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ORIGINAL ARTICLE

Efficacy and safety of bleselumab in kidney transplant recipients: A phase 2, randomized, open-label, noninferiority study

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This study assessed the efficacy and safety of the anti-CD40 monoclonal antibody bleselumab (ASKP1240) in de novo kidney transplant recipients over 36 months post-transplant. Transplant recipients were randomized (1:1:1) to standard of care (SoC: 0.1 mg/kg per day immediate-release tacrolimus [IR-TAC]; target minimum blood concentration [C_{trough}] 4-11 ng/mL plus 1 g mycophenolate mofetil [MMF] twice daily) or bleselumab (200 mg on days 0/7/14/28/42/56/70/90, and monthly thereafter) plus either MMF or IR-TAC (0.1 mg/kg per day; target C_{trough} 4-11 ng/mL days 0-30, then 2-5 ng/mL). All received basiliximab induction (20 mg pretransplant and on days 3-5 posttransplant) and corticosteroids. One hundred thirty-eight transplant recipients received ≥1 dose of study drug (SoC [n = 48]; bleselumab + MMF [n = 46]; bleselumab + IR-TAC [n = 44]). For the primary endpoint (incidence of biopsy-proven acute rejection [BPAR] at 6 months), bleselumab + IR-TAC was noninferior to SoC (difference 2.8%; 95% confidence interval [CI] −8.1% to 13.8%), and bleselumab + MMF did not demonstrate noninferiority to SoC (difference 30.7%; 95% CI 15.2%-46.2%). BPAR incidence slightly increased through month 36 in all groups, with bleselumab + IR-TAC continuing to demonstrate noninferiority to SoC. Bleselumab had a favorable benefit–risk ratio. Most treatment-emergent adverse events were as expected for kidney transplant recipients (ClinicalTrials.gov NCT01780844).

KEYWORDS
clinical research/practice, immunosuppressant—antiproliferative agent: mycophenolate mofetil, immunosuppressant—calcineurin inhibitor: tacrolimus, immunosuppressant —fusion proteins and monoclonal antibodies, immunosuppression/immune modulation, kidney transplantation/nephrology, kidney transplantation: living donor, translational research/science

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BPAR, biopsy-proven acute rejection; CI, confidence interval; CMV, cytomegalovirus; C_{trough}, minimum blood concentration; DRAE, drug-related adverse event; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; FAS, full analysis set; GI, gastrointestinal; HLA, human leukocyte antigen; IgG, immunoglobulin G; IRB, Institutional Review Board; IR-TAC, immediate-release tacrolimus; LS, least squares; MMF, mycophenolate mofetil; NODAT, new-onset diabetes mellitus; SAE, serious adverse event; SAF, safety analysis set; SAS, statistical analysis software; SD, standard deviation; SoC, standard of care; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

1 | INTRODUCTION

Kidney transplantation is the preferred renal replacement therapy for most patients with end-stage renal disease[1,2]; compared with dialysis, kidney transplantation is associated with significantly lower mortality and improved quality of life.[3-5] The current standard of care (SoC) immunosuppressive regimen for the prevention of graft rejection in kidney transplantation includes calcineurin inhibitors, such as tacrolimus or cyclosporine.[6,7] Because calcineurin inhibitors are associated with the development of nephrotoxicity and cardiometabolic events, and have long-term failure rates with a high incidence of chronic antibody-mediated rejection, interstitial fibrosis, and tubular atrophy, there is a need to develop effective immunosuppressive regimens with reduced exposure to calcineurin inhibitors.[8-14]

Bleselumab (ASKP1240) is a fully human anti-CD40 monoclonal antibody that inhibits both humoral and cellular immune responses by blocking the interaction of the cell surface receptor CD40 and its ligand CD40L (CD154) between T cells, B cells, and antigen-presenting cells.[15,16] Blocking this interaction prevents the generation of costimulatory signals required for effective T cell activation.[16] Several humanized anti-CD40L monoclonal antibodies have demonstrated efficacy in nonhuman primate renal allograft models, but development was halted following unexpected thromboembolic events.[15,17] Chimeric monoclonal antibodies against CD40 demonstrated effective immunosuppression in nonhuman primate models without thromboembolic events, but were associated with some other important limitations including cytotoxicity associated with the use of immunoglobulin G1 (IgG1) and immunogenicity associated with the use of chimeric molecules.[15,18,19] Bleselumab aims to circumvent these limitations because it is an IgG4 isotype, and therefore has a low binding affinity for Fc gamma receptors, which are known to cross-link antibodies to induce antagonistic activity and cellular cytotoxicity. Because it is a fully human molecule, it is similarly expected to have low immunogenicity.[15] For the prophylaxis of graft rejection post–kidney transplantation, bleselumab has been investigated in 3 phase 1 studies: 2 in healthy volunteers (NCT01565681 and NCT01582399) and 1 in de novo kidney transplant recipients (NCT01279538). In kidney transplant recipients, bleselumab was well tolerated, with no evidence of cytokine release syndrome or thromboembolic events.[20]

Here we describe the results of a phase 2a, randomized, open-label, noninferiority study designed to evaluate the efficacy and safety of bleselumab in combination with either mycophenolate mofetil (MMF) or immediate-release tacrolimus (IR-TAC) compared with SoC (containing MMF + IR-TAC) in kidney transplant recipients who also received low-dose maintenance corticosteroids over 36 months posttransplant.

2 | MATERIALS AND METHODS

2.1 | Study design

This phase 2a, randomized, open-label, active control, multicenter study was conducted at 42 sites in the United States between March 2013 and January 2017 (Clinicaltrials.gov NCT01780844) (Figure 1). Kidney transplant recipients were randomized in a 1:1:1 ratio to 1 of 3 treatment groups: SoC, bleselumab + MMF, or bleselumab + IR-TAC. Bleselumab was administered as a 200-mg intravenous infusion (dose selected based on the results of 2 phase 1 studies[20] [ClinicalTrials.gov NCT01279538]) on days 0, 7, 14, 28, 42, 56, 70, and 90, and monthly thereafter, relative to the day of transplantation (day 0). MMF was administered orally or intravenously at a dose of 1 g twice daily. In the SoC group, IR-TAC was administered at an initial dose of 0.1 mg/kg per day with a target minimum blood concentration (C_{trough}) of 4-11 ng/mL for the

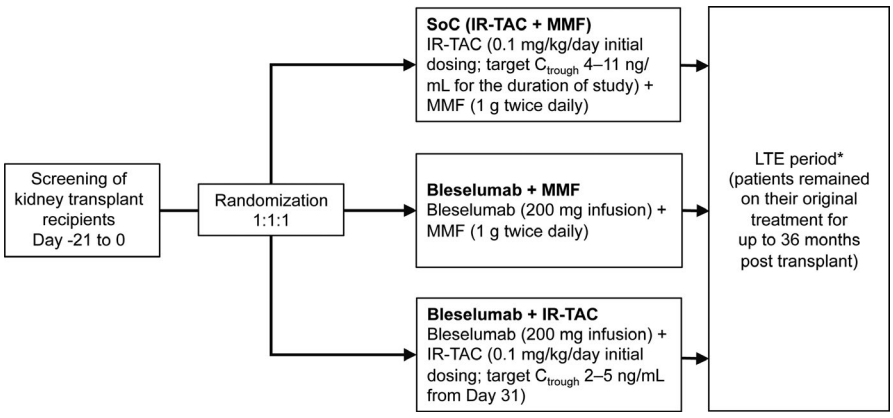

FIGURE 1 Study design. *After 6 months of treatment, kidney transplant recipients continued to receive their original treatment in the LTE (unless the sponsor discontinued development of bleselumab, or the transplant recipient no longer wished to participate in the study or they were switched to SoC for clinical reasons). All kidney transplant recipients received corticosteroids and 1 bolus injection of basiliximab 20 mg prior to transplantation, and a second bolus injection of basiliximab 20 mg between days 3 and 5 posttransplant. Bleselumab 200 mg was administered on days 0, 7, 14, 28, 42, 56, 70, and 90, and monthly thereafter, relative to the day of transplantation (day 0). C_{trough}, minimum blood concentration; IR-TAC, immediate-release tacrolimus; LTE, long-term extension; MMF, mycophenolate mofetil; SoC, standard of care

duration of the study. In the bleselumab + IR-TAC group, IR-TAC was administered at an initial dose of 0.1 mg/kg per day with a target C_{trough} of 4-11 ng/mL on day 0 to day 30, and a lower target C_{trough} of 2-5 ng/mL from day 31 onward. All kidney transplant recipients received corticosteroids as an intravenous bolus of 500, 250, 125, and 60 mg of methylprednisolone (or equivalent oral/intravenous corticosteroid dose), on days 0, 1, 2, and 3, respectively, with subsequent tapering to a maintenance dose of 5-10 mg oral prednisone (or equivalent) by day 29. All kidney transplant recipients also received basiliximab as induction therapy: one 20-mg bolus injection prior to transplantation or intraoperatively before revascularization, and a second 20-mg bolus injection on days 3-5 posttransplant. For cytomegalovirus (CMV) prophylaxis, valganciclovir was administered in accordance with the package insert instructions for ≈200 days in high-risk CMV-seronegative patients who received a kidney from a CMV-seropositive donor, ≈100 days in moderate-risk CMV-seropositive patients, and was not administered to low-risk CMV-seronegative patients who received a CMV-seronegative kidney. *Pneumocystis jiroveci*, fungal, and bacterial prophylaxis were administered to all kidney transplant recipients as per institutional protocol. After completion of the initial 6-month study period, kidney transplant recipients entered a long-term extension period of up to 36 months posttransplant, during which they were to remain on their original treatment (unless the sponsor discontinued the development of bleselumab and/or the kidney transplant recipient no longer wished to participate in the study or they were switched to SoC for clinical reasons).

The Institutional Review Board (IRB; protocol number 7163-CL-0108) of each site reviewed the ethical, scientific, and medical appropriateness of the study before it was conducted. IRB approval of the protocol, informed consent, and patient information were obtained prior to the authorization of drug shipment to a study site (see Table S1 for the list of IRBs). The study was conducted in accordance with the protocol, Good Clinical Practice, the International Council for Harmonization guidelines, applicable regulations and guidelines governing clinical study conduct, and ethical principles that have their origin in the Declaration of Helsinki.

2.2 | Transplant recipients

Adult (≥18 years of age) men and women who were the recipient of a kidney from a living or deceased donor were considered eligible. Kidney transplant recipients (and their partners) of childbearing age were required to take effective measures to avoid pregnancy and were not lactating or breastfeeding at screening, during the study period, and for 90 days after final study drug administration. Exclusion criteria included the following: induction therapy, other than basiliximab planned as part of the initial immunosuppressive regimen; previous organ transplant other than a kidney; having received an ABO-incompatible donor kidney; most recent calculated panel reactive antibody level of >50%; human immunodeficiency virus seropositivity; a positive T cell or B cell crossmatch by the National Institutes of Health antiglobulin lymphocytotoxicity method, if performed; a positive T cell or B cell flow cytometry crossmatch and donor-specific anti-human leukocyte antigen (HLA) antibody detected by flow cytometry/Luminex®-based (Luminex Corporation, Austin, TX), specific anti-HLA antibody testing, if performed; malignancy or history of malignancy within the last 5 years (except nonmetastatic basal or squamous cell carcinoma of the skin that has been successfully treated, or a renal cell carcinoma that had been successfully treated >2 years prior to transplantation); significant liver disease; current (or within 8 weeks prior to transplant) treatment with an immunologic biologic compound; and previous treatment with bleselumab.

2.3 | Endpoints

The primary study objective was to assess the noninferiority of bleselumab + MMF or bleselumab + IR-TAC compared with the SoC for the primary efficacy endpoint, which was the proportion of kidney transplant recipients with biopsy-proven acute (T or B cell) rejection (BPAR; Banff grade ≥1) by local review through 6 months. Secondary efficacy endpoints, through 6 months, were the estimated glomerular filtration rate (eGFR), kidney transplant recipient survival, and graft survival. Exploratory efficacy endpoints, through 36 months, included efficacy failure (defined as death, graft loss, BPAR, or lost to follow-up), time to first BPAR, time to first clinically treated BPAR, maximum grade of BPAR, incidence of transplant recipients experiencing multiple rejection episodes, incidence of the need for anti-lymphocyte antibody therapy, incidence of anti-HLA antibody formation, and incidence of new-onset diabetes mellitus after transplantation (NODAT). NODAT for the at-risk population (patients with no history of diabetes mellitus) was defined as an elevated glucose level (>126 mg/dL) on 2 occasions >30 days apart, a hemoglobin A1c >6.5%, a patient who died and their last glucose value was >126 mg/dL, or a patient who was lost to follow-up or discontinued early with a last glucose value >126 mg/dL. Samples for the analysis of the presence of anti-HLA antibodies were collected at screening, day 90, and months 6, 8, 10, 12, 15, 18, 21, 24, 27, 30, 33, and 36 posttransplant. The allelic specificity of the anti-HLA antibody was compared with the corresponding alleles of the donor. If they matched the donor, then the recipient was considered to have donor-specific antibodies (DSAs).

Safety assessments included treatment-emergent adverse events (TEAEs, reported using the National Cancer Institute—Common Terminology Criteria for Adverse Events version 4.03 grading scale) through 6 months, serious adverse events (SAEs) through 36 months, vital signs, clinical laboratory tests (hematology, biochemistry, coagulation/thrombotic pathway, hepatic profile, fasting lipid profile, urinalysis, and pregnancy testing), anti-bleselumab antibodies, viral serology, and viral loads. Details of the definition of specific adverse events can be found in Table S2. A post-hoc analysis of peak BK viral load in patients in the safety analysis set (SAF) was conducted using an analysis of variance. Serum and urine were collected for BK viral load analysis at days 14, 28, 56, and 90, and months 4, 5, and 6.

Safety events were aggregated to describe clusters based on adverse events, laboratory values, and vital signs. These clusters were those commonly seen following transplantation and treatment with IR-TAC, MMF, and corticosteroids, and included BK virus infection (replicative infection; defined as quantitative BK viral DNA load in blood or urine above the detection threshold for the given laboratory's assay), cardiac, cardiovascular, cytomegalovirus, diarrhea, dyspepsia, gastrointestinal disturbances, gastroenteritis, gastrointestinal pain/discomfort, glucose abnormality, hepatic events, hypertension, lipids, malignancy, neurotoxicity, opportunistic infections, renal events, respiratory tract infections, upper gastrointestinal complex, urinary tract infections, other infections, and infestations.

If laboratory testing showed a moderate hepatic abnormality (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3 × the upper limit of normal [ULN], or bilirubin >2 × ULN), all 4 serum hepatic measures were to be repeated (ALT, AST, alkaline phosphatase, and total bilirubin). Confirmed hepatic abnormalities were thoroughly characterized by obtaining appropriate expert consultations, a detailed pertinent history, physical examination, and laboratory tests. Treatment discontinuation was considered if any of the following marked hepatic abnormalities occurred: ALT or AST >8 × ULN, ALT or AST >5 × ULN for >2 weeks, ALT or AST >3 × ULN and total bilirubin >2 × ULN, or international normalized ratio >1.5 and ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). If it was not possible to closely monitor a patient with moderate or marked hepatic abnormalities, treatment was discontinued.

2.4 | Pharmacokinetics

Following initiation of IR-TAC dosing for those patients in the SoC and bleselumab + IR-TAC treatment groups, blood samples for IR-TAC whole blood C_{trough} monitoring were collected 11-13 hours postdose and immediately before the next dose on days 1, 4, 7, 14, 28, 42, 56, 70, and 90, and then monthly thereafter through month 36.

2.5 | Statistical analyses

Efficacy assessments were conducted using the full analysis set (FAS), which included all randomized patients who received at least 1 dose of study drug (basiliximab, bleselumab, MMF, or IR-TAC), and received a kidney transplant. Safety assessments were conducted using the SAF, which included all randomized patients who received at least 1 dose of study drug. TEAEs were assessed during the 6-month posttransplant period, beyond which only SAEs were assessed.

The sample size was estimated based on a noninferiority test of BPAR through month 6 for at least 1 of the 2 treatment groups that received bleselumab, compared with the SoC treatment group. BPAR rate at 6 months was assumed to be 12% for all treatment groups based on previous data. The noninferiority margin for the treatment difference was set at 20%, requiring an estimated sample size of 42 evaluable kidney transplant recipients per treatment group to provide 80% power with a 2.5% (1-sided) level of significance to demonstrate noninferiority of either of the treatment groups that received bleselumab, vs the SoC treatment group. To test for noninferiority of each of the treatment groups that received bleselumab compared with the SoC treatment group for the primary endpoint, a 2-sided 95% confidence interval (CI) for the difference in BPAR rate was constructed using the normal approximation. Positive differences indicated a greater BPAR rate in the bleselumab treatment groups, and an upper confidence limit of <20% indicated achievement of noninferiority. All remaining statistical comparisons were made using 2-sided tests with type 1 error controlled at a .05 significance level with no adjustments for multiplicity.

For continuous variables, descriptive statistics included the number of patients, mean, standard deviation, median, and range. For categorical variables, incidence and percentage were displayed for each treatment group. Percentages by category were based on the number of kidney transplant recipients within each treatment group. Analyses of treatment differences were conducted using Fisher's exact test, analysis of variance, or analysis of covariance (for the analysis of eGFR, baseline eGFR at 28 days was the covariate). Calculations of eGFR used an abbreviated version of the Modification of Diet in Renal Disease Study equation ($eGFR = 186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times [1.212 \text{ if black}] \times [0.742 \text{ if female}]$), where serum creatinine was measured in mg/dL and age was measured in integer years at baseline. All data processing, summarization, and analyses were performed using SAS® v9.3 (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Patient disposition and demographics

Of the 158 patients who provided informed consent, 149 were randomized (SoC [n = 50]; bleselumab + MMF [n = 49]; bleselumab + IR-TAC [n = 50]) and 139 received at least 1 dose of study drug (SAF; Figure 2). One patient in the SoC treatment group did not receive a transplant, leaving 138 kidney transplant recipients in the FAS. Overall, 93 (62.4%) transplant recipients completed 6 months of treatment (SoC [78.0%]; bleselumab + MMF [44.9%]; bleselumab + IR-TAC [64.0%]), and 60 (40.3%) completed 36 months of treatment (SoC [56.0%]; bleselumab + MMF [24.5%]; bleselumab + IR-TAC [40.0%]). The most common reason for discontinuation was adverse events by month 6 (n = 35: with n = 2, n = 21, and n = 12 in the SoC, bleselumab + MMF, and bleselumab + IR-TAC groups, respectively) and by month 36 (n = 52: with n = 3, n = 28, and n = 21 in the SoC, bleselumab + MMF, and bleselumab + IR-TAC groups, respectively).

Most transplant recipients (66.9%) were male, white (74.1%), with a mean (standard deviation [SD]) age of 52.1 (12.4) years, and a

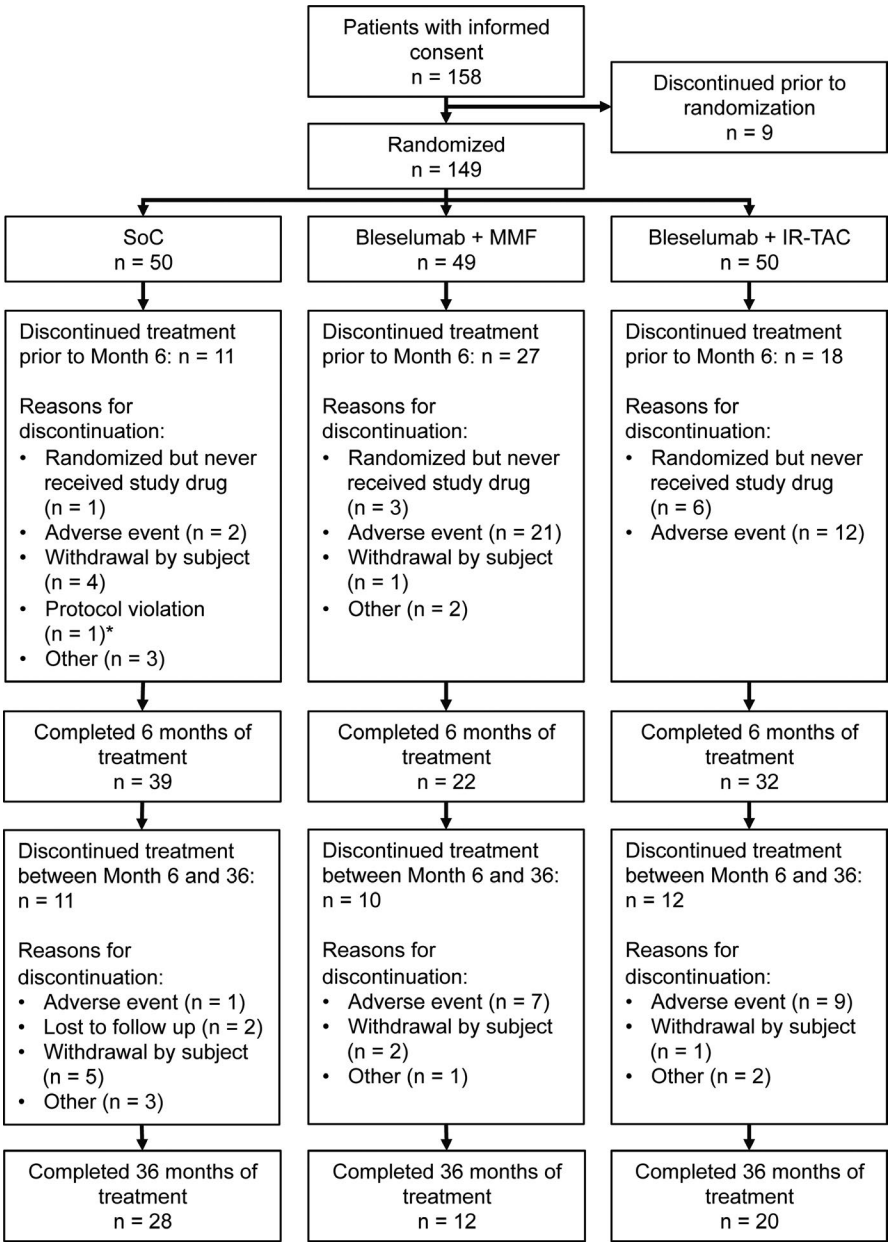

FIGURE 2 Patient disposition. *The patient received a prohibited medication (thymoglobulin). IR-TAC, immediate-release tacrolimus; MMF, mycophenolate mofetil; SoC, standard of care

mean (SD) body mass index of 28.8 (5.4) kg/m^2. There were no statistically significant differences between treatment groups for any baseline demographics or characteristics of kidney transplant recipients or donors (Table 1).

3.2 | Efficacy: primary endpoint

For the primary endpoint (incidence of BPAR at month 6), bleselumab + IR-TAC was noninferior to SoC (Figure 3A); the BPAR rate was 6.3% (n = 3/48) for the SoC group and 9.1% (n = 4/44) for the bleselumab + IR-TAC group (difference 2.8%; 95% CI −8.1% to 13.8%). The incidence of BPAR at month 6 in the bleselumab + MMF group was 37.0% (n = 17/46), which did not demonstrate noninferiority to SoC (difference 30.7%; 95% CI 15.2%-46.2%). Counting those who were lost to follow-up as a BPAR also resulted in bleselumab + IR-TAC being noninferior to SoC at month 6 (difference −5.5%; 95% CI −18.6% to 7.6%; Figure 3B). The bleselumab + MMF group did not demonstrate noninferiority to SoC when counting those who were lost to follow-up as BPAR at month 6 (difference 26.7%; 95% CI 9.3%-44.1%). The incidence of BPAR slightly increased through month 36 for all treatment groups, with bleselumab + IR-TAC continuing to demonstrate noninferiority to SoC (Figure 3C,D).

3.3 | Efficacy: secondary endpoints

At months 6 and 36 there were no statistically significant differences between the SoC group and either of the bleselumab groups for least squares (LS) mean eGFR; however, LS mean change from baseline eGFR was positive at all time points posttransplant in

TABLE 1 Demographic and baseline characteristics (SAF)

	SoC (n = 49)	Bleselumab + MMF (n = 46)	Bleselumab + IR-TAC (n = 44)	Bleselumab total (n = 90)	*P* value[a]
Recipient characteristics					
Male, n (%)	33 (67.3)	30 (65.2)	30 (68.2)	60 (66.7)	.949
Hispanic or Latino, n (%)[b]	7 (14.3)	6 (13.0)	10 (22.7)	16 (17.8)	.468
Race, n (%)[b]					
White	36 (73.5)	36 (78.3)	31 (70.5)	67 (74.4)	.941
Black	10 (20.4)	9 (19.6)	11 (25.0)	20 (22.2)	
Asian	2 (4.1)	1 (2.2)	2 (4.5)	3 (3.3)	
Other	1 (2.0)	0	0	0	
Age (y), mean (SD)	52.8 (11.2)	51.1 (14.7)	52.4 (11.1)	51.7 (13.0)	.798
BMI (kg/m^2), mean (SD)	29.2 (5.6)	28.5 (5.5)	28.6 (5.0)	28.5 (5.3)	.791
Panel reactive antibody, mean (SD)	4.1 (8.9)[c]	1.6 (5.0)	3.5 (8.7)	2.6 (7.1)	.275
Panel reactive antibody group, n (%)					
≤0%	35 (72.9)	37 (80.4)	31 (70.5)	68 (75.6)	.337
>0%–20%	7 (14.6)	8 (17.4)	10 (22.7)	18 (20.0)	
>20%–50%	6 (12.5)	1 (2.2)	3 (6.8)	4 (4.4)	
>50%	0	0	0	0	
Previously received a transplant, n (%)	2 (4.2)	3 (6.5)	1 (2.3)	4 (4.4)	.780
Reason for ESRD, n (%)					
Hypertensive nephrosclerosis	11 (22.9)	10 (21.7)	13 (29.5)	23 (25.6)	.793
Diabetes mellitus	8 (16.7)	11 (23.9)	11 (25.0)	22 (24.4)	
IgA nephropathy	6 (12.5)	6 (13.0)	3 (6.8)	9 (10.0)	
Polycystic kidney disease	5 (10.4)	3 (6.5)	6 (13.6)	9 (10.0)	
Glomerulonephritis	5 (10.4)	2 (4.3)	3 (6.8)	5 (5.6)	
Other	13 (27.1)	14 (30.4)	8 (18.2)	22 (24.4)	
Dialysis prior to transplant, n (%)	33 (68.8)	37 (80.4)	39 (88.6)	76 (84.4)	.063
Donor characteristics					
Male, n (%)	28 (57.1)	23 (50.0)	21 (47.7)	44 (48.9)	.667
Race, n (%)					
White	43 (87.8)	37 (80.4)	38 (86.4)	75 (83.3)	.775
Black	3 (6.1)	7 (15.2)	5 (11.4)	12 (13.3)	
Asian	2 (4.1)	1 (2.2)	1 (2.3)	2 (2.2)	
Other	1 (2.0)	1 (2.2)	0	1 (1.1)	
Age (y), mean (SD)	42.7 (13.0)	42.5 (12.1)	42.7 (12.3)	42.6 (12.1)	.998
BMI (kg/m^2), mean (SD)	27.2 (4.8)	26.1 (4.6)	26.8 (4.6)	26.4 (4.6)	.535
Source of current transplant, n (%)					
Deceased donor	21 (42.9)	21 (45.7)	20 (45.5)	41 (45.6)	.637
Living unrelated donor	15 (30.6)	11 (23.9)	16 (36.4)	27 (30.0)	
Living related donor	12 (24.5)	14 (30.4)	8 (18.2)	22 (24.4)	
Longest primary organ preservation method, n (%)					
Cold storage	45 (91.8)	43 (93.5)	39 (88.6)	82 (91.1)	.392
Pump	3 (6.1)	1 (2.2)	4 (9.1)	5 (5.6)	
Cold ischemic time (h), mean (SD)					
Living donors	n = 26	n = 23	n = 22	n = 45	.607
	2.21 (2.95)	1.64 (1.13)	1.79 (1.42)	1.7 (1.3)	
Deceased donors	n = 21	n = 21	n = 19	n = 40	.316
	15.90 (7.53)	18.86 (5.29)	16.66 (6.41)	17.8 (5.9)	

ANCOVA, analysis of covariance; BMI, body mass index; ESRD, end-stage renal disease; IgA, immunoglobulin A; IR-TAC, immediate-release tacrolimus; MMF, mycophenolate mofetil; SAF, safety analysis set; SD, standard deviation; SoC, standard of care.

[a]Fisher's exact test for categorical variables and 1-way ANOVA with treatment as a predictor for continuous variables.

[b]Ethnicity and race were self-reported.

[c]n = 48.

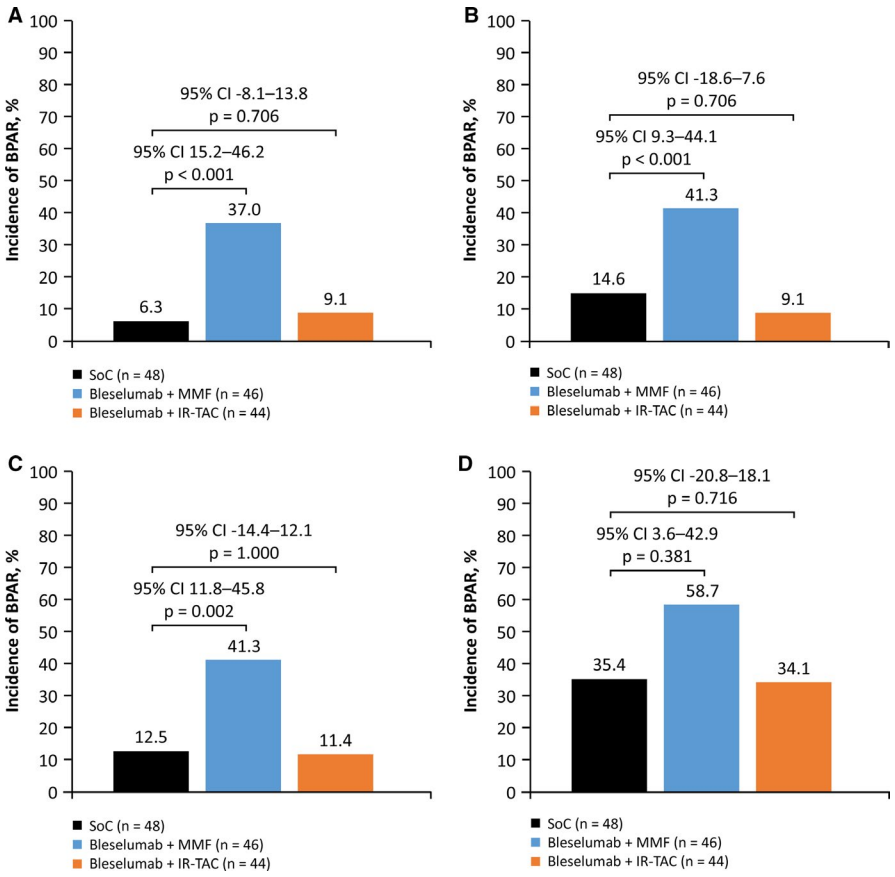

FIGURE 3 Incidence of biopsy-proven acute rejection (FAS). A, Month 6: Not including transplant recipients who were lost to follow-up. B, Month 6: Including transplant recipients who were lost to follow-up. C, Month 36: Not including transplant recipients who were lost to follow-up. D, Month 36: Including transplant recipients who were lost to follow-up. Transplant recipients who were lost to follow-up were counted as a BPAR event. BPAR, biopsy-proven acute rejection; CI, confidence interval; FAS, full analysis set; IR-TAC, immediate-release tacrolimus; MMF, mycophenolate mofetil; SoC, standard of care

the bleselumab + IR-TAC group (Figure 4A). In addition, there were no statistically significant differences between the SoC group and either of the bleselumab groups for transplant recipient survival (Figure 4B) or graft survival (Figure 4C) at months 6 and 36.

3.4 | Efficacy: exploratory endpoints

The incidence of efficacy failure by months 6 and 36 were significantly greater in the bleselumab + MMF treatment group compared with the SoC treatment group (month 6 $P = .0028$; month 36 $P = .0128$), and was similar between the bleselumab + IR-TAC and SoC treatment groups (month 6 [$P = 1.0000$]; month 36 [$P = .6692$]) (Figure 5).

Compared with the SoC group, the bleselumab + MMF group demonstrated a significantly earlier time to first BPAR (Figure 6A; $P = .001$) and time to first clinically treated acute rejection (Figure 6B; $P < .0001$). There were no statistically significant differences between the SoC group and the bleselumab + IR-TAC group for time to first BPAR ($P = .765$) or time to first clinically treated acute rejection ($P = .681$). The majority of BPARs and clinically treated acute rejections occurred within the first 2 months post-transplant. There were no statistically significant differences for the cumulative incidence of multiple rejection episodes between either of the bleselumab treatment groups and the SoC group at month 6 or month 36 (Table S3). Higher grade T cell–mediated BPARs were more common in the bleselumab + MMF treatment group at month 6 and month 36 compared with the SoC treatment group (Table S4). There were minimal differences in the number and grade of T cell–mediated BPARs between the bleselumab + IR-TAC treatment group and the SoC treatment group at month 6 and month 36.

DSAs were detected in a total of 11 transplant recipients (Table S5). In the SoC treatment group, 6 transplant recipients became DSA-positive after screening, 4 of whom had rejections. In the bleselumab + MMF treatment group, 2 transplant recipients were DSA-positive at screening, and both had rejections. In the bleselumab + IR-TAC treatment group, 2 transplant recipients were DSA-positive pre- and postscreening, and 1 was DSA-positive post-screening; none of these 3 patients had rejections.

In patients with no history of diabetes mellitus (SoC [n = 33]; bleselumab + MMF [n = 25]; bleselumab + IR-TAC [n = 23]), there was no statistically significant difference in the incidence of NODAT between the bleselumab + IR-TAC and SoC treatment groups ($P = .588$). The incidence of NODAT in the bleselumab + MMF treatment group was marginally lower than in the SoC treatment group ($P = .067$; Table S6).

The need for anti-lymphocyte antibody therapy was significantly greater in the bleselumab + MMF treatment group compared with the SoC treatment group at month 6 ($P = .0379$) and month 36 ($P = .0286$; Table S7). The need for anti-lymphocyte antibody therapy was not significantly different between the bleselumab + IR-TAC and SoC treatment groups at month 6 and month 36.

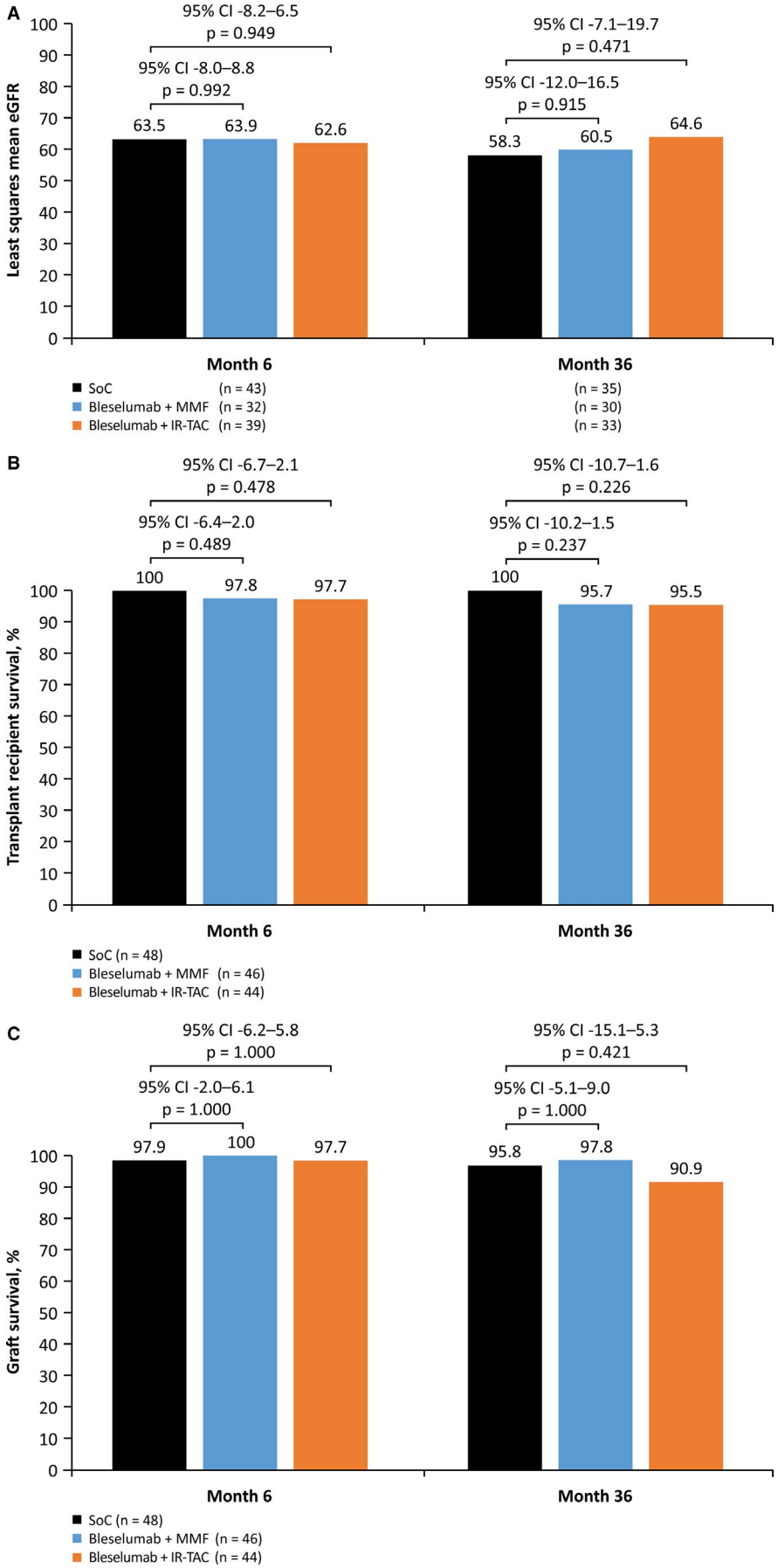

FIGURE 4 A, Estimated glomerular filtration rate. B, Patient survival. C, Graft survival (FAS). CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; IR-TAC, immediate-release tacrolimus; MMF, mycophenolate mofetil; SoC, standard of care

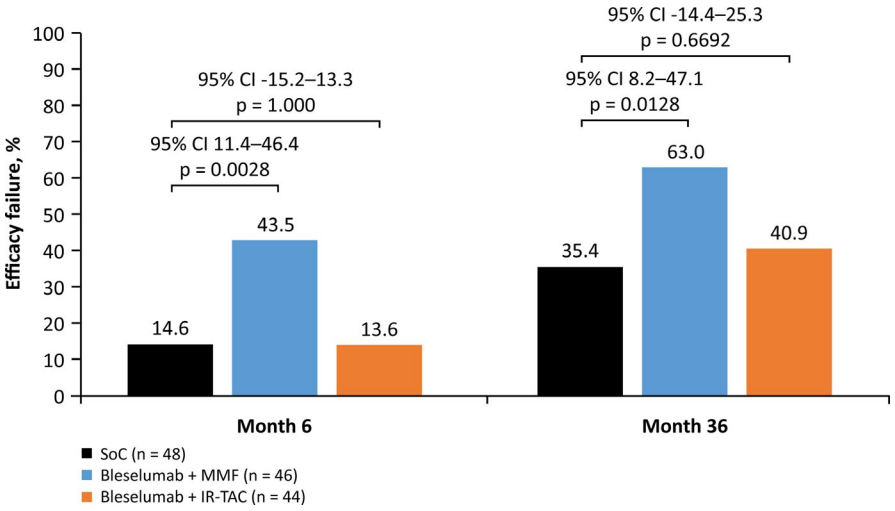

FIGURE 5 Efficacy failure. Efficacy failure was defined as death, graft loss, any BPAR, or lost to follow-up. BPAR, biopsy-proven acute rejection; CI, confidence interval; IR-TAC, immediate-release tacrolimus; MMF, mycophenolate mofetil; SoC, standard of care

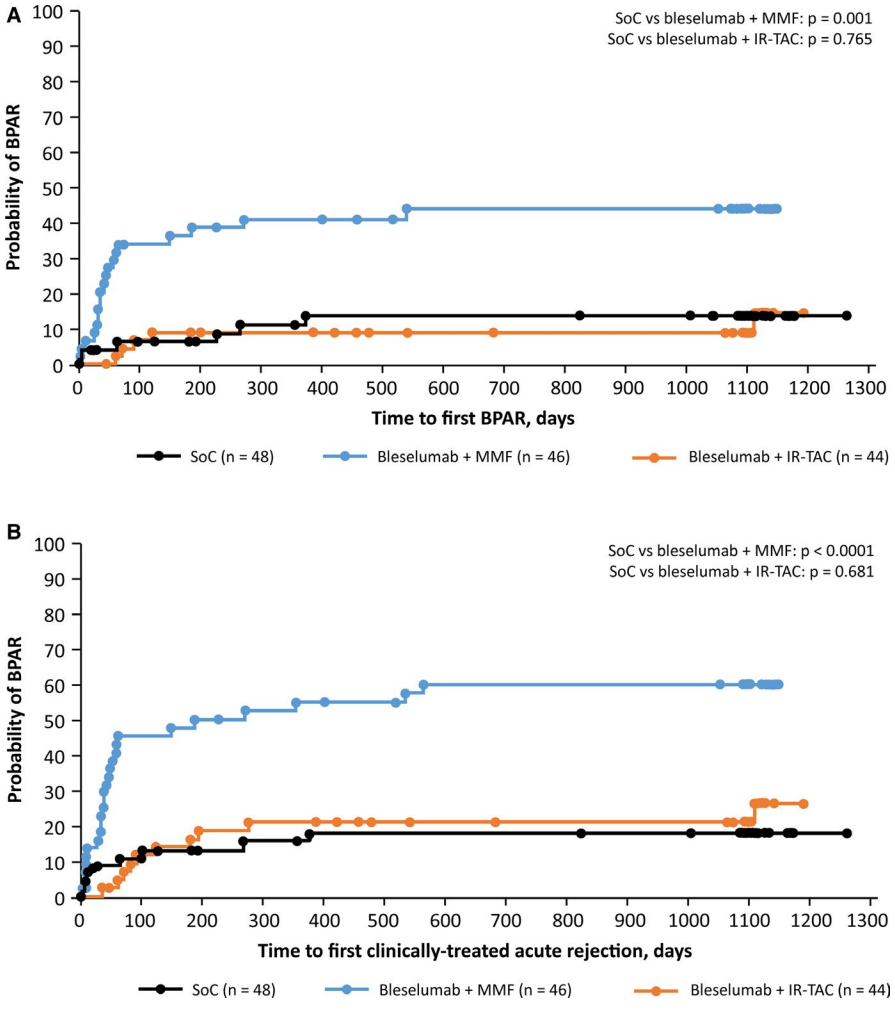

FIGURE 6 A, Time to first biopsy-proven acute rejection (FAS). B, Time to first clinically treated acute rejection. BPAR, biopsy-proven acute rejection; FAS, full analysis set; IR-TAC, immediate-release tacrolimus; MMF, mycophenolate mofetil; SoC, standard of care

3.5 | Safety

Overall, 138 patients (99.3%) reported at least 1 TEAE during the 6 months posttransplant (Tables 2 and S8). The most commonly reported TEAEs were procedural pain (n = 77 [55.4%]), constipation (n = 75 [54.0%]), nausea (n = 64 [46.0%]), hypomagnesemia (n = 57 [41.0%]), and hypophosphatemia (n = 56 [40.3%]). SAEs were reported by 108 patients (77.7%) during the 36 months posttransplant. The most commonly reported SAEs were BK virus infection (n = 16 [11.5%]), acute renal failure (n = 15 [10.8%]), and complications of kidney transplant (n = 13 [9.4%]). Drug-related adverse events (DRAEs) were reported by 106 patients (76.3%). The incidence of

TABLE 2 Summary of TEAEs (6 months and LTE period[a]; SAF)

Number of patients (%)	SoC (n = 49)	Bleselumab + MMF (n = 46)	Bleselumab + IR-TAC (n = 44)	Bleselumab total (n = 90)
Any TEAEs through month 6	48 (98.0)	46 (100)	44 (100)	90 (100)
SAEs through month 36	32 (65.3)	42 (91.3)	34 (77.3)	76 (84.4)
DRAEs through month 6	34 (69.4)	36 (78.3)	36 (81.8)	72 (80.0)
Related to bleselumab	NA	32 (69.6)	31 (70.5)	63 (70.0)
Related to tacrolimus	29 (59.2)	3 (6.5)	32 (72.7)	35 (38.9)
Related to MMF	31 (63.3)	30 (65.2)	NA	30 (33.3)
Related to basiliximab	7 (14.3)	19 (41.3)	9 (20.5)	28 (31.1)
TEAEs leading to permanent discontinuation of study drug through month 6	0	22 (47.8)	15 (34.1)	37 (41.1)
Clusters of TEAEs through month 6[a]				
GI disturbances	43 (87.8)	36 (78.3)	36 (81.8)	72 (80.0)
Constipation, nausea, diarrhea, vomiting, or dyspepsia	42 (85.7)	35 (76.1)	36 (81.8)	71 (78.9)
Constipation, diarrhea, ileus, or gastroenteritis	37 (75.5)	29 (63.0)	25 (56.8)	54 (60.0)
Renal events	31 (63.3)	26 (56.5)	28 (63.6)	54 (60.0)
Nausea, vomiting, dyspepsia, gastroesophageal reflux disease, dysphagia, gastritis, or *Helicobacter* gastritis	31 (63.3)	22 (47.8)	24 (54.5)	46 (51.1)
Anemia, leukopenia, or neutropenia	21 (42.9)	29 (63.0)	16 (36.4)	45 (50.0)
Opportunistic infections	20 (40.8)	18 (39.1)	24 (54.5)	42 (46.7)
Glucose abnormality	27 (55.1)	24 (52.2)	17 (38.6)	41 (45.6)
Viral and fungal infections	22 (44.9)	17 (37.0)	24 (54.5)	41 (45.6)
Neurotoxicity	18 (36.7)	16 (34.8)	12 (27.3)	28 (31.1)
BK infection	14 (28.6)	9 (19.6)	16 (36.4)	25 (27.8)
Cardiac	15 (30.6)	14 (30.4)	11 (25.0)	25 (27.8)
Hepatic events	6 (12.2)	11 (23.9)	13 (29.5)	24 (26.7)
Urinary tract infections	13 (26.5)	10 (21.7)	13 (29.5)	23 (25.6)
Hypertension	10 (20.4)	12 (26.1)	10 (22.7)	22 (24.4)
Diarrhea	21 (42.9)	10 (21.7)	10 (22.7)	20 (22.2)
Upper GI complex	9 (18.4)	6 (13.0)	9 (20.5)	15 (16.7)
Dyspepsia	8 (16.3)	6 (13.0)	8 (18.2)	14 (15.6)
Abdominal distension, abdominal pain, abdominal pain lower, abdominal discomfort, abdominal pain upper, or GI hemorrhage	9 (18.4)	9 (19.6)	4 (9.1)	13 (14.4)
Cardiovascular	5 (10.2)	8 (17.4)	5 (11.4)	13 (14.4)
CMV	4 (8.2)	7 (15.2)	6 (13.6)	13 (14.4)
Respiratory tract infections	12 (24.5)	8 (17.4)	4 (9.1)	12 (13.3)
Malignancy	2 (4.1)	3 (6.5)	6 (13.6)	9 (10.0)
GI pain/discomfort	9 (18.4)	5 (10.9)	3 (6.8)	8 (8.9)
Lipids	5 (10.2)	5 (10.9)	3 (6.8)	8 (8.9)
Gastroenteritis	4 (8.2)	1 (2.2)	0	1 (1.1)

CMV, cytomegalovirus; DRAE, drug-related adverse event; GI, gastrointestinal; IR-TAC, immediate-release tacrolimus; LTE, long-term extension; MMF, mycophenolate mofetil; NA, not applicable; SAE, serious adverse event; SAF, safety analysis set; SoC, standard of care; TEAEs, treatment-emergent adverse event.

[a]Clusters of TEAEs were determined based on the investigator-reported terms after the study was completed.

TABLE 3 Potentially clinically significant liver enzymes and total bilirubin (SAF)

Number of patients (%)					
Parameter	**Criteria[a]**	**SoC (n = 49)**	**Bleselumab + MMF (n = 46)**	**Bleselumab + IR-TAC (n = 44)**	**Bleselumab total (n = 90)**
ALT	>3 × ULN[b]	7/48 (14.6)	10 (21.7)	6 (13.6)	16 (17.8)
	>5 × ULN[b]	4/48 (8.3)	6 (13.0)	3 (6.8)	9 (10.0)
AST	>3 × ULN[b]	3/48 (6.3)	1 (2.2)	4 (9.1)	5 (5.6)
	>5 × ULN[b]	2/48 (4.2)	1 (2.2)	3 (6.8)	4 (4.4)
ALT or AST	>3 × ULN[b]	7/48 (14.6)	10 (21.7)	6 (13.6)	16 (17.8)
Total bilirubin	>2 × ULN[b]	0/48	0	1 (2.3)	1 (1.1)
ALP	>1.5 × ULN	7/48 (14.6)	10 (21.7)	13 (29.5)	23 (25.6)
ALP or AST and total bilirubin	>3 × ULN and >2 × ULN[b]	0/48	0	0	0

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IR-TAC, immediate-release tacrolimus; MMF, mycophenolate mofetil; SAF, safety analysis set; SoC, standard of care; ULN, upper limit of normal.
[a]Thresholds as defined by local laboratory normal ranges. For each patient, the worst value among all postbaseline measurements was used.
[b]Patients requiring additional liver safety monitoring.

DRAEs was higher in the bleselumab + MMF (n = 36 [78.3%]) and bleselumab + IR-TAC (n = 36 [81.8%]) treatment groups compared with the SoC treatment group (n = 34 [69.4%]). TEAEs led to treatment discontinuation in 37 (26.6%) cases, mostly in the bleselumab + MMF treatment group (n = 22 [47.8%]; Table S9). Kidney transplant rejection was the most common adverse event leading to study discontinuation in the bleselumab + MMF group (n = 17/22 [77.3%]). There were 4 deaths during the study: 2 in the bleselumab + MMF treatment group (1 cardiac arrest on day 3 and 1 unknown cause on day 517 posttransplant) and 2 in the bleselumab + IR-TAC group (1 case of sepsis on day 44 posttransplant, possibly related to IR-TAC, and 1 unknown cause on day 420 posttransplant).

After 6 months of treatment, safety events clustered under the term "hepatic events" occurred more commonly in the bleselumab + MMF (n = 11 [23.9%]) and bleselumab + IR-TAC (n = 13 [29.5%]) groups compared with the SoC treatment group (n = 6 [12.2%]). No patients had both elevations in ALT or AST >3 × ULN and total bilirubin >2 × ULN. All patients with elevated levels of liver enzymes had additional liver safety monitoring until liver function tests returned to, or approached, normal levels (Table 3).

During the 6 months posttransplant, BK virus infection occurred more frequently in the bleselumab + IR-TAC treatment group (n = 12 [27.3%]) compared with the SoC (n = 6 [12.2%]) and bleselumab + MMF (n = 7 [15.2%]) treatment groups. In a post-hoc analysis of peak BK viral load in patients in the SAF, serum BK viral loads were significantly greater in the bleselumab + IR-TAC group compared with the SoC group (P = .006), while there were no significant differences between the bleselumab + MMF group and the SoC group. There were no statistically significant differences in urine BK viral loads between either of the bleselumab groups and the SoC group. There were also no differences between the treatment groups for BK virus–associated nephropathy during the 6 months posttransplant (SoC [n = 1 (2.0%)]; bleselumab + MMF [n = 1 (2.2%)]; bleselumab + IR-TAC [n = 1 (2.3%)]).

Malignancies occurred more frequently in the bleselumab + IR-TAC treatment group (n = 6 [13.6%]) compared with the SoC (n = 2 [4.1%]) and bleselumab + MMF (n = 3 [6.5%]) treatment groups; the malignancies were the following: SoC group (n = 2), renal cell carcinoma on day 667 and squamous cell carcinoma on day 977; bleselumab + MMF group (n = 3), basal cell carcinoma on day 831, squamous cell carcinoma on day 194 plus lung neoplasm malignant on day 627, renal cell carcinoma on day 43; bleselumab + IR-TAC group (n = 6), basal cell carcinoma plus squamous cell carcinoma of skin on day 398, basal cell carcinoma on day 301, polycythemia vera on day 256, non–small cell lung cancer stage IV on day 482, pancreatic carcinoma on day 422, and squamous cell carcinoma of skin on day 117. There were no events of posttransplant lymphoproliferative disorder in this study.

3.6 | IR-TAC levels

Mean tacrolimus dose and C_{trough} levels were similar in the SoC and bleselumab + IR-TAC groups through day 28, and were generally maintained in the range of 4-11 ng/mL (Figure 7). In the bleselumab + IR-TAC treatment group, a tacrolimus target C_{trough} of 2-5 ng/mL was specified from day 31 onwards; in this group, mean IR-TAC dose per visit decreased after day 28, but mean IR-TAC C_{trough} levels decreased slowly and only reached the targeted 2-5 ng/mL at month 4; this target level was then sustained for the rest of the study.

4 | DISCUSSION

In this study, treatment with bleselumab + IR-TAC demonstrated noninferiority compared with SoC treatment for the prevention of BPAR in kidney transplant recipients at months 6 and 36. Treatment with bleselumab + MMF did not meet the noninferiority criteria when compared with SoC at month 6 or 36, and demonstrated a greater incidence of BPAR compared with bleselumab + IR-TAC at months 6 and 36. Early BPARs did not appear to have a negative impact on kidney function or survival, regardless of the grade of rejection. One patient in each of the bleselumab + IR-TAC and SoC

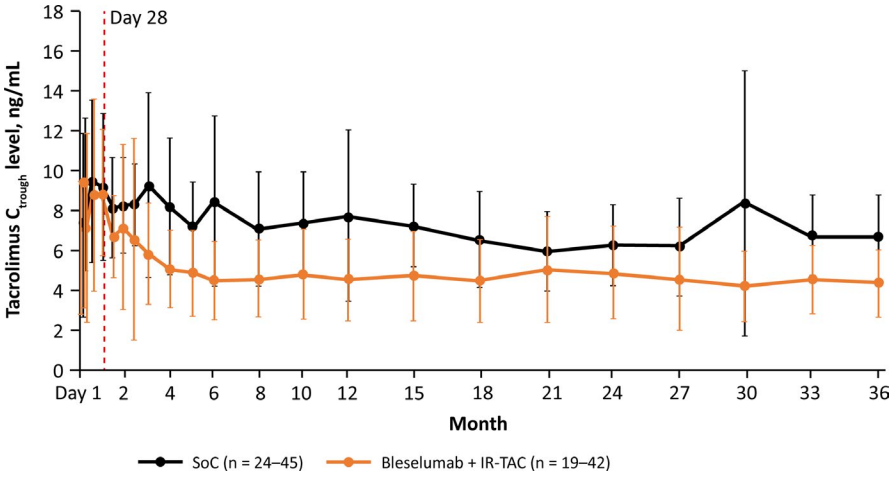

FIGURE 7 Tacrolimus C_{trough} levels during the 36 months posttransplant. C_{trough}, minimum blood concentration; IR-TAC, immediate-release tacrolimus; SoC, standard of care

groups with a BPAR completed <24 months of the study, and 8 of 19 subjects who had a BPAR in the bleselumab + IR-TAC group completed <6 months (n = 2) or between 12 and 36 months (n = 6) of the study. Complete follow-up of patients in the bleselumab + MMF group may have shown an impact on kidney function and survival in this group. There were no differences in eGFR between either of the bleselumab groups and the SoC group at month 6 or 36. However, there were patients who discontinued the study, notably before month 36 in the bleselumab + MMF group, meaning that estimates of eGFR are subject to ascertainment bias.

Overall, bleselumab had a favorable benefit–risk ratio, with few transplant recipients experiencing TEAEs that are not commonly observed in kidney transplant recipients receiving immunosuppressive therapies, such as MMF or IR-TAC.[21,22] During this study there were no thromboembolic events deemed related to bleselumab, such as those reported with other anti-CD40 compounds.[15] Instances of clinically significant liver enzyme changes did occur, which is consistent with other monoclonal antibodies.[23] The incidence of DSAs was low, and there were no statistically significant differences in the incidence of NODAT between groups. It should be noted that the definition of NODAT used in this study was stringent and very inclusive, resulting in a relatively high, but similar, incidence in all groups. There was a trend of higher incidences of some infectious complications, such as CMV and BK virus infections, in patients treated with bleselumab vs SoC. A post-hoc analysis demonstrated that serum BK viral loads were significantly greater in the bleselumab + IR-TAC group compared with the SoC group (P = .006). These patients may be at an increased risk of BK virus nephropathy and may require a modified immunosuppression regimen until their BK virus titers are undetectable.

To minimize calcineurin inhibitor-associated adverse events, this study sought to decrease IR-TAC C_{trough} levels to 4-11 ng/mL in the SoC group, and to 2-5 ng/mL in the bleselumab + IR-TAC group. A limitation of this study was that the target IR-TAC C_{trough} levels in the bleselumab + IR-TAC group were not achieved until month 4, which could be attributed to the investigators' familiarity with customary tacrolimus doses and the associated positive efficacy, meaning that they were hesitant to decrease the IR-TAC dose early posttransplant. It is possible that the negative effects of higher IR-TAC levels limited the identification of a positive effect on eGFR. The achievement of noninferiority of the bleselumab + IR-TAC regimen, which utilized low-dose IR-TAC, vs the SoC regimen for the prevention of BPAR, provides impetus for further study. As the quality of transplanted kidneys declines over time as the population ages, kidneys from donors with diabetes mellitus, hypertension, and other illnesses that decrease kidney function are increasingly being used for transplantation. Maintenance of an adequate eGFR by avoiding the negative effects of high-dose calcineurin inhibitors could be key to maximizing the duration of sufficient kidney function.

In conclusion, treatment with bleselumab + IR-TAC demonstrated noninferiority compared with the SoC for the prevention of BPAR in kidney transplant recipients at month 6 and at month 36. The incidence of efficacy failure was significantly greater in the bleselumab + MMF treatment group compared with the SoC treatment group, and was similar in the bleselumab + IR-TAC and SoC treatment groups.

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DISCLOSURE

Robert C. Harland, Goran Klintmalm, Stephen Jensik, Harold Yang, and Jonathan Bromberg have no conflicts of interest to disclose. John Holman was employed by Astellas Pharma Global Development, Inc. during the conduct of this study. Anil Kumar, Vicki Santos, Tami Jo Larson, and Xuegong Wang are employees of Astellas Pharma Global Development, Inc.

DATA AVAILABILITY STATEMENT

Studies conducted with product indications or formulations that remain in development are assessed after study completion to determine whether Individual Participant Data can be shared. The plan to share Individual Participant Data is based on the status of product approval or termination of the compound, in addition to other study-specific criteria described on www.clinicalstudydatarequest.com under "Sponsor Specific Details for Astellas."

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SUPPORTING INFORMATION

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

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