# Eculizumab Inhibits Thrombotic Microangiopathy and Improves Renal Function in Pediatric Patients With Atypical Hemolytic Uremic Syndrome

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#### INTRODUCTION

- Atypical hemolytic uremic syndrome (aHUS) is a genetic, life-threatening, progressive disease resulting from chronic, uncontrolled complement activation. It is characterized by systemic thrombotic microangiopathy (TMA) leading to renal damage and, frequently, damage to other end organs.
- The efficacy and safety of eculizumab has been proven in 2 prospective Phase 2 trials in patients with evidence of progressing TMA and those with long disease duration and chronic kidney disease.1
- Plasma exchange and infusion (PE/PI) has been used historically to manage aHUS<sup>2</sup>; however, evidence shows that PE/PI affords limited clinical benefit.<sup>2</sup>
- Within 1 year of aHUS diagnosis, up to 65% of patients managed with PE/PI sustain permanent renal damage, progress to end-stage renal disease (ESRD), or die.3

#### STUDY RATIONALE

- Eculizumab (Soliris®; Alexion Pharmaceuticals, Inc., Cheshire, CT), 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-9.1 It is the first and only approved treatment for aHUS in pediatric and adult patients.4
- Multiple published cases have reported the efficacy of eculizumab in treating pediatric patients with aHUS,5-9 yet, to date, no prospective trial of alternate treatment options has ever been conducted in children with aHUS.
- In addition, a previous retrospective study demonstrated the efficacy of eculizumab in a pediatric population with aHUS in a clinical practice setting.7
- Eculizumab has, therefore, been recommended as first-line therapy in children with aHUS.9
- Herein, we report safety and efficacy results at 26 weeks from the first prospective trial of pediatric patients with aHUS.

#### METHODS

#### Study Design

Primary outcome

- Open-label, single-arm, multicenter, multinational, interventional clinical trial.
- Proportion of patients who achieved complete TMA response during 26 weeks, defined as:
- Platelet count normalization (≥150 x 10<sup>9</sup>/L).
- Normalization of lactate dehydrogenase (LDH; < upper limit of the normal range [ULN]).</li>
- ≥25% improvement in serum creatinine (SCr) from baseline. All 3 parameters had to be met on 2 consecutive measurements obtained ≥4 weeks apart.
- Secondary outcomes included:
- Hematologic normalization (platelet count normalization [≥150 x 10<sup>9</sup>/L] and LDH normalization [LDH < ULN]) sustained</li>
- for  $\geq 2$  consecutive measurements obtained  $\geq 4$  weeks apart.
- TMA event-free status: No decrease in platelet count >25% from baseline, no PE/PI, and no new dialysis.
- Hemoglobin increase of ≥20 g/L from baseline sustained for ≥2 consecutive measurements obtained ≥4 weeks apart.
- ≥25% decrease in SCr from baseline (sustained for ≥2 consecutive measurements obtained ≥4 weeks apart). Change from baseline in estimated glomerular filtration rate (eGFR).
- eGFR improvement ≥15 mL/min/1.73 m² from baseline sustained for ≥2 consecutive measurements obtained ≥4 weeks apart.
- Change in health-related quality of life (as measured by Pediatric FACIT-F).
- Pharmacokinetic/pharmacodynamic (PK/PD) measures.

#### **Inclusion Criteria**

- Pediatric patients with aHUS aged 1 month to <18 years with a body weight ≥5 kg.</li>
- Platelet count at screening and baseline visit <150 x 10<sup>9</sup>/L. Exhibited signs or symptoms of hemolysis at start of current aHUS episode:
- LDH ≥1.5 x ULN.
- Hemoglobin ≤ lower limit of normal range (LLN).
- Fragmented RBC with a negative Coombs test.
- 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 unavailability of a vaccine for under 2 years, patients in this age group were
- to receive antibiotic prophylaxis throughout the treatment period.

#### **Exclusion Criteria**

- Chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy for ESRD)
- Shiga toxin-producing Escherichia coli (STEC-HUS) infection.
- Genetic or acquired severe ADAMTS-13 deficiency (ADAMTS-13 activity <5% [as measured during the screening period of the trial]).
- PE/PI for >5 weeks prior to enrollment.
- Prior eculizumab use or hypersensitivity to eculizumab, to murine proteins, or to 1 of the excipients

- 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

Induction	Maintenance
900 mg weekly x 4	1200 mg week 5; 1200 mg q2 weeks
600 mg weekly x 2	900 mg week 3; 900 mg q2 weeks
600 mg weekly x 2	600 mg week 3; 600 mg q2 weeks
600 mg weekly x 1	300 mg week 2; 300 mg q2 weeks
300 mg weekly x 1	300 mg week 2; 300 mg q3 weeks
	900 mg weekly x 4 600 mg weekly x 2 600 mg weekly x 2 600 mg weekly x 1

#### Statistical Analysis

- The primary efficacy endpoint was the proportion of patients with a complete TMA response during the first 26 weeks of the study period in the intent-to-treat (ITT) population.
- The ITT population was defined as all patients who signed an informed consent and received ≥1 dose of eculizumab. • Proportion of patients with eGFR change from baseline ≥15 mL/min/1.73 m<sup>2</sup> was calculated similarly to primary endpoint (as per the statistical analysis plan). While the patient was on dialysis, the eGFR value was set at 10 mL/min/1.73 m<sup>2</sup>.
- All statistical tests were assessed at the 2-sided  $\alpha = 5\%$  level without adjusting for multiplicity. The primary analysis was assessed at the 1-sided  $\alpha = 5\%$  level.
- For the composite endpoints, if the post-baseline or baseline data for any component were missing, then the patient was treated as censored at the last follow-up day. Patients who did not have valid baseline values or any valid post-baseline values were also treated as a failure for endpoints.
- The eGFR was calculated using the Schwartz formula: eGFR (mL/min/1.73 m²) = [0.413 x height (cm)] / SCr (mg/dL)].

#### RESULTS

#### **Patient Disposition**

• Twenty-two pediatric patients were treated with eculizumab and 19 patients (86%) completed the 26-week study period

#### **Table 2. Trial C10-003: Patient Disposition**

Category	Intent-to-Treat Population (N=22)
Enrolled	27
Not treated, n (%) Positive test for Shiga toxin Platelet count normalized Final diagnosis not aHUS Unspecified reasons	5 (19) 1 1 2 1
Treated	22
Discontinued eculizumab treatment before completing 26-week study period, n (%)	3 (14)
Completed 26-week study period, n (%)	19 (86)
Reason for withdrawal, n (%)  Confirmed diagnosis of STEC-HUS  Serious adverse event (agitation)  Family request to withdraw patient	1 (5) 1 (5) 1 (5)

aHUS, atypical hemolytic uremic syndrome; STEC-HUS, Shiga toxin-producing *E. coli* infection.

#### Patient Demographics and Baseline Laboratory Values (Table 3)

- The median duration from the onset of the clinical manifestation to screening was 6 days.
- A total of 12 patients (55%) had no PE/PI prior to eculizumab initiation.
- Twenty patients (91%) had eGFR <90 mL/min/1.73 m<sup>2</sup>.

Eleven patients (50%) were on dialysis at baseline.

#### Table 3. Trial C10-003: Demographics and Baseline Laboratory Values

egory ————————————————————————————————————	(N=22)
at first infusion (years) – median (range)	6.5 (0.0–17.0)
e, n (%) I month to <23 months ≥23 months to <5 years ≥5 to <12 years ≥12 to <18 years	5 (22.7) 5 (22.7) 8 (36.4) 4 (18.2)
nale gender, n (%)	10 (45)
ce, n (%) Asian Black or African American Caucasian Other	2 (9) 0 (0) 18 (82) 2 (9)
ient-reported family history of aHUS, n (%)	6 (27)
Intified genetic mutations, n (%) Anti-Complement Factor Antibody: Factor H autoantibody positive Anti-Complement Factor Antibody: Factor H autoantibody positive, CFHR1, CFHR3 Complement Protein 3 (C3) Gain-of-Function Mutation Factor H Factor I Membrane Cofactor Protein (MCP)	10 (45) 1 (5) 1 (5) 1 (5) 2 (9) 2 (9) 3 (14)
ents with CFHR1/3 polymorphism, n (%)	1 (5)
dentified mutation, n (%)	11 (50)
dian duration (range) from aHUS diagnosis until screening (months)	0.6 (0.03–191)
dian duration (range) from current manifestation to first dose (months)	0.20 (0.03–4.3)
t clinical TMA manifestation, n (%)	16 (72.7)
PE/PI during current manifestation, n (%)	12 (55)
ysis at baseline, n (%)*	11 (50)
r renal transplant, n (%)	2 (9)
elet count (x 10 <sup>9</sup> /L) – mean (SD)	87.5 (42.3)
ents with platelet count <150 x 10 <sup>9</sup> /L, n (%)	22 (100)
I (U/L) – mean (SD)	1943.7 (1824.4)
I > ULN	19 (86.4)
noglobin concentration (g/L) – mean (SD)	80.2 (15.3)
um creatinine (umol/L) – mean (SD)	154.5 (116.43)
R (mL/min/1.73 m²) – mean (SD)	32.7 (30.37)
FR (mL/min/1.73 m²), n (%) <15 5–29 80–44 85–59 80–89 £90	10 (45.5) 4 (18.2) 2 (9.1) 2 (9.1) 2 (9.1) 2 (9.1)
JS, atypical hemolytic uremic syndrome; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrog standard deviation; TMA, thrombotic microangiopathy; ULN, upper limit of normal.	genase; PE/PI, plasma exchange/plasma infusion;

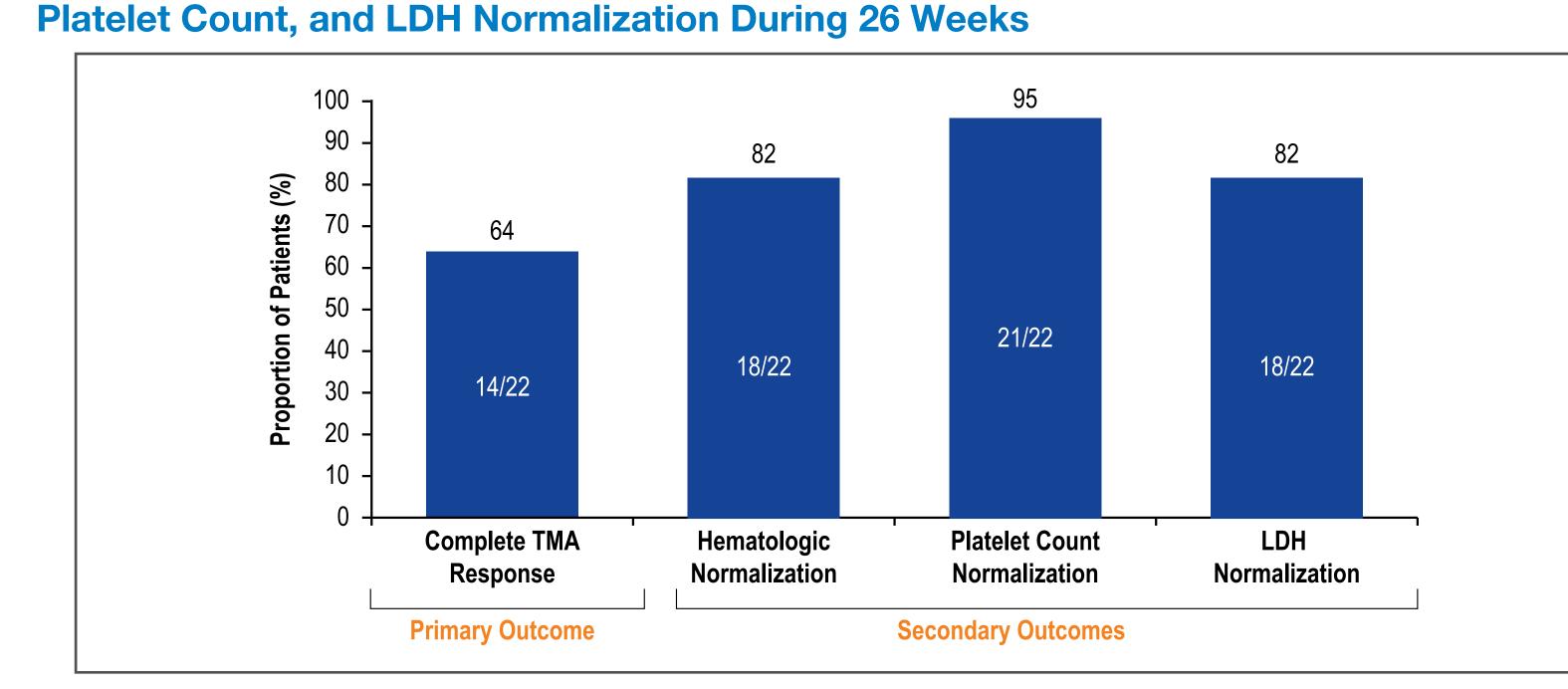
\*One patient who was on dialysis at baseline discontinued dialysis during the baseline window prior to the first dose of eculizumab.

#### Efficacy Outcomes

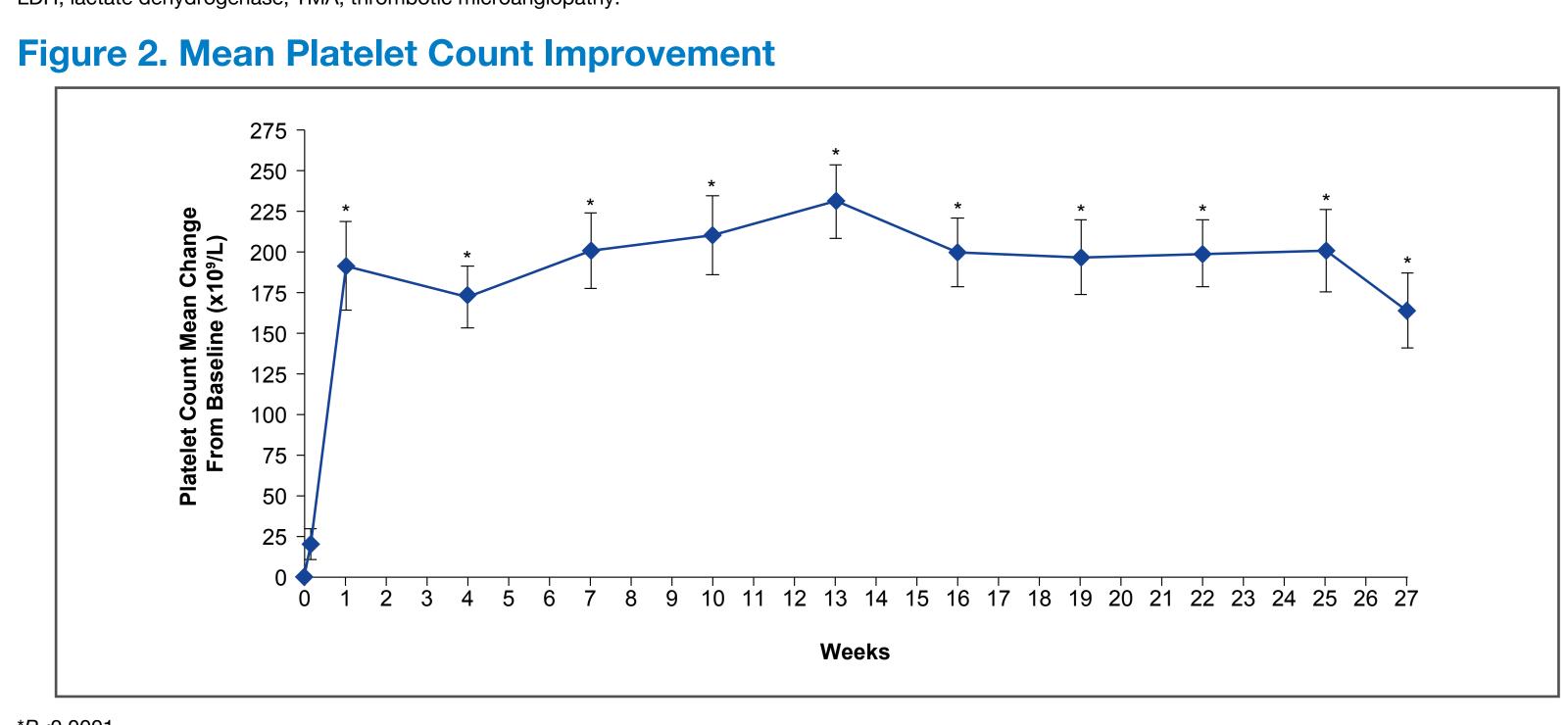
#### Primary Outcome: Complete TMA Response Through 26 Weeks

- Complete TMA response was achieved in 14 of 22 patients (64%; 95% CI: 41–83) from baseline to 26 weeks (Figure 1). - Median (range) time to complete TMA response was 60.0 (7.0-153.0) days. **Hematologic Outcomes Over 26 Weeks**
- Twenty-one of 22 patients (95%; 95% CI: 77–99.9) achieved TMA event-free status during 26 weeks.
- Hematologic normalization was observed in 18 of 22 patients (82%; 95% CI: 60–95) (Figure 1) after 26 weeks. • Twenty-one of 22 patients (95%; 95% CI: 77–99.9) achieved platelet count normalization from baseline (Figure 1).
- Median (range) time to platelet count normalization was 7.0 (1.0-80.0) days.
- Eighteen of 22 patients (82%; 95% CI: 60–95) achieved LDH normalization from baseline to 26 weeks of eculizumab treatment (Figure 1).
- Fifteen of 22 patients (68%; 95% CI: 45–86) had improvement in hemoglobin concentration of ≥20 g/L from baseline through 26 weeks
- Of 10 patients on PE/PI at baseline, all (100%) discontinued by the end of the 26-week study.

#### Figure 1. Proportion of Patients Achieving Complete TMA Response and Hematologic,



LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy



#### Bars represent standard error of the mean

#### **Renal Outcomes Over 26 Weeks**

- Nineteen patients (86%) had eGFR improvement ≥15 mL/min/1.73 m² from baseline through 26 weeks (Table 4). Mean improvement from baseline in eGFR was 64 mL/min/1.73 m². Decrease in SCr (≥25%) was observed in 16 patients
- (73%) (**Table 4**, **Figure 3**). • Of the 11 patients on dialysis at baseline, 9 discontinued during the 26-week study period (**Table 4**).
- Of the 11 patients not on dialysis at baseline, 11 (100%) remained dialysis-free during 26 weeks.

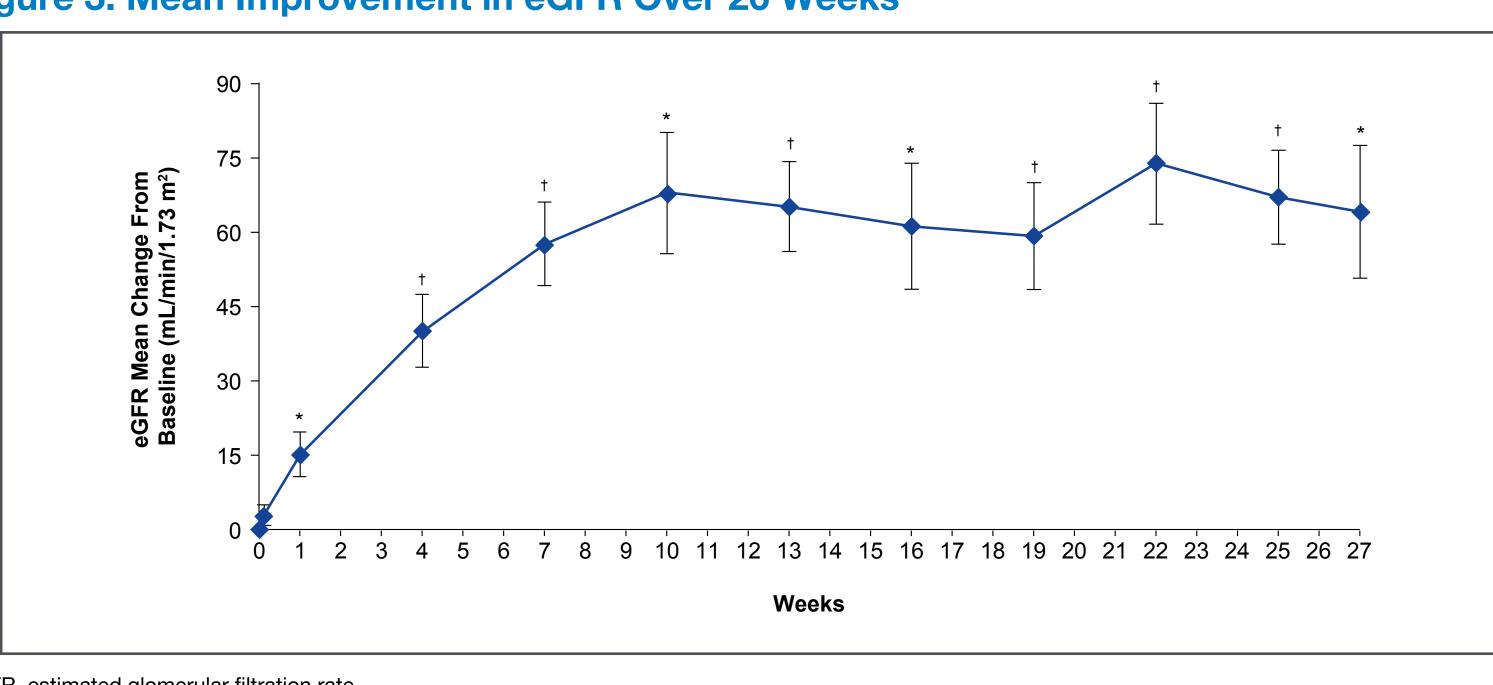
## **Table 4. Summary of Renal Outcomes**

eGFR improvement from baseline ≥15 mL/min/1.73 m², n (%)	19 (86)
Serum creatinine decrease ≥25%, n (%)	16 (73)
CKD improvement ≥1 stage from baseline, n (%)	17 (77)
Patients on dialysis at baseline (n=11) who discontinued during study, n (%)	9/11 (82)
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.	

Intent-to-Treat Population

(N=22)

Figure 3. Mean Improvement in eGFR Over 26 Weeks



eGFR, estimated glomerular filtration rate Bars represent standard error of the mean

#### Improvement in Health-Related Quality of Life

• The Pediatric FACIT-F LS mean change from baseline to data cutoff was 19.7 (range, 15.6–23.7), which was statistically

#### Pharmacokinetics and Pharmacodynamics

- The population PK analysis suggests that the approved eculizumab pediatric dosing regimen in Study C10-003 resulted in concentrations within the target concentration range (50-700 µg/mL) during the induction and maintenance phases for
- Results from the population PK/PD analysis demonstrate that the dosing strategy of eculizumab resulted in complete terminal complement inhibition (as measured by hemolytic activity) in all but 1 patient.

#### 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.
- Twenty of 22 patients enrolled (91%) reported at least 1 treatment-emergent adverse event (TEAE), the majority of which were mild to moderate in severity (**Table 5**).
- None of the infection-related TEAEs were considered severe.
- Thirteen of 22 patients (59%) reported at least 1 serious TEAE (**Table 5**). - One patient discontinued due to agitation, a serious TEAE.
- One patient had a human anti-human antibody response, and continued eculizumab treatment without apparent adverse effect.

#### Table 5. Safety of Eculizumab Treatment and Summary of TEAEs

	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)
Vomiting	6 (27)
Nasopharyngitis	6 (27)
Patients with any serious TEAE, n (%)	13 (59)
Severity, n (%)	
Mild	3 (14)
Moderate	7 (32)
Severe	3 (14)
Relationship to eculizumab treatment, n (%)	
Unrelated	10 (45)
Possible	3 (14)
SAEs occurring in 2 or more patients, n (%)	
Fever	2 (9)
Gastroenteritis viral	2 (9)
Upper respiratory tract infection	2 (9)
Hypertension	2 (9)

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

#### CONCLUSIONS

- In this, the first-ever prospective trial of pediatric patients with aHUS, the use of eculizumab led to rapid and sustained improvement in platelet counts and significant and continuous improvement over time in eGFR.
- Most patients (73%) were newly diagnosed.
- The median time from current manifestation to first dose of eculizumab was 6 days. • Twelve of the 22 patients (55%) received no PE/PI prior to treatment with eculizumab.
- Complete TMA response the primary endpoint was achieved in 14 of 22 patients (64%) after 26 weeks.
- A total of 21 patients (95%) achieved platelet count normalization from baseline to 26 weeks. • Nineteen patients (86%) had eGFR improvement ≥15 mL/min/1.73 m² after 26 weeks; 64 mL/min/1.73 m² mean
- improvement in eGFR from baseline.

Eculizumab treatment facilitated discontinuation of dialysis and PE/PI.

- Of the 10 patients receiving PE/PI at baseline, all discontinued.
- Nine of 11 patients on dialysis at baseline were able to discontinue by 26 weeks.
- Of the 11 patients not on dialysis at baseline, 11 (100%) remained dialysis-free through 26 weeks. There were no meningococcal infections reported, and no new safety concerns arose during the 26-week study period • The safety and efficacy demonstrated in the trial confirm the results observed in the C09-001 pediatric retrospective
- study, 10 as well as the published Phase 2 prospective trials. 1,7 • These results also support the recommendation that eculizumab be used as first-line treatment in pediatric patients
- with aHUS.9
- The trial is ongoing.

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