the actual and final eGFR gains observed between subgroups
- These data are consistent with what has been previously reported in a subanalysis of patients with clinical evidence of progressing TMA who did and did not have a history of dialysis at the time of eculizumab initiation[8]
  - In both subanalyses, eculizumab improved hematologic and renal outcomes irrespective of baseline dialysis status
  - Importantly, in both subanalyses, a similar proportion of patients on dialysis at baseline were able to discontinue dialysis by data cutoff
- In addition, patients with no history of dialysis at baseline did not require new dialysis during eculizumab treatment, which is consistent with previously reported data from a retrospective eculizumab trial in 19 pediatric patients (aged 2 months to 17 years)[7]
- There were no meningococcal infections or new safety concerns reported
- Together, these data provide additional support that eculizumab is a proven, effective, and safe treatment in all pediatric patients with aHUS, regardless of dialysis history

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## ACKNOWLEDGMENTS


The authors would like to acknowledge Kenyon Ogburn of Alexion Pharmaceuticals, Inc., and Peloton Advantage, LLC, for providing editorial support with funding from Alexion Pharmaceuticals, Inc.

**Disclosures:** [To come upon finalization].