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Safety and efficacy of eculizumab in the prevention of antibody-mediated rejection in living-donor kidney transplant recipients requiring desensitization therapy: A randomized trial

William H. Marks[1,2] | Nizam Mamode[3] | Robert A. Montgomery[4] | Mark D. Stegall[5] |
Lloyd E. Ratner[6] | Lynn D. Cornell[7] | Ajda T. Rowshani[8] | Robert B. Colvin[9] |
Bradley Dain[1,10] | Judith A. Boice[1] | Denis Glotz[11,12] | C10-001 Study Group[*]

[1]Formerly Alexion Pharmaceuticals, Boston, Massachusetts

[2]Independent Consultant, Bellevue, Washington

[3]Department of Transplant Surgery, Guy's and St Thomas', Evelina London Children's and Great Ormond Street Hospitals NHS Trust, London, UK

[4]NYU Langone Transplant Institute, New York University Langone Medical Center, New York, New York

[5]The William J. von Liebig Center for Transplantation and Clinical Regeneration and Division of Transplantation Surgery, Department of Surgery, Mayo Clinic, Rochester, Minnesota

[6]Department of Surgery, Columbia University, New York, New York

[7]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota

[8]Department of Internal Medicine, Section of Nephrology and Transplantation, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

[9]Department of Pathology, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts

[10]Independent statistics consultant, Guilford, Connecticut

[11]Paris Translational Research Center for Organ Transplantation, Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche-S970, Paris, France

[12]Department of Nephrology and Organ Transplantation, Saint-Louis Hospital, Assistance Publique-Hôpitaux de Paris, Institut National de la Santé et de la Recherche Médicale, Unité U1160, Paris, France

Correspondence
Denis Glotz
Email: denis.glotz@aphp.fr

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We report results of a phase 2, randomized, multicenter, open-label, two-arm study evaluating the safety and efficacy of eculizumab in preventing acute antibody-mediated rejection (AMR) in sensitized recipients of living-donor kidney transplants requiring pretransplant desensitization (NCT01399593). In total, 102 patients underwent desensitization. Posttransplant, 51 patients received standard of care (SOC) and 51 received eculizumab. The primary end point was week 9 posttransplant treatment failure rate, a composite of: biopsy-proven acute AMR (Banff 2007 grade II or III; assessed by blinded central pathology); graft loss; death; or loss to follow-up.

Eculizumab was well tolerated with no new safety concerns. No significant difference in treatment failure rate was observed between eculizumab (9.8%) and SOC (13.7%; P = .760). To determine whether data assessment assumptions affected study outcome, biopsies were reanalyzed by central pathologists using clinical information. The resulting treatment failure rates were 11.8% and 21.6% for the eculizumab and SOC groups, respectively (nominal P = .288). When reassessment included grade I AMR, the treatment failure rates were 11.8% (eculizumab) and 29.4% (SOC; nominal P = .048). This finding suggests a potential benefit for eculizumab compared with SOC in preventing acute AMR in recipients sensitized to their living-donor kidney transplants (EudraCT 2010-019630-28).

1 | INTRODUCTION

Transplant candidates with a potential living donor may be unable to benefit from transplantation if they are sensitized to their donor.[1,2] Due to sensitization, approximately 4000 patients in the United States who have a potential living donor are waiting for a kidney transplant from a deceased donor.[3] Although recent advances in desensitization and donor pairing allow more sensitized individuals than in the past to receive transplants, there remains a need for new strategies to facilitate transplantation in many sensitized patients. Sensitization arises from previous exposure to allogenic human leukocyte antigens (HLAs) due to previous transplantation, blood transfusion, or pregnancies. The presence of donor-specific antibodies (DSAs) in kidney transplant recipients is a risk factor for, and correlates strongly with, posttransplant antibody-mediated rejection (AMR).[4-7] Early acute AMR, which usually occurs within the first 9 weeks, is triggered when recipient DSAs bind to donor HLAs on the allograft's vascular endothelium, activating the classical complement pathway,[8,9] leading to graft endothelial injury.[10] The prevalence of early acute AMR in kidney transplant recipients with preformed DSAs has been reported to be as high as 60%, and it is associated with poor clinical outcomes, including graft loss or decreased graft survival.[4,7,11-16]

A variety of desensitization protocols have been developed to facilitate HLA-incompatible transplantation.[17-19] Despite inconsistent results, plasmapheresis (PP) and intravenous immunoglobulin (IVIg) have become the standard of care (SOC) for desensitization.[20-24] Antibody-mediated rejection remains a significant problem, however, and preventing AMR could improve both access to transplantation and outcomes.[25]

Eculizumab is a humanized monoclonal antibody that blocks cleavage of the human complement component C5 and thereby prevents terminal complement activation. In a single-center pilot study, eculizumab lowered the incidence of acute AMR in highly sensitized recipients of living-donor kidney transplants compared with a historic control group (AMR incidences of 7.7% and 41.2%, respectively).[26] The primary objective of this study was to evaluate the safety and efficacy of eculizumab in preventing acute AMR in kidney transplant recipients who required desensitization.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a phase 2, randomized, multicenter, open-label, two-arm, parallel-group study and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice. The study protocol was approved by the appropriate oversight committee for each study site (Table S1). Participants provided written informed consent before study entry. The study (clinicaltrials.gov identifier NCT01399593; EudraCT number 2010-019630-28) was sponsored by Alexion Pharmaceuticals.

Eligible patients (section 2.3) underwent pretransplant desensitization according to their transplant center's standard protocol (PP and IVIg [93.1%] or PP alone [6.9%]). All patients received immunosuppression, prophylactic medications, and posttransplant care based on SOC at each site (Figure 1). After desensitization and approval for transplantation, participants were randomized in a one-to-one ratio to receive either eculizumab (Soliris, Alexion Pharmaceuticals, Inc., Boston, MA; eculizumab group), or standard posttransplant care only (SOC group), which could have included any combination of PP and/or IVIg, for 9 weeks from the day of transplantation (Figure 1). Randomization, via a web-based randomization system, was conducted by Sharp Clinical Services (Phoenixville, PA). Randomization was stratified by the pretransplant desensitization protocol used but not by site.

Patients in the eculizumab group received one dose of eculizumab (1200 mg) approximately 1 hour before reperfusion of the

FIGURE 1 Study design. AMR, antibody-mediated rejection; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; PP, plasmapheresis; SOC, standard of care; TAC, tacrolimus

allograft (day 0) and then for 9 weeks posttransplant according to the dosing regimen described in Figure 1. For-cause allograft biopsies were performed if there were clinical signs of allograft dysfunction with or without elevation of DSA based upon at least one of the following criteria, from baseline (day of transplantation): a decrease in serum creatinine (SCr) of less than 10% per day on 3 consecutive days in the first week posttransplant; an increase in SCr; proteinuria; oliguria; or clinical suspicion of AMR. Protocol-mandated biopsies were to be performed postreperfusion (intraoperative), at day 14 posttransplant, and at months 3, 12, and 36 posttransplant.

2.2 | Pathology analyses and patient management

All biopsies were processed and analyzed by each transplant center's pathology laboratory (referred to as local pathology). Local pathologists had access to clinical information and were involved in patient management decisions including the diagnosis and treatment of acute AMR. To reduce variability in evaluations between multiple pathologists, a panel of three independent pathologists (two primary pathologists and one adjudicator for cases on which the primary pathologists disagreed) conducted a review of all biopsies blinded to treatment, local pathology diagnoses, clinical information, DSA status, and C4d status by immunofluorescence, for study end point evaluation only, using a standardized process established before study initiation (central pathology analyses). The central pathologists scored whole images of light microscopic slides from local pathology and performed immunohistochemistry to determine C4d status.

Patients from both groups diagnosed with acute AMR were initially treated with PP and/or IVIg. Patients could subsequently be treated with eculizumab for up to 9 weeks (minimum of 5 weeks), at the discretion of the principal investigator. Patients in the eculizumab group who were treated with PP received supplemental eculizumab (600 mg) within 1 hour to maintain therapeutic eculizumab levels.[27]

2.3 | Study population

Patients were recruited from 41 sites in 10 countries in Europe, North America, and Australia.

Patients aged 18 years or older were eligible for inclusion if they had stage IV or V chronic kidney disease and were to receive a kidney transplant from a living donor to whom they were sensitized, and therefore required pretransplant desensitization. The presence of DSAs was determined by single-antigen bead assay (Luminex LABScreen, One Lambda, CA) performed by the central laboratory. In addition to a history of previous exposure to HLAs and the presence of DSAs, eligible patients had to have either a positive complement-dependent cytotoxicity (CDC) crossmatch (current or historic), or a negative CDC with a positive B-cell flow crossmatch (BFXM) and/or T-cell flow crossmatch (TFXM; according to local thresholds) before desensitization.

Women of childbearing potential were required to have a negative pregnancy test and use effective contraception for 5 months after their last dose of eculizumab. All participants who were not vaccinated against *Neisseria meningitidis* on study entry received the vaccination at least 14 days before their first dose of eculizumab and a booster 30 days after their first vaccination. Patients who had been vaccinated against *N. meningitidis* before enrollment received a booster. Prophylactic antibiotics could be provided during eculizumab treatment, according to local practice.

2.4 | Primary efficacy end point

The primary end point was the week 9 posttransplant treatment failure rate, which was a composite of the occurrence of: biopsy-proven AMR (Banff 2007 grade II or III); graft loss; patient death; or loss to follow-up (including discontinuation).

Diagnosis of acute AMR for the primary end point was based on review of for-cause kidney biopsies performed by the central pathologists according to Banff 2007 criteria, which included the requirement for C4d+ staining for diagnosis of acute AMR.[23,28] Grade I AMR was not included because it is impossible to distinguish it from acute tubular injury with incidental C4d deposition using only pathological criteria. Because only grades II and III, acute AMR were included in the primary end point, this was defined as the presence of circulating DSAs and morphologic evidence of acute tissue injury as determined by the central pathologists.

2.5 | Sensitivity and post hoc analyses

A prespecified sensitivity analysis of local pathologists' biopsy results was performed and compared with the primary analysis of central pathologists' results. To explore possible reasons for the discordance observed between central and local pathology results, additional analyses were performed. As grade I AMR was not included in the primary analysis, a post hoc sensitivity analysis of local and central pathology results including grade I acute AMR was conducted, recognizing that grade I acute AMR is also a pattern of early acute AMR.

A reassessment of biopsies by the central pathologists was also performed for all grades of AMR in which they remained blinded to treatment but were provided with relevant clinical information for each patient to more closely simulate real clinical practice.

In addition, post hoc analyses were performed to assess agreement between the original central pathology biopsy results and the

local pathology results, and the reassessed central results and the local results, including grade I AMR, using a kappa measure of agreement.

2.6 | Safety end points

Safety was assessed throughout the study and is reported for until each patient's final study visit. Safety assessments included monitoring of all treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).

2.7 | Statistical methods

All patients who received a living-donor kidney transplant and their randomized treatment were included in the efficacy and safety analyses.

The expected background rate of treatment failure for the SOC arm was estimated to be 36.3%, based on a pooled analysis of published AMR incidence, although it is recognized that the definition of sensitized patients varies between centers.[21,29-32] The expected treatment failure rate at week 9 posttransplant (primary end point) in the eculizumab group was estimated from the pilot study of highly sensitized patients (with baseline BFXM mean channel shift [mcs] of over 320) to be 10%.[26] These estimates were used to determine sample size and power. This study was powered at over 90% based on these expected failure rates. The observed difference in the treatment failure rates at week 9 posttransplant between the eculizumab and the SOC groups was calculated with a 95% confidence interval (CI) using an exact unconditional method.[33] The null hypothesis was tested using
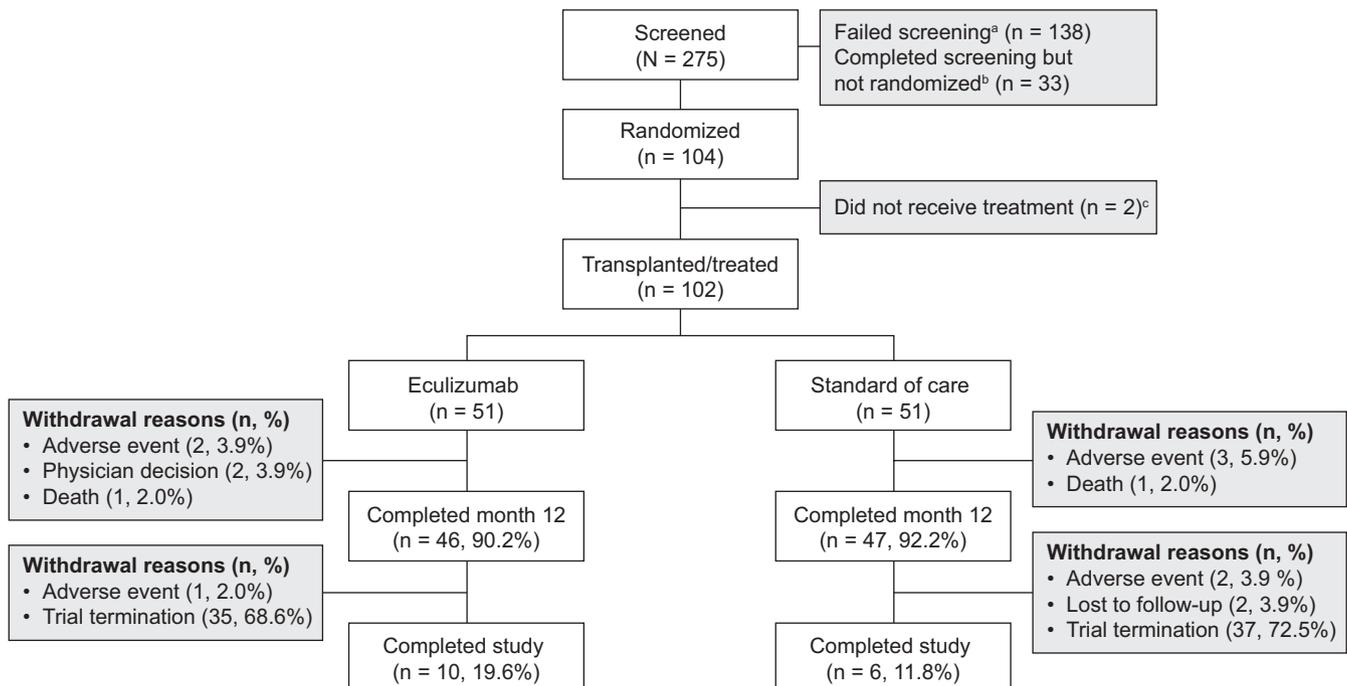
FIGURE 2 Patient disposition. [a]Failed screening (n, %): did not meet inclusion/exclusion criteria (62, 22.5%), physician decision (n = 13, 4.7%), adverse event (3, 1.1%), withdrawal by patient (3, 1.1%), death (1, 0.4%), other (56, 20.4%). [b]Screened but not randomized (n, %): failed desensitization (18, 6.5%), adverse event (4, 1.5%), enrollment failure (3, 1.2%), failed inclusion/exclusion criteria (1, 0.4%), withdrawal by patient (1, 0.4%), other (6, 2.2%). [c]Did not receive treatment (n, %): donor changed mind (1, 0.4%), issues with donor kidney (1, 0.4%)

Fisher's exact test,[34] with a two-sided *P* value of .05 or below indicating statistical significance.

3 | RESULTS

3.1 | Patient disposition and characteristics

The first patient was screened on November 2, 2011. The study was terminated early (November 13, 2015) because of failure to meet the primary efficacy end point. The date of last patient contact was February 11, 2016.

In total, 275 patients were screened for study inclusion, of whom 104 (37.8%) were randomized (Figure 2). Of these, 102 (98.1%) received a transplant from a living donor and their randomized therapy (eculizumab or SOC alone) and were analyzed. Randomized and treated patients were equally distributed between the eculizumab group (n = 51) and the SOC group (n = 51) (Figure 1).

Descriptive recipient characteristics are in Tables 1 and 2. Baseline demographics were generally similar between the two treatment groups, although there were more women in the eculizumab group (72.5%) than in the SOC group (58.8%). Patients in the eculizumab group had a slightly shorter median (range) duration of pretransplant chronic renal failure (89.0 [3-385] months) compared with the SOC group (139.0 [7-593] months). More patients in the eculizumab group (36/51; 70.6%) than in the SOC group (28/51; 54.9%) had a positive CDC crossmatch during screening. According to central laboratory results, 94.1% of all patients were positive for class I or class II DSA before transplantation. The study population's median (range) DSA was 12 737.5 (932-85 358) mean fluorescence intensity (Table 3).

All patients in the eculizumab group received at least one dose of eculizumab. By week 9, all except two of these patients had received at least nine infusions. Complete inhibition of terminal complement was achieved at all visits in ≥95% of patients. Subsequently, six patients (11.2%) in the eculizumab group received additional doses of

TABLE 1 Baseline characteristics

Characteristic, unit Statistic or category	Eculizumab (N = 51)	SOC (N = 51)	Total (N = 102)
Age, y			
Mean (SD)	45.0 (14.48)	40.9 (13.24)	43.0 (13.96)
Median (min-max)	45.0 (18-75)	37.0 (19-79)	42.5 (18-79)
Age group, n (%)			
<65 y	47 (92.2)	49 (96.1)	96 (94.1)
≥65 y	4 (7.8)	2 (3.9)	6 (5.9)
Sex, n (%)			
Male	14 (27.5)	21 (41.2)	35 (34.3)
Female	37 (72.5)	30 (58.8)	67 (65.7)
Race[a], n (%)			
White	37 (72.5)	36 (70.6)	73 (71.6)
Black or African-American	6 (11.8)	6 (11.8)	12 (11.8)
Asian	2 (3.9)	3 (5.9)	5 (4.9)
Duration of chronic renal failure before transplantation, mo[b]			
Mean (SD)	124.6 (99.1)	171.0 (130.6)	147.8 (117.7)
Median (min-max)	89.0 (3-385)	139.0 (7-593)	131.9 (3-593)
Patient on dialysis at the time of transplantation? n (%)			
Yes	46 (90.2)	46 (90.2)	92 (90.2)
No	5 (9.8)	5 (9.8)	10 (9.8)
Duration of dialysis before transplantation, mo[c]			
n	46	46	92
Mean (SD)	95.9 (100.38)	128.0 (112.74)	112.0 (107.37)
Median (min-max)	40.3 (2-361)	77.0 (5-377)	58.1 (2-377)

Max, maximum; min, minimum; SD, standard deviation; SOC, standard of care.
[a]Collection of race data is not permitted in some European countries.
[b]Duration (mo) = ([date of transplantation or date of first dose of treatment]-[date of chronic renal failure])/30.4.
[c]Duration (mo) = ([date of transplantation or date of first dose of treatment]-[date of first dialysis])/30.4.

TABLE 2 Previous kidney transplantation information

Parameter, unit Statistic or category	Eculizumab (N = 51)	SOC (N = 51)	Total (N = 102)
Patients who had a previous kidney transplant, n (%)	24 (47.1)	35 (68.6)	59 (57.8)
Number of previous kidney transplants, n (%)			
1	17 (33.3)	23 (45.1)	40 (39.2)
2	6 (11.8)	8 (15.7)	14 (13.7)
>3	1 (2.0)	4 (7.8)	5 (4.9)
Type of previous transplant, n (%)			
Live donor	10 (19.6)	15 (29.4)	25 (24.5)
Deceased donor	14 (27.5)	20 (39.2)	34 (33.3)

SOC, standard of care.

eculizumab for the treatment of AMR that was diagnosed after the first 9 weeks.

Twenty-two patients (43.1%) in the SOC group received at least one dose of eculizumab for treatment of AMR during the study, including 14 (27.5%) who developed AMR and received eculizumab for its treatment during the initial 9 weeks of the study, at the investigator's discretion. One additional patient in the SOC group developed acute AMR during the first 9 weeks posttransplant but was never treated with eculizumab.

Most patients completed the month-12 visit: 46 (90.2%) and 47 (92.2%) in the eculizumab and SOC groups, respectively. At the time of study termination, 87 patients had completed the month-18 visit. Mean duration (± standard deviation [SD]) of participation in the study was 28.6 (±9.58) and 26.9 (±8.77) months for the eculizumab and SOC groups, respectively.

3.2 | Treatment outcomes

Treatment failure (composite primary end point) was observed in five patients (9.8%) in the eculizumab group and seven patients (13.7%) in the SOC group in the first 9 weeks posttransplant (Table 4). Acute AMR (grade II or III) occurred in five patients in the eculizumab group at a mean of 19.4 (SD 11.33) days posttransplant and in five patients in the SOC group at a mean of 16.6 (SD 12.99) days posttransplant. Treatment failure rates were not significantly different between the two groups (P = .760; difference −3.9%; 95% CI −23.9, 16.3). At month 12, there was no significant difference in treatment failure rates between the eculizumab group (10/51 patients, 19.6%) and the SOC group (9/51 patients, 17.6%) (P = .800; difference–2.0%; 95% CI −18.2, 22.0).

Over 90% of protocol-mandated biopsies showed no transplant glomerulopathy (chronic glomerulopathy grade 0) through month 12 (Table S2).

Estimated glomerular filtration rates and creatinine levels at baseline, week 9, and month 12 are presented in Table S3.

Graft losses occurred in both groups, but the small number of these events limits further interpretation. By week 9, there were no graft losses in the eculizumab group and three graft losses in the

SOC group, which were attributed to a technical complication, acute AMR, and graft vascular dysfunction. By month 12, two patients in the eculizumab group had experienced graft loss owing to acute renal failure with unknown cause and recurrent anti-glomerular basement membrane disease. There was one additional case of graft loss in the SOC group by month 12, which was due to acute AMR.

No significant differences in patient or graft survival were observed between treatment groups. Patient survival posttransplant through month 36 was 98.0% (95% CI 86.9-99.7) for both the eculizumab and SOC groups. The proportion of grafts that survived through month 36 was 91.8% (95% CI 79.7-96.9) for the eculizumab group and 78.5% (95% CI 59.3-89.4) for the SOC group (Figures 3 and S1).

3.3 | Sensitivity analyses

3.3.1 | Comparison of local and central pathology results for grades II and III AMR

The treatment failure rate determined by local pathology was quite different from the central pathology results. There was an overall higher incidence of acute AMR (grades II and III) and corresponding treatment failure rate reported by local pathology (eculizumab 13.7%; SOC 29.4%; P = .091) than by central pathology (eculizumab 9.8%; SOC 13.7%; P = .760) (Table S4).

3.3.2 | Comparison of local and central pathology results for grades I, II, and III AMR

To understand whether the differences between the central and local pathology results were primarily due to differences in the interpretation of grades I and II AMR, a post hoc sensitivity analysis of treatment failure rates including grade I AMR was conducted for both central and local pathology results. This analysis also showed discordance between local pathology (eculizumab 19.6%; SOC 41.2%; P = .031) and central pathology (eculizumab 9.8%; SOC 17.6%; P = .389) (Table S4). Of note, most cases of acute AMR in this study were grade I or II as interpreted by the local and central pathologists (Table S5).

TABLE 3 Central laboratory baseline immunology information

Parameter, unit Statistic or category	Eculizumab (N = 51)	SOC (N = 51)	Total (N = 102)
CDC/FXM status, n (%)[a]			
CDC-negative/FXM-negative	12 (23.5)	18 (35.3)	30 (29.4)
CDC-negative/FXM-positive	3 (5.9)	3 (5.9)	6 (5.9)
CDC-positive/FXM-negative	24 (47.1)	15 (29.4)	39 (38.2)
CDC-positive/FXM-positive	12 (23.5)	13 (25.5)	25 (24.5)
Missing CDC/FXM status	0 (0.0)	2 (3.9)	2 (2.0)
B-cell flow crossmatch, mcs			
n	50	48	98
Mean (SD)	196.4 (115.68)	193.4 (107.51)	194.9 (111.18)
Median (min-max)	192.9 (−29-418)	169.6 (1-457)	184.4 (−29-457)
T-cell flow crossmatch, mcs			
n	49	48	97
Mean (SD)	140.7 (107.71)	170.1 (122.76)	155.2 (115.74)
Median (min-max)	125.0 (−16-383)	160.3 (−8-431)	149.8 (−16-431)
DSA overall (class I/II), n (%)			
Positive	49 (96.1)	47 (92.2)	96 (94.1)
Negative	1 (2.0)	2 (3.9)	3 (2.9)
Missing/unknown	1 (2.0)	2 (3.9)	3 (2.9)
DSA class I, n (%)			
Positive	43 (84.3)	39 (76.5)	82 (80.4)
Negative	5 (9.8)	10 (19.6)	15 (14.7)
Missing/unknown	3 (5.9)	2 (3.9)	5 (4.9)
DSA class II, n (%)			
Positive	33 (64.7)	33 (64.7)	66 (64.7)
Negative	16 (31.4)	13 (25.5)	29 (28.4)
Missing/unknown	2 (3.9)	5 (9.8)	7 (6.9)
Total number of DSAs			
n	50	48	98
Mean (SD)	2.7 (1.41)	2.8 (1.51)	2.7 (1.45)
Median (min-max)	3.0 (1-6)	3.0 (1-7)	3.0 (1-7)
Immunodominant DSA (highest single DSA), MFI			
n	50	48	98
Mean (SD)	8135.0 (4048.08)	8740.7 (4289.97)	8431.7 (4157.87)
Median (min-max)	8148.5 (932-16 177)	8985.0 (1218-18 973)	8620.5 (932-18 973)
Total DSA, MFI			
n	50	48	98
Mean (SD)	15 394.7 (14 163.78)	17 469.8 (12 573.44)	16 411.1 (13 380.16)
Median (min-max)	11 921.0 (932-85 358)	15 031.0 (1218-64 254)	12 737.5 (932-85 358)

CDC, complement-dependent cytotoxicity; DSA, donor-specific antibody; FXM, flow crossmatch (B- or T-cell); max, maximum; mcs, mean channel shift; MFI, mean fluorescence intensity; min, minimum; SD, standard deviation; SOC, standard of care.

[a]CDC status was CDC status during screening, not historic CDC status; FXM-positive status was based on either B- or T-cell FXM values >285 mcs.

3.3.3 | Central and local pathology agreement analysis

Given the observed differences between the treatment failure rates reported by the central and local pathologists, an agreement analysis of all pathology results was undertaken retrospectively.

The AMR grades for the initial evaluations by local and central pathology of each of the 241 per-protocol and for-cause biopsies

assessed during the 9-week primary end point period are shown in Table S5. The kappa coefficient measures the level of agreement between the respective laboratories' gradings, accounting for expected agreement by chance. Most biopsies (75.5%) were assessed to be negative for acute AMR by both central and local pathologists. There was, however, generally poor agreement between the central and local pathologists for biopsies scored as grade I, II, or III acute AMR. The kappa score overall was 0.225, which would be considered only

TABLE 4   Primary end point as determined by the central pathologists

	Eculizumab (N = 51) n (%)	SOC (N = 51) n (%)	Difference (exact 95% CI)	P value
Composite primary end point				
Treatment failure rate (including grades II and III AMR)	5 (9.8)	7 (13.7)	−3.9% (−23.9, 16.3)	.760
Composite primary end point components				
Acute AMR (grade II or III)	5 (9.8)	5 (9.8)		
Graft loss	0 (0.0)	3 (5.9)		
Death	1 (2.0)	1 (2.0)		
Loss to follow-up	0 (0.0)	2 (3.9)		

AMR, antibody-mediated rejection; SOC, standard of care.

slight agreement.[35] Discordance in acute AMR diagnoses between the individual central pathologists was also observed (Table S6).

3.3.4 | Reassessment of central pathology analyses

A major difference between local and central pathology analyses was that only local pathologists had access to clinical information related to the biopsies. Because acute AMR is a clinicopathologic diagnosis, experts including pathologists recommended a reassessment of the biopsies by the central pathologists using the relevant clinical information on each patient (Table S7) while remaining blinded to treatment arm.

This reassessment improved agreement between local and central pathologists (Tables 5 and S5) to a kappa score of 0.496 (considered moderate agreement).[35] After reassessment of 109 biopsies, the number categorized as grade II or III AMR increased from 10 to 15. When grade I AMR was included, there were 12 cases before reassessment compared with 19 cases after reassessment, including four additional cases of grade I AMR and four additional cases of grade II/III AMR. Of the 10 patients identified as having AMR by the original central biopsy assessment, nine were also diagnosed during the reassessment. Importantly, 12/15 (80%) and 16/19 (84%) of the patients diagnosed with AMR in the central pathology reassessment had also been diagnosed with AMR excluding and including grade I, respectively, by the local biopsy assessment.

This post hoc reassessment revealed treatment failure rates of 11.8% and 21.6% (P = .288) for the eculizumab and SOC treatment groups, respectively (Table 5). Inclusion of grade I AMR resulted in a larger observed treatment difference between eculizumab and SOC for both central pathology (11.8% and 29.4%, respectively; nominal P = .048) and local pathology (19.6% and 41.2%, respectively; nominal P = .031). Among the 25 patients who were positive for both CDC and BFXM or TFXM (>285 mcs) during screening, nine were diagnosed with AMR of grade I, II, or III according to this reassessment: 16.7% of this subgroup who received eculizumab and 53.8% of this subgroup who received SOC experienced AMR (Table S8).

3.4 | Safety assessments

During the study, all patients experienced at least one TEAE and most patients had at least one SAE (Tables 6 and S9). The incidence
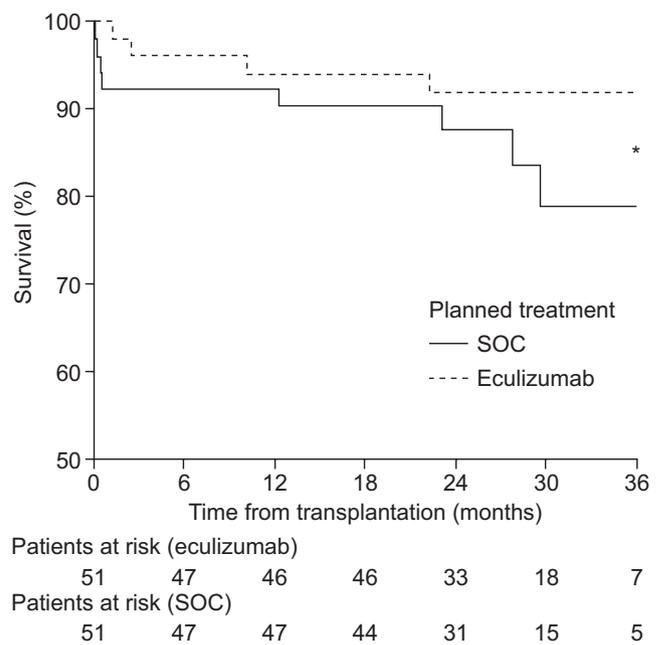
FIGURE 3   Graft survival through 36 months. Graft survival time was defined as the time from transplantation until the date of death or date of graft loss. A patient who did not die or have graft loss was censored at the time of last contact. *P = .209 at 36 months. SOC, standard of care

of SAEs was 94.1% in the SOC group and 84.3% in the eculizumab group.

There were no meningococcal infections during this study. Twelve patients did not complete the study owing to safety-related reasons (adverse events or death). One patient in each group died during the study. In the eculizumab group, a 45-year-old woman died of bacterial sepsis on day 38. She experienced clinically significant infections that were considered by the investigator to be possibly related to eculizumab and were attributed to a bowel perforation following a kidney biopsy and her posttransplant immunosuppressive burden. In the SOC group, a 43-year-old woman who received no eculizumab died on day 5 of cardiac arrest, which was considered by the investigator to be due to preexisting cardiac disease.

By month 12, a total of 12 patients (23.5%) in the SOC group and 11 patients (21.6%) in the eculizumab group had experienced

TABLE 5 Treatment failure rate (reassessed central and local pathology, with and without grade I antibody-mediated rejection included)

AMR	Location	End point	Eculizumab (N = 51) n (%)	SOC (N = 51) n (%)	Difference (exact 95% CI)	P value
Grade II or III acute AMR only	Central[a,b]	Treatment failure	6 (11.8)	11 (21.6)	−9.8% (−29.6, 10.5)	.288
		AMR	6 (11.8)	9 (17.6)		
		Graft loss	1 (2.0)	4 (7.8)		
		Death	1 (2.0)	1 (2.0)		
		Loss to follow-up	0 (0.0)	0 (0.0)		
	Local[c]	Treatment failure	7 (13.7)	15 (29.4)	−15.7% (−35.1, 4.7)	.091
		AMR	7 (13.7)	12 (23.5)		
		Graft loss	1 (2.0)	4 (7.8)		
		Death	1 (2.0)	1 (2.0)		
		Loss to follow-up	0 (0.0)	0 (0.0)		
Grade I, II, or III acute AMR	Central[a,b]	Treatment failure	6 (11.8)	15 (29.4)	−17.7% (−37.0, 2.7)	.048
		AMR	6 (11.8)	13 (25.5)		
		Graft loss	1 (2.0)	4 (7.8)		
		Death	1 (2.0)	1 (2.0)		
		Loss to follow-up	0 (0.0)	0 (0.0)		
	Local[c]	Treatment failure	10 (19.9)	21 (41.2)	−21.6% (−40.6, −1.2)	.031
		AMR	10 (19.6)	18 (35.3)		
		Graft loss	1 (2.0)	4 (7.8)		
		Death	1 (2.0)	1 (2.0)		
		Loss to follow-up	0 (0.0)	0 (0.0)		

AMR, antibody-mediated rejection; CI, confidence interval; SOC, standard of care.
[a]Reassessed using clinical information available to local pathologists.
[b]Including initial results for 132 biopsies considered negative for acute AMR by the local and both central pathologists that were not reassessed.
[c]Initial biopsy results.

biopsy-proven acute cellular rejection (this was detected by month 3 in most [65.2%] of these cases).

4 | DISCUSSION

Transplant candidates who are sensitized to their potential living donors may be unable to benefit from transplantation. Although paired kidney exchange has increased access to living-donor transplantation in sensitized individuals with a calculated panel-reactive antibody of ≥80%, the absolute number of transplants it has facilitated is small (Schinstock et al., 2019, unpublished data). A need therefore remains for other novel strategies, such as complement inhibition, to facilitate kidney transplantation in sensitized individuals.[38]

This study was conducted in a population of kidney transplant recipients who were at high risk of acute AMR because they were sensitized to their living donors. There was no significant difference in treatment failure rate (including grade II or III acute AMR) between the eculizumab and SOC groups. In a post hoc analysis including grade I AMR, the treatment failure rate was lower in the eculizumab

group than in the SOC group, suggesting that terminal complement inhibition may prevent early acute AMR. The treatment failure rate (including grade II or III acute AMR) in the eculizumab group in this study was similar to the rates estimated from a previously published pilot study (10%),[26] and from a single-arm study of sensitized recipients of deceased-donor kidney transplants who received eculizumab for AMR prevention without pretransplant desensitization therapy (<10%),[37] compared with the expected rate of 30% to 40% reported in the literature.

Graft survival at 36 months posttransplant for eculizumab-treated patients was 91.8% compared with 78.5% in the SOC group, which was the expected rate for sensitized recipients. Although this difference is not statistically significant, the direction of the effect is promising, considering the long duration of pretransplant dialysis experienced by the patients in this study (mean, 112 months) and the well-known inverse relationship between patient survival and time on dialysis.

A post hoc analysis of subgroups based on CDC and FXM baseline status (Table S8) revealed that the rate of AMR was higher in patients who were both CDC-positive and FXM-positive than in the

TABLE 6 Incidence of serious treatment-emergent adverse events that occurred in at least 3% of patients in either treatment group throughout the study (until each patient's final study visit)

MedDRA system organ class Preferred term	Eculizumab (N = 51) n (%)	SOC (N = 51)
Patients with any serious TEAE	43 (84.3)	48 (94.1)
Immune system disorders	22 (43.1)	28 (54.9)
Kidney transplant rejection	22 (43.1)	28 (54.9)
Infections and infestations	32 (62.7)	25 (49.0)
Escherichia urinary tract infection bacterial	4 (7.8)	6 (11.8)
Urinary tract infection	2 (3.9)	7 (13.7)
Pneumonia	3 (5.9)	4 (7.8)
Pyelonephritis	4 (7.8)	2 (3.9)
Urosepsis	4 (7.8)	2 (3.9)
Bronchitis	2 (3.9)	3 (5.9)
Cellulitis	2 (3.9)	2 (3.9)
Gastroenteritis	0 (0.0)	4 (7.8)
Gastroenteritis viral	1 (2.0)	2 (3.9)
Urinary tract infection bacterial	2 (3.9)	1 (2.0)
Urinary tract infection enterococcal	1 (2.0)	2 (3.9)
Lower respiratory tract infection	2 (3.9)	0 (0.0)
Gastrointestinal disorders	9 (17.6)	17 (33.3)
Diarrhea	3 (5.9)	8 (15.7)
Pancreatitis acute	1 (2.0)	2 (3.9)
Injury, poisoning, and procedural complications	9 (17.6)	12 (23.5)
Post procedural hemorrhage	1 (2.0)	3 (5.9)
Delayed graft function	2 (3.9)	1 (2.0)
Incisional hernia	2 (3.9)	1 (2.0)
Post procedural hematuria	0 (0.0)	2 (3.9)
Wound dehiscence	0 (0.0)	2 (3.9)
Renal and urinary disorders	9 (17.6)	12 (23.5)
Acute kidney injury	2 (3.9)	3 (5.9)
Hematuria	1 (2.0)	2 (3.9)
Hydronephrosis	2 (3.9)	3 (5.9)
Vascular disorders	8 (15.7)	9 (17.6)
Deep vein thrombosis	2 (3.9)	0 (0.0)
Lymphocele	3 (5.9)	5 (9.8)
Blood and lymphatic system disorders	3 (5.9)	7 (13.7)
Anemia	1 (2.0)	2 (3.9)
General disorders and administration site conditions	6 (11.8)	1 (2.0)
Chest pain	2 (3.9)	0 (0.0)
Edema peripheral	2 (3.9)	0 (0.0)

(Continues)

TABLE 6 (Continued)

MedDRA system organ class Preferred term	Eculizumab (N = 51) n (%)	SOC (N = 51)
Nervous system disorders	4 (7.8)	3 (5.9)
Headache	0 (0.0)	2 (3.9)
Migraine	2 (3.9)	0 (0.0)
Cardiac disorders	3 (5.9)	3 (5.9)
Cardiac failure	0 (0.0)	2 (3.9)
Investigations	5 (9.8)	1 (2.0)
Blood creatinine increased	3 (5.9)	1 (2.0)

MedDRA, Medical Dictionary for Regulatory Activities; SOC, standard of care; TEAE, treatment-emergent adverse event.

Both fatal and nonfatal serious TEAEs are included in this table. System organ classes are sorted by decreasing frequency for the combined incidence. Patients with more than one event within a system organ class are counted only once.

other baseline immune status subgroups. This suggests that there may be different subtypes of acute AMR in these subgroups. For the CDC-positive/FXM-positive subgroup, terminal complement activity may be primarily responsible for tissue injury, while for the other subgroups, downstream complement-initiated activities may contribute more to tissue injury.

The treatment failure rate in this study was lower than expected under SOC (13.7% compared with 36.3% estimated from the literature). One potential explanation for this is because only grades II and III acute AMR were initially considered a treatment failure, and not grade I. The treatment failure rate in the SOC group increased from 13.6% to 17.6% when grade I AMR was included in the post hoc analysis. The Banff classification grades of acute AMR reflect patterns of injury and not necessarily clinical severity, and common patterns of early acute AMR, for example acute tubular necrosis-like minimal inflammation, were excluded with grade I AMR.[7] Diagnosis of early grade I acute AMR is clinically meaningful because it may progress to severe graft injury and loss.[12] In practice, transplant clinicians frequently consider AMR to be present or absent without distinguishing between grades, and they therefore treat patients with grade I AMR in the context of diminished graft function. In patients receiving prophylactic eculizumab, however, the interpretation of grade I acute AMR may be difficult without information on renal function, as normal grafts with effective terminal complement inhibition can still show C4d deposition in peritubular capillaries if there are high levels of circulating DSA. Further, the difference between grades I and II acute AMR may be subject to interpretation and bias, because of limited reproducibility of capillaritis and glomerulitis scores between pathologists.[38,39] The majority rules method (as implemented in this study by involvement of the adjudicating central pathologist) has been shown to reduce variation in Banff scoring.[40]

Secondly, biopsy diagnoses of grade II/III acute AMR were originally made by central pathologists without clinical information. In a typical clinical setting, however, pathologists have access to all relevant clinical information, including serum DSA levels and creatinine

increases. When the central pathologists reassessed biopsies using clinical information, but still blinded to treatment, the treatment failure rate including grade I AMR in the SOC group, increased from 17.6% to 29.4%. In addition, the treatment failure rate including grade I AMR in the SOC group, assessed by local pathology using both biopsies and clinical information, was 41.2% Both these reassessment rates are close to the expected rate of 36.3% estimated from the literature review. These findings demonstrate the importance of clinical information in AMR diagnosis.

Another potential explanation for the low treatment failure rate in the SOC group is differences in enrollment criteria between sites, particularly in DSA inclusion thresholds and crossmatch definitions, which may have affected acute AMR rates, as patients with higher baseline DSA levels are generally at higher risk of early acute AMR.[4-7]

It is interesting that, despite treatment failure rates of up to 41.2%, the rate of transplant glomerulopathy found on 1-year surveillance biopsies was low (<10%) compared with previous studies of positive crossmatch kidney transplant recipients (44% to 63% at 12-24 months posttransplant).[41,42]

The types of TEAEs observed in this study were characteristic of transplant populations and were similar in the two treatment groups. All patients received immunosuppressive agents during the study, which increased their risk of infections. Overall, the incidence of serious TEAEs was numerically higher in the SOC group, while that of serious infections was numerically higher in the eculizumab group. The safety profile of eculizumab was consistent with that reported in eculizumab's other approved indications, atypical hemolytic uremic syndrome[43,44] and paroxysmal nocturnal hemoglobinuria,[45] over 10 years.

The main limitations of this study were its open-label design and the assessment of biopsies without clinical information or inclusion of clinically relevant grade I AMR to diagnose AMR for the primary end point. In addition, no analyses of the pathological findings or of long-term outcomes were conducted on the patients in the SOC group who received eculizumab for AMR treatment within 9 weeks of transplantation.

Eculizumab use has previously been shown to result in a lower AMR incidence in the first 3 months posttransplant in kidney recipients sensitized to their living donors than in a well-matched historical control group (7.7% [2/26] and 41.2% [21/51], respectively; $P = .0031$).[26] Eculizumab may prove to be most effective in the early posttransplant phase, because this is when grafts are more likely to be subjected to high serum DSA levels (associated with complement-fixing DSA); biopsies from this period tend to show complement deposition (C4d+).[7,46] Together, these data suggest that eculizumab has the potential to have meaningful positive effects on preventing acute AMR in kidney transplant recipients who are sensitized to their donors, particularly when all grades of AMR are considered. This is supported by the recent finding that complement-activating DSA-mediated kidney allograft rejection can be abrogated by eculizumab.[47] The effects of terminal complement inhibition by eculizumab need to be confirmed in future trials that address the issues raised here. Such trials should include uniform inclusion criteria based on current understanding of histocompatibility risk factors (for example, standardized DSA thresholds and stratification according to the complement-binding capacity of DSAs),[48] recognize acute AMR as a clinicopathologic diagnosis, and address issues affecting the reproducibility of AMR diagnosis. Importantly, in future studies, attempts should be made to understand which histocompatibility tests and other biomarkers are most accurate in identifying sensitized patients who would benefit most from terminal complement inhibition by eculizumab.

DISCLOSURE

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DATA AVAILABILITY STATEMENT

Qualified academic investigators may request participant-level, de-identified clinical data and supporting documents (statistical analysis plan and protocol) pertaining to this study. Further details regarding data availability, instructions for requesting information, and our data disclosure policy will be available on the Alexion.com website (http://alexion.com/research-development).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.