STATISTICAL ANALYSIS PLAN

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A Phase 2a, Randomized, Open-Label, Active Control, Multi-Center Study to Assess the Efficacy and Safety of Bleselumab in Preventing the Recurrence of Focal Segmental Glomerulosclerosis in de novo Kidney Transplant Recipients

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ABO	Blood group system (A, AB, B, O)
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APGD	Astellas Pharma Global Development, Inc.
AST	Aspartate aminotransferase (SGOT)
BKV	BK virus
BKVAN	BK virus associate nephropathy
BPAR	Biopsy-proven acute rejection
BUN	Blood urea nitrogen
CD	Cluster of differentiation
C_{max}	Maximum concentration
CMV	Cytomegalovirus
CNS	Central nervous system
cPRA	Calculated panel reactive antibody
DCD	Donation after cardiac death
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
EBV	Epstein-Barr virus
ECD	Extended Criteria Donor
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of Treatment
EQ-5D-5L	European quality of life – 5 dimensions – 5 levels
ESRD	End stage renal disease
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
GSD	Geometric Standard Deviation
HBV	Hepatitis B Virus
HbsAg	Hepatitis B surface Antigen
HBc	Hepatitis B core (antigen)
HBcAb IgM	Hepatitis B core antibody IgM
HCV	Hepatitis C Virus
HLA	Human Lymphocyte Antigen
hx	history
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
IRT	Interactive response technology
LA-CRF	Liver abnormality case report form
LDH	Lactate dehydrogenase

Abbreviations	Description of abbreviations
LFT	Liver function test
KTQ	Kidney transplant questionnaire
MDRD	Modification of Diet in Renal Disease
MMF	Mycophenolate mofetil
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NODAT	New Onset of Diabetes after Transplant
PKAS	Pharmacokinetic analysis set
PTLD	Post-transplant lymphoproliferative disorder
rFSGS	Recurrent focal segmental glomerulosclerosis
SAE	Serious adverse event
SAF	Safety analysis set
SOC	Standard of Care
SOC	System Organ Class
TBL	Total bilirubin
TLF	Tables, listings and figures
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

List of Key Terms

Terms	Definition of terms
Assigned Treatment Regimen	Arm 1 - Standard of Care regimen (basiliximab induction, tacrolimus, steroids and mycophenolate mofetil [MMF]). Arm 2 – Bleselumab regimen (basiliximab induction, tacrolimus, steroids and bleselumab). In this study, when a subject permanently discontinues or replaces any treatment within in the assigned regimen, he/she has reached end of treatment (EOT). See EOT term.
Baseline	Time when 'baseline' parameters are observed. The last protocol-defined assessment prior to first dose of study drug in the assigned treatment regimen (Days -21 to -1, prior to transplant) is considered the baseline measurement unless otherwise indicated.
Biopsy-Proven Acute Rejection	Acute rejection episode of which the diagnosis is supported by renal allograft histologic evaluation.
Clinically Treated Acute Rejection	Any acute rejection episode that is treated with supplemental immunosuppressive agents.
De novo	First line therapy after kidney transplantation. This differentiates the "de novo" transplant recipient from a stable transplant recipient that is converted from one regimen to another (conversion study).
End of Study (EOS)	End of study (EOS) for each subject has occurred when the final, protocol-defined assessment has been completed. The last protocol-defined assessment is approximately 30 days after the last study drug dose. If a subject permanently discontinues with the assigned treatment regimen AND discontinues participation in the study, he/she is considered to have reached EOS.
Electronic Patient Reported Outcomes (ePRO)	An electronic patient-reported outcome (ePRO) is a patient-reported outcome that is collected by electronic methods. In this study these include the EQ-5D-5L, the KTQ and the SF-36.
End of Treatment (EOT)	Subjects that permanently discontinue or replace bleselumab, tacrolimus or MMF in the post-transplant period will be considered to have reached End of Treatment (EOT) and are to continue with the protocol-defined visit schedule (Table 1: Schedule of Assessments – Screening through 12 months Post-Transplant), for the collection of safety and clinical assessment information.

Terms	Definition of terms
Enroll	The point in time when a subject signs the informed consent.
Intervention	The drug, device, therapy or process under investigation in a clinical trial which has an effect on outcome of interest in a study (e.g., health-related quality of life, efficacy and/or safety).
Hepatic enzymes	Also called liver enzymes: Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP).
Liver Function Test	Liver Function Test Includes aspartate aminotransferase, (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and Bilirubin
Post-transplant Period	Period of time starting on the day of Transplant (Day 0/post-skin closure) through visit 20/month 12 when a subject is on the assigned treatment regimen and fully participating in the study.
Randomization	Action to allocate a subject to the treatment group or treatment cohort. Randomization is to occur after consent has been obtained and the subject has met entry criteria, but prior to giving initial dose of study drug in any assigned treatment regimen.
Screening	The process for identifying a candidate for the study and for evaluation of his/her eligibility to participate in the study.
Screen failure	A subject who signs the informed consent and undergoes the protocol-specific screening procedures, but does not fulfill the protocol inclusion and/or exclusion criteria. This subject should not be randomized.
Screening Period	The period of time after a subject is enrolled (signs the informed consent form) until randomization (assigned to a treatment regimen).
Study period	The study will consist of the following study periods: screening, transplant and post-transplant. The entire Study Period includes the time from screening (visit 1/Days -21 to 0) through post-transplant (visit 20/month 12).

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP is finalized and signed prior to any of the following: study unblinding, database hard lock, interim analysis, or accumulation of substantial amount of data in an open-label study to ensure lack of bias.

This statistical analysis is coordinated by the responsible biostatistician of Astellas Development Data Science - US. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review of data and TLFs meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database hard lock.

2 FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart

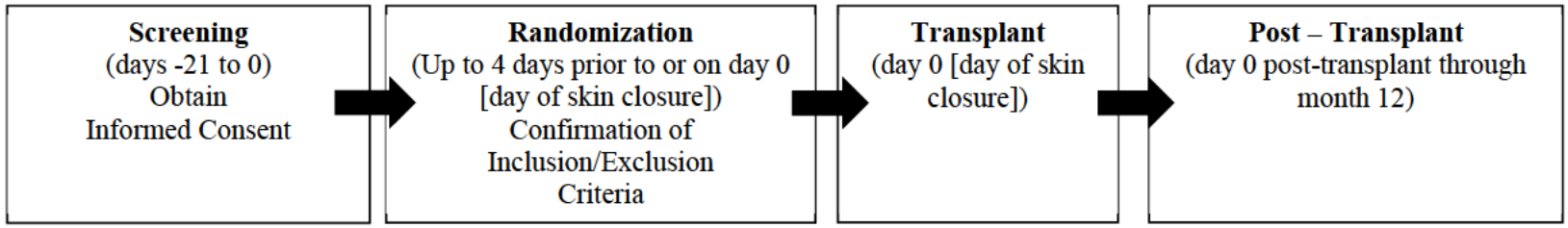


Table 1 Schedule of Assessments– Screening Through 12 Months Post-Transplant

Period	Screening	Transplant	Post-Transplant																		
Visit	1[1]	**2[1]**	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21/EOS[2]
Day	-21 to -1	**0[3]**	1	4	7	14	28	42	56	70	90										
Week	-3 to 1	**1**	1	1	1	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
Month		**1**	1	1	1	1	1	2	2	3	3	4	5	6	7	8	9	10	11	12	12
Visit Window (days)	none	**none**	0	-1	±1	±1	±2	±2	±2	±2	±2	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7
ASSESSMENTS																					
Informed consent	X																				
Demographics	X																				
Physical examination [4]	X										X										X
Height and weight [5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (body temperature, BP and HR)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical/surgical history [4, 6]	X																				
Medication history and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray	X										X										X
Electrocardiogram	X										X										X
Histocompatibility and cross match	X																				
Pregnancy test [7]	X						X		X		X	X	X	X	X	X	X	X	X	X	X
Laboratory tests (hematology, biochemistry and urinalysis) [8]	X		X	X	X	X	X		X		X	X	X	X							X
Laboratory tests – hematology panel and hepatic profile [8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transplant information [9]		X																			
Verify eligibility criteria	X																				
Randomization [10]		X																			
Bleselumab dosing [11]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Sampling for pharmacokinetics [12]		X			X	X	X	X	X	X	X			X			X				X
Anti-bleselumab antibody sampling [12]		X				X	X				X			X			X				X

Table continued on next page

Period	**Screening**	**Transplant**	**Post-Transplant**																		
Visit	1[1]	**2[1]**	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21/EOS[2]
Day	-21 to -1	**0[3]**	1	4	7	14	28	42	56	70	90										
Week	-3 to 1	**1**	1	1	1	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
Month		**1**	1	1	1	1	1	2	2	3	3	4	5	6	7	8	9	10	11	12	12
Visit Window (days)	none	**none**	0	-1	±1	±1	±2	±2	±2	±2	±2	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7
ASSESSMENTS																					
Bleselumab bi-specific antibody sampling [12]		X									X			X			X				X
Auto-Anti-CD40 antibody sampling [12]	X	X			X	X	X		X		X			X			X				X
Urine protein-creatinine [13]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine albumin-creatinine [13]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tacrolimus level [14]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sampling for pharmacogenomics [15]	X																				
Clinical assessment [16]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SF-36s [17]	X					X					X			X							X
EQ-5D-5L [18]	X										X										X
KTQ [19]	X					X					X			X							X
Adverse events [20]	X	**X**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biopsy [21]											X										

EOT = End of Treatment - If bleselumab is permanently discontinued, subjects in Arm 2 can continue to receive study-supplied Prograf through 12 months post-transplant as previously assigned; however, any alternate therapy(ies) will not be provided by the Sponsor. Furthermore, subjects that permanently discontinue or replace bleselumab, tacrolimus, or MMF in the post-transplant period will be considered to have reached EOT and are to continue with the protocol-defined visit schedule for the collection of safety and clinical assessment information. If a subject declines to be followed upon permanently discontinuing bleselumab, tacrolimus or MMF, the end of study (EOS, visit 21/month 12) procedures are to be completed within 30 days post-last dose.

EOS = End of Study (visit 21/month 12). EOS for each subject has occurred when the final, protocol-defined assessment has been completed. The last protocol defined assessment is approximately 30 days after the last study drug dose. If a subject discontinues with the assigned treatment regimen **AND** discontinues participation (withdraws consent) in the study, he/she is considered to have reached EOS.

Footnotes appear on the next page

ABO: absent bed occupant blood group system (A, AB, B and O); AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BKV: BK polyomavirus; BP: blood pressure; BUN: blood urea nitrogen; CD40: cluster of differentiation 40; CMV: cytomegalovirus; CPK: creatine phosphokinase; EBV: Epstein-Barr virus; EQ-5D-5L: European Quality of Life-5 Dimensions–5 Levels; HBcAb IgM (or Anti-HBc IgM): hepatitis B core antibody IgM; HbsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HDL: high-density lipoprotein; INR: international normalized ratio; KTQ: Kidney Transplant Questionnaire; LDH: lactate dehydrogenase; LDL: low-density lipoprotein; HDL: high density lipoprotein; MMF: mycophenolate mofetil; PR: pulse rate; PRA: panel reactive antibodies; rFSGS: recurrence of focal segmental glomerulosclerosis; RBC: red blood cells; SAE: serious adverse event; SF-36s: Short Form 36-Item Health Survey Score; WBC: white blood cells.

1. Visits 1 (screening [days -21 to -1]) and 2 (day 0/transplant) can be combined as one.
2. Also unscheduled visit. Unscheduled visit assessments to be conducted are at the discretion of the Investigator. Urine protein-creatinine and urine albumin-creatinine must be collected at all unscheduled visits.
3. The day of Transplant (day 0) is day/date of transplant completion (skin closure). For transplants that span midnight, assessments may be conducted on day -1.
4. The screening physical examination includes significant, ongoing medical conditions. Any changes between screening and Randomization are to be captured in the Medical/Surgical History.
5. Height will be measured one time at screening ONLY. Weight will be collected AT ALL VISITS.
6. Medical/Surgical history includes: diagnosis for renal failure, duration and severity of renal disease at Randomization, and Screening medications (30 days prior to Transplant).
7. Serum pregnancy test at screening is to be collected on admission to the hospital or within 7 days prior to transplant. All subsequent urine pregnancy tests are to be collected prior to continued treatment.
8. Laboratory tests –

   ABO blood-typing at screening ONLY.

   Coagulation/thrombotic pathway (prothrombin time, activated partial thromboplastin time, INR). Lipid profile (total cholesterol [including LDL, HDL and triglycerides]).

   Hematology includes: hemoglobin, hematocrit, RBC, WBC with differential and bands (where available), and platelet count. Biochemistry includes: phosphorous, total protein, serum creatinine, BUN, albumin, CPK, LDH, amylase, electrolytes (sodium, potassium, calcium, magnesium, bicarbonate, chloride), and fasting glucose.

   The Hematology panel and Hepatic profile (total bilirubin, direct bilirubin, AST, ALT and ALP) are to be collected at EVERY visit. For subjects not making urine at screening, urinalysis for BKV will not be required.

   Recipient viral serologies (i.e., antibodies [e.g., HBV, HCV, CMV and EBV]) performed > 1 year prior to transplant are to be repeated within the screening period (up to 21 days prior to transplant). Results do not need to be available for randomization. Post-screening testing is to be conducted at day 90/month 3 and month 12/EOS.

   If HBsAg is positive, HBcAb IgM and envelope (HBe) antigens are to be analyzed. If the subject has previously been tested for antibodies to HBsAg and the results are positive, then HBsAg testing does not need to be repeated at screening.

   If HCV is positive, quantitative HCV ribonucleic acid is to be analyzed. If the screening results indicate the presence of antibodies, no further testing is required during the study. If the screening results are negative, testing needs to be repeated at day 90/month 3 and month 12/EOS.

   Recipient viral load testing (CMV, BKV [serum an urine] and EBV) is to be conducted at screening, days 14, 28, 56 and 90/month 3, and months 4, 5, 6 and 12/EOS, ONLY if recipient viral serologies were positive at any time.

Footnotes appear on the next page

9. Transplant information to be collected includes: donor demographics (age, sex, race), donor viral serology (HBV, HCV, CMV and EBV, if available), type of transplant (living related, living non-related, or deceased donor), total ischemia time, length of surgery, and most recent PRA results prior to transplant. A copy of the donor kidney biopsy report is to be collected where available.
10. Randomization will occur once subject has met ALL entry criteria and prior to initial dose of study drug. Randomization should occur on day 0, or the day prior to skin closure, but not more than 4 days prior to transplant start.
11. Bleselumab dosing is to be initiated on day 0 (intravenous intra-operatively and prior to revascularization of the allograft) and may continue during reperfusion; days 7, 14, 28, 42, 56, 70 and 90/month 3, and once per month through month 12/EOS as a single, 30-minute infusion.
12. **SUBJECTS IN ARMS 1 AND 2**

    Auto-anti-CD40 antibody samples are to be collected at screening, and prior to each infusion at baseline (day 0), visit days 7, 14, 28, 56, 90/month 3, and months 6, 9 and 12/EOS.

    SUBJECTS IN ARM 2 ONLY

    Pharmacokinetic (bleselumab blood concentration) samples are to be collected within 30 minutes or less pre-initial, and post-initial, intraoperative, bleselumab infusion at baseline (day 0). Two single, pharmacokinetic samples are to be collected at each subsequent 30-minute intravenous infusion: one within 30 minutes or less prior to the infusion (trough concentration), and the other at the end of the infusion (peak concentration) up through visit day 28. After that only trough concentrations (within 30 minutes or less pre-infusion) are to be collected up through day 90/month 3, and months 6, 9 and 12/EOS visits.

    Anti-bleselumab antibody samples are to be collected prior to each infusion at baseline (day 0), visit days 14, 28, 90/month 3, and months 6, 9, and 12/EOS.

    Bleselumab bi-specific antibody samples are to be collected prior to each infusion at baseline (day 0), visit day 90/month 3, and months 6, 9, and 12/EOS..
13. Urine collection via a spot urine is to occur within 72 hours prior to transplant.
14. Whole blood trough samples are to be drawn 11 - 13 hours' post-initial tacrolimus dose and immediately prior to all subsequent doses.
15. Sample to be collected one time, preferably prior to first dose on day 0; however, can be collected any time during the study.
16. Clinical assessment is to include: BPAR, clinically-treated acute rejection episodes, graft and patient survival, and rFSGS.
17. SF-36s, version 2.0. Subjects are to complete the questionnaire at screening, days 14 and 90/month 3, and months 6 and 12/EOS
18. EQ-5D-5L. The baseline EQ-5D-5L is to be completed by the subject at screening (or at any visit up through day 10) and 90/month 3, and month 12/EOS.
19. KTQ. Subjects are to complete the KTQ at screening, days 14 and 90/ month 3, and months 6 and 12/EOS.
20. All AEs will be recorded from the time of consent through 30 days post-last dose. The transplantation that occurs on day 0 is not considered an AE or an SAE. Planned surgical procedures such as removal of venous catheter or peritoneal catheter, post-transplant, are not considered an AE or an SAE.
21. All subjects who have not had a biopsy with a diagnosis of rFSGS by 3 months post- transplant will have a protocol-defined biopsy at the day 90/month 3 visit. There are no other protocol-required biopsies. Biopsies other than the protocol-indicated one at day 90/month 3 will be considered 'for cause' only. All images for electron microscopy (EM) and slides for light microscopy (LM) utilized for local pathological review for evaluation of possible BPAR and/or rFSGS are to be forwarded for a blinded, central review by an independent pathologist to assess (via EM and LM) rFSGS.

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objective(s)

3.1.1 Primary Objective

The primary objective of the study is to assess the efficacy of the bleselumab regimen (basiliximab induction, tacrolimus, steroids and bleselumab) compared with the Standard of Care (SOC) regimen (basiliximab induction, tacrolimus, steroids and mycophenolate mofetil (MMF)) in the prevention of the recurrence of Focal Segmental Glomerulosclerosis (FSGS). FSGS recurrence is defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g) through 3 months post-transplant. Death, graft loss or lost to follow-up will be imputed as recurrent FSGS (rFSGS).

3.1.2 Secondary Objectives

The secondary objectives include:

- To assess the incidence of nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g) through 6 and 12 months' post-transplant. Death, graft loss or lost to follow-up will be imputed as rFSGS.
- To assess the incidence of Biopsy-proven acute rejection (BPAR) (Banff Grade ≥ 1; local read) through 3, 6 and 12 months' post-transplant
- To assess the incidence of efficacy failure defined as BPAR (Banff Grade ≥ 1; local read), death, graft loss or lost to follow-up through 12 months post-transplant
- To assess the incidence of biopsy-proven (blinded, central read) recurrence of FSGS through 3, 6 and 12 months' post-transplant.
- To assess the safety of the bleselumab regimen compared with the SOC regimen

3.1.3 Exploratory Objectives

- To assess graft and patient status through 12 months post-transplant.
- To assess the Glomerular Filtration Rate (GFR, based on Modification of Diet in Renal Disease [MDRD] criteria) through 12 months post-transplant.
- To assess the incidence of FSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g).
- To assess the time to rFSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g).
- To assess the time to rFSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g) or initiation of plasmapheresis.
- To assess the time to rFSGS defined as recurrence of nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g), death, graft loss or lost to follow-up.
- To assess the time to recurrence of biopsy-proven (blinded, central read) FSGS.
- To assess the time to first BPAR (Banff Grade ≥ 1, local read).
- To assess the urine protein-creatinine ratio through 6 and 12 months post-transplant.
- To assess the urine albumin-creatinine ratio through 3, 6 and 12 months post-transplant.
- To assess the change in anti-CD40 autoantibodies from baseline.

- To assess the change in patient-reported outcomes from baseline (Short Form 36-Item Health Survey Score [SF-36s]), European Quality of Life-5 Dimensions-5 Levels [EQ-5D-5L], and Kidney Transplant Questionnaire [KTQ]).

3.2 Study Design

This is a Phase 2a, randomized, open-label, active control, multi-center study to assess the efficacy and safety of bleselumab in preventing the recurrence of FSGS in de novo kidney transplant subjects.

The study will consist of the following periods:

- Screening (Days -21 to -1)
- Transplant (Day 0)
- Post-Transplant (Day 0/post skin closure through 12 months' post-transplant)

Prior to any study-related assessment, the subject will sign the informed consent form (ICF)/authorization (visit 1). All subjects will enter into a screening period (Days -21 to -1 prior to transplant), undergo a transplant (Day 0) and will be followed for up to 12 months in the post-transplant period (Day 0 / post-skin closure through 12 months post-transplant) for efficacy and safety.

Randomization can occur up to 4 days prior to or on Day 0 (prior to transplant). Subjects will be assigned in a 1:1 ratio to open-label treatment of one of two arms as follows:

- Arm 1 - SOC regimen (basiliximab induction, tacrolimus, steroids and MMF)
- Arm 2 – Bleselumab regimen (basiliximab induction, tacrolimus, steroids and bleselumab)

All subjects who have not had a biopsy with a diagnosis of rFSGS by 3 months post-transplant will have a protocol-defined biopsy at the Day 90/month 3 visit. There are no other protocol-defined biopsies. Biopsies other than the protocol-indicated one at Day 90/month3 will be considered 'for cause' only. All episodes of kidney dysfunction based on clinical signs and symptoms will be evaluated for possible BPAR and/or rFSGS. All subjects should have a biopsy confirmation of a rejection episode prior to the initiation of treatment for rejection, or within 48 hours of initiation of treatment for acute rejection. BPAR (T- or B-cell) will be determined via local review at the study center using the 2007 Banff criteria.

All images for electron microscopy (EM) and slides for light microscopy (LM) reviewed by the local pathologist to evaluate possible BPAR and/or rFSGS will be forwarded for a blinded, central assessment of rFSGS by an independent pathologist.

If bleselumab is permanently discontinued, subjects in Arm 2 can continue to receive study-supplied tacrolimus through 12 months post-transplant as previously assigned; however, any alternate therapy (ies) will not be provided by the Sponsor.

Subjects that permanently discontinue bleselumab, tacrolimus or MMF in the post-transplant period will be considered to have reached End of Treatment (EOT) and are to continue with the protocol-defined visit schedule (Table 1, Schedule of Assessments) for the collection of

safety and clinical assessment information. If a subject declines to be followed upon permanently discontinuing bleselumab, tacrolimus or MMF, the End of Study (EOS, visit 20/month 12) procedures are to be completed within 30 days post-last treatment.

Data reviews by an independent Data Monitoring Committee (DMC) were planned as follows for the following time points during the study:

- 50% of the subjects have completed 3 months' post-transplant follow-up
- 100% of the subjects have completed 3 months' post-transplant follow-up
- 100% of the subjects have completed 6 months' post-transplant follow-up.

A separate DMC Charter has been created providing the details and the output needed for each of the reviews.

An interim analysis was planned when all subjects completed 3 months' post-transplant follow-up. The purpose of the interim analysis was to evaluate treatment differences for the recurrence of FSGS to support strategic decision making for future project development and study design. Instead, due to slow enrollment the first 50 subjects transplanted and dosed will be analyzed and the results used to support strategic decisions. The interim analyses that were planned once all 60 subjects completed 3 months of follow-up and 6 months of follow-up will not occur. The final analysis will occur once all subjects have been followed through 12 months.

The first subject was enrolled in May 2017. There are 50 subjects transplanted and dosed as of mid July 2019 with an additional 10 subjects planned. Due to the slow enrollment Astellas and the development partner, Kyowa Kirin Co., Ltd. (KKC) plan to follow these 50 subjects for three months (the time of the primary endpoint), and conduct an interim analysis to evaluate response in the two treatment groups. This interim analysis will serve as the foundation for a Briefing Document to support a Type C meeting with the FDA, if the results merit a go forward decision. TLFs from this interim analysis will be discussed in an open session with the members of the DMC.

3.3 Randomization

Subjects who meet the inclusion criteria and exhibit none of the exclusion criteria will be randomly assigned to receive one of two study treatments using a 1:1 ratio. Randomization will be central with treatment assignments balanced between the two study arms. There will be no stratification by site since an individual site is expected to enroll a small number of subjects; balancing within a site could lead to selection bias. Randomization will be stratified by previous transplant (yes, no). Randomization will be performed via Interactive Response Technology (IRT) from Cenduit LLC.

4 SAMPLE SIZE

The primary aim of this study is to assess the rFSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g) through 3 months post-transplant. Death, graft loss or lost to follow-up will be imputed as rFSGS.

This proof of concept study will provide an estimate of the effect size for the difference in the rFSGS between the standard of care and the experimental group and provide estimates of the recurrence rates for each treatment group. The estimate of the effect size will be needed to plan a future study.

The following table provides a subset of estimates and the 95% confidence interval for the FSGS recurrence rate with 30 subjects per treatment group. The width of these confidence intervals varies between 17% and 36% indicating the limit of the precision for the estimate.

Proportion (%)	95% Confidence Interval with 30 subjects (%)
3.3 (1/30)	0.1 - 17.2*
16.7 (5/30)	3.4 - 30.0
33.3 (10/30)	16.4 - 50.2
50.0 (15/30)	32.1 - 67.9
66.7 (20/30)	49.8 - 83.6
83.3 (25/30)	70.0 - 96.6
96.7 (29/30)	82.8 - 99.9*

*Exact binomial confidence interval using Clopper-Pearson (Exact method based on the Beta distribution); for all others the normal approximation was used to calculate the intervals.

Literature estimates show that the expected FSGS recurrence rate for the SOC group is between 30% and 50% with most occurring by three months post-transplant. Imputing death, graft loss or lost to follow-up as rFSGS is not anticipated to have a sizeable impact on the rFSGS estimates. In a previous study that included two of the treatment arms planned for the current study, there were 4/48 in the SOC group and 3/44 in the ASKP1240 (Bleselumab) +Tac group who experienced death, graft loss or lost to follow-up by 6 months. Literature estimates of rFSGS were used to examine the precision of the treatment difference provided with 30 subjects per treatment group.

Bleselumab was assumed to decrease the recurrence rate in the experimental arm by 20% to 60% relative to SOC. The following table provides the difference in the observed rates and the associated two-sided 95% confidence interval with 30 subjects per group. The width of the confidence interval for the difference between the two treatment groups ranges between 47% and 57%. The width of the confidence interval provides the precision of the estimate for the difference in recurrence between the two groups.

Bleselumab Rate	**SOC Rate**		
	50% (15/30)	**40% (12/30)**	**30% (9/30)**
60% Reduction from SOC	0.20 (6/30)	0.167 (5/30)	0.133 (4/30)
Difference in rates and 95% CI (2-sided)	0.30 0.038 to 0.562	0.233 -0.021 to 0.487	0.167 -0.07 to 0.404
50% Reduction from SOC	0.267 (8/30)	0.20 (6/30)	0.167 (5/30)

Table continued on next page

Bleselumab Rate	SOC Rate		
	50% (15/30)	**40% (12/30)**	**30% (9/30)**
Difference in rates and 95% CI (2-sided)	0.233 -0.039 to 0.505	0.20 -0.06 to 0.46	0.133 -0.112 to .355
40 % Reduction from SOC	0.30 (9/30)	0.267 (8/30)	0.20 (6/30)
Difference in rates and 95% CI (2-sided)	0.20 -0.068 to .434	0.133 -0.137 to 0.40	0.10 -0.151 to 0.351
30% Reduction from SOC	0.367 (11/30)	0.30 (9/30)	0.23 (7/30)
Difference in rates and 95% CI (2-sided)	0.133 -0.149 to 0.415	0.10 -0.173 to 0.373	0.07 -0.186 to 0.326
20 % Reduction from SOC	0.40 (12/30)	0.333 (10/30)	0.267 (8/30)
Difference in rates and 95% CI (2-sided)	0.10 -0.184 to 0.384	0.067 -0.21 to 0.344	0.033 -0.228 to 0.294

5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses. Unless otherwise stated, the Full Analysis Set (FAS) will be used for analysis of efficacy data and the Safety Analysis Set (SAF) will be used for analysis of safety data. The PK Analysis Set (PKAS) will be used for analysis of pharmacokinetic parameters.

5.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) consists of all subjects who are randomized, receive at least one dose of study drug and receive a transplanted kidney. Subjects who enroll in the study and later documentation reveals that the subject does not have primary FSGS, will not be included in the FAS since they are not included in the population of interest, primary FSGS, and are not at risk for recurrence of their primary FSGS. The FAS will be the primary analysis set for efficacy analyses.

5.2 Per Protocol Set (PPS)

No Per Protocol Set (PPS) is planned for this study. However, exploratory analyses excluding certain subjects may be performed if clinically meaningful. These analyses, if performed, are for the purpose of gaining additional insight.

5.3 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) consists of all randomized subjects who received at least one dose of study drug, and will be used for safety analyses. Study drug includes basiliximab, tacrolimus, MMF and bleselumab.

5.4 Pharmacokinetics Analysis Set (PKAS)

The Pharmacokinetics Analysis Set (PKAS) consists of subjects from the SAF who have at least one measurable peak or trough pharmacokinetic concentration. The PKAS will be used for summaries and exploratory analysis of the pharmacokinetic data.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the percentage of subjects who have rFSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g) through 3 months post-transplant. Death, graft loss or lost to follow-up will be imputed as rFSGS. Subjects with a protein-creatinine ratio (≥ 3.0 g/g) on Day 0 only (day of skin closure) will not be considered to have a recurrence if this is the only day with the elevated ratio and subsequent values do not meet this limit. This specification for Day 0 will apply to all rFSGS endpoints.

6.1.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be assessed:

- Recurrence of FSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0g/g) through 6 and 12 months' post-transplant. Death, graft loss or lost to follow-up will be imputed as rFSGS.
- BPAR (Banff Grade ≥ 1, local read) through 3, 6 and 12 months post-transplant.
- Efficacy failure defined as BPAR (Banff Grade ≥ 1; local read), death, graft loss or lost to follow-up through 12 months post-transplant.
- Biopsy-proven (blinded, central read) rFSGS through 3, 6 and 12 months post-transplant.

6.1.2.1 Blinded, Central Read for Recurrence of Focal Segmental Glomerulosclerosis

All episodes of kidney dysfunction based on clinical signs and symptoms will be evaluated for recurrence of FSGS and for possible rejection after exclusion of other causes. A sample of the biopsy will be sent to a central pathology lab and read without knowledge of the subject's treatment regimen by an independent pathologist to determine if FSGS has recurred.

Subjects who have not had a biopsy with a diagnosis of rFSGS by three months post-transplant will have a protocol-defined biopsy at the Day 90 / 3 month visit. If there is an earlier biopsy indicating rFSGS, then the protocol-defined biopsy at 3 months is not required. Biopsies after the protocol-defined biopsy at three months will be for-cause only. There will are no additional protocol-defined biopsies required at 6 and 12 months post-transplant.

6.1.2.2 Biopsy Proven Acute Rejection

All episodes of kidney dysfunction based on clinical signs and symptoms will be evaluated for possible rejection. The pathologist at the clinical site will grade all biopsies using the 2007 Banff criteria (Section 9.1). The date of the first positive biopsy for an event will constitute the start of the BPAR event.

6.1.3 Exploratory Endpoints

The following exploratory endpoints will be assessed:

Efficacy

- Graft and subject status through 12 months' post-transplant
- GFR, based on MDRD criteria through 12 months' post-transplant
- Recurrence of FSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g); there is no imputation for death, graft loss, or lost to follow-up for this endpoint.
- Recurrence of FSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g) or initiation of plasmapheresis.
- Time to rFSGS defined by nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0g/g)
- Time to rFSGS defined by nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0g/g) or initiation of plasmapheresis.
- Time to rFSGS defined by nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0g/g), death, graft loss or lost to follow-up
- Time to biopsy-proven (blinded, central read) rFSGS
- Time to first BPAR (Banff Grade ≥ 1, local read)
- Urine protein-creatinine ratio through 3, 6 and 12 months' post-transplant
- Urine albumin-creatinine ratio through 3, 6 and 12 months' post-transplant
- Change in anti-CD40 auto-antibodies (protocol term: auto-anti-CD40 antibody) from baseline; the anti-CD40 auto-antibodies obtained prior to the first dose of ASKP1240, at screening or on Day 0, will be the baseline value. Anti-CD40 auto-antibodies will be assessed for both treatment groups.
- Change in patient-reported outcomes from baseline (Short Form-36 Item Health Survey [SF-36s], European Quality of Life - 5 Dimensions - 5 Levels [EQ-5D-5L] and Kidney Transplant Questionnaire [KTQ]); baseline will be obtained prior to transplant for all patient reported outcomes.

Safety

- Adverse events (AEs) graded by National Cancer Institute Common Terminology Criteria for Adverse Events criteria (NCI CTCAE)
- Vital sign measurements.
- Clinical laboratory tests.
- Viral serology (hepatitis B virus [HBV], hepatitis C virus [HCV], CMV, BK polyomavirus [BKV] and EBV).

- Viral load testing (CMV, BKV and EBV).
- Anti-bleselumab antibodies.
- Bleselumab bi-specific antibodies
- NODAT (New Onset Diabetes Mellitus after Transplant)
- Bleselumab pharmacokinetics

6.1.3.1 Patient Survival

Patient survival is defined as any subject who does not have a fatal event during the study.

6.1.3.2 Graft Survival

Graft survival is defined as any subject who does not experience graft loss during the study. Graft loss is defined as subject death, re-transplant, nephrectomy, or return to permanent dialysis (greater than 30 days).

6.1.3.3 Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate (eGFR) will be calculated using the Modification of Diet in Renal Disease criteria. eGFR = 186 x Serum Creatinine$^{-1.154}$ x Age$^{-0.203}$ x [1.212 if Black] x [0.742 if Female], where Serum Creatinine is in mg/dL and Age is in integer years at study baseline. Baseline eGFR will be calculated using the serum creatinine obtained on Day 28 post-transplant.

6.1.3.4 Urine Protein-Creatinine Ratio and Urine Albumin-Creatinine Ratio

Urine protein-creatinine ratio and albumin-creatinine ratio, will be summarized by visit and treatment group and compared between treatment groups. Higher values indicate worsening kidney function. These data are usually right-skewed and will be log-transformed to achieve a normal distribution. Values of 0, if any, will have 0.5 added to enable calculation of the log-transformation. The transformed data will be analyzed and back-transformed to provide the summaries.

6.1.3.5 Short Form-36 Item Health Survey

The SF-36 Version 2.0 is a measure of health status. The SF-36 provides scores for each of the eight health domains, a psychometrically-based physical component summary (PCS) and mental component summary (MCS). The eight domains are the weighted sums of questions in their section. Each domain is directly transformed into a 0 -100 scale on the assumption that each question carries equal weight. The higher the score the less disability (i.e., a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability).

Subjects will complete this self-assessment at baseline, Day 14, month 3, 6 and 12/EOS.

6.1.3.6 European Quality of Life - 5 Dimensions - 5 Levels

The EQ-5D-5L is an international standardized non-disease specific (i.e., generic) instrument for describing and valuing health status.

This questionnaire consists of two parts:

- 5-dimensions (EQ-5D-5L): mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each dimension there are 5 levels (i.e., scores 1 to 5) to classify the severity the dimension, ranging from no problems to inability to do things
- VAS, where 0 represents the worst imaginable health state and 100 the best imaginable health state.

For the total VAS Score, change from baseline at Month 3 and 12/EOS will be defined as the Month 3, or Month 12/EOS Visit value minus the baseline value obtained at Screening.

6.1.3.7 Kidney Transplant Questionnaire

The KTQ is a 25-item questionnaire designed specifically for use with kidney transplant patients that includes five domains for subscales (i.e., physical symptoms, fatigue, uncertainty/fear, appearance, and emotional). A mean score ranging from 1 to 7 is reported for each of the five subscales, with higher scores representing better functioning, well-being, or fewer problems [Laupacis et al, 1993].

Subjects are to complete this self-assessment at the baseline, Day 14, month 3, 6 and 12/EOS.

6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAE) by: frequency, severity graded by NCI CTCAE criteria, relationship to bleselumab, relationship to tacrolimus, relationship to MMF, relationship to basiliximab, seriousness, and outcome.
- Vital signs (systolic and diastolic blood pressure, heart rate, oral temperature, height and weight, body mass index)
- Clinical laboratory variables
    - Hematology
    - Biochemistry
    - Coagulation/thrombotic pathway (prothrombin time, activated partial thromboplastin time, INR)
    - Hepatic profile
    - Lipid profile
    - Urine quantitative
    - Urinalysis
    - Pregnancy Testing
- Viral serology (HBV, HCV, CMV, BKV and EBV)
- Viral load testing (CMV, BKV and EBV)
- Anti-bleselumab antibodies, anti-bleselumab neutralizing antibodies
- Bleselumab Bi-specific antibodies
- NODAT (New Onset of Diabetes after Transplant)

6.2.1 Treatment Emergent Adverse Events

TEAE is defined as an adverse event observed after starting administration of bleselumab or MMF. If the adverse event occurs on Day 0 (day of skin closure) and the onset check box is marked “Onset after first dose of study drug” or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 0 and the onset check box is marked “Onset before first dose of study drug”, then the adverse event will not be considered treatment emergent. If a subject experiences an event both during the pre-investigational period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity. All adverse events collected that begin within 30 days after taking the last dose of study drug will also be counted as TEAE.

6.2.2 Anti-bleselumab antibodies, anti-bleselumab neutralizing antibodies and bleselumab bi-specific antibodies

Samples for anti-bleselumab, anti-bleselumab neutralizing and bleselumab bi-specific antibodies will be collected only for subjects treated with bleselumab.

Anti-bleselumab antibody samples are to be collected prior to each infusion at baseline (Day 0), visit Days 14, 28, 90/month 3, and months 6, 9, and 12/EOS. If the antibody sample is positive with a titer, the sample will be tested to determine if it is neutralizing.

Bleselumab bi-specific antibody samples are to be collected prior to each infusion at baseline (Day 0), visit Day 90/month 3, and months 6, 9, and 12/EOS.

6.2.3 Anti CD40 auto-antibody

Anti-CD40 auto-antibodies are present in the serum of rFSGS subjects and pre-transplant elevation of anti-CD40 auto-antibody is reported to be associated with the risk of rFSGS post-transplant. Samples for anti-CD40 auto-antibody will be collected from both treatment groups at screening, and prior to each infusion at baseline (Day 0), visit Days 7, 14, 28, 56, 90/month 3, and months 6, 9 and 12/EOS.

6.3 Pharmacokinetic Variables

Bleselumab samples for trough concentrations (30 minutes or less prior to infusion) will be collected on visit Days 0, 7, 14, 28, 42, 56, 70, 90 and months 6, 9 and 12/EOS. Samples for peak concentrations (at the Bleselumab infusion completion) will be collected on visit Days 0, 7, 14 and 28.

7 STATISTICAL METHODOLOGY

7.1 General Considerations

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. When needed, other percentiles, (10%, 25%, 75% and 90%) will be provided. Frequencies and percentage will be displayed for categorical data by treatment group. Percentages by category will be based on the number of subjects with no missing data. Subjects with missing data will be treated as a separate

category and not included in the denominator, unless specific methods for imputation are stated.

If there are a sufficient number of subjects with a second transplant in each of the treatment groups then the analysis will be modified to include 2nd transplant (yes, no) as a factor or stratification variable. For an analysis of variance (ANOVA) or analysis of covariance (ANCOVA), previous kidney transplantation (no, yes) will be included as a factor in the model if there are a sufficient number of subjects with second transplants. Endpoints analyzed with Fisher's Exact test may be analyzed with a CMH test stratifying by previous kidney transplantation (no, yes) if there are a sufficient number of subjects with second transplants and the outcome does not produce a missing row for the strata of second transplants. For time-to-event endpoints, Cox regression will be used comparing the two treatment groups and will include previous kidney transplantation (no, yes) in the model.

All statistical comparisons will be made using two-sided test at α=0.05 significance level with no adjustments for multiplicity unless specifically stated otherwise. All null hypotheses will be of no treatment difference. All hypotheses testing will be two-sided.

The primary analysis will be the comparison between standard of care regimen (Arm 1) and the bleselumab regimen (Arm 2).

For purpose of data presentation and analyses, Study Day is defined relative to the day of skin closure (Day 0) and unless specifically stated otherwise, the term baseline will refer to the last assessment/evaluation up to and including Day 0.

There is a slight modification for defining Day 0 for patients given Bleselumab intraoperatively on the day prior to the day of skin closure. Subjects may have their transplant surgery initiated before midnight and end after midnight on the next day. Assigning Day 0 as skin closure results in the appearance that study drug was given prior to Day 0. Subjects who are given Bleselumab on the day prior to skin closure with their transplant spanning midnight will have Day 0 defined as the day surgery is initiated.

All data processing, summaries, and analyses will be performed using SAS® Version 9.1.3 or higher on Unix. Specifications for table, figures, and data listing formats can be found in the TLF specifications for this study.

7.2 Study Population

7.2.1 Disposition of Subjects

Disposition will include the number of subjects in the following categories:

- subjects completing informed consent,
- subjects discontinued prior to randomization,
- subjects randomized,
- subjects dosed (received any study drug: bleselumab, tacrolimus, MMF, steroids, or basiliximab) and
- subjects dosed and transplanted.

The following subject data will be summarized and presented for each treatment group and for the total:

- Number and percentage of subjects in each analysis set (Randomized; and Safety, Full, Pharmacokinetic Analysis Sets);
- Screening Disposition: number and percentage of all subjects who signed the informed consent by screening status (Screen Failure, Primary Screening Status (Completed, Screen Failure)).
- Treatment Disposition: number and percentage all randomized subjects by treatment discontinuation (Yes, No). For those who did not complete the regimen, the number and percentage for each reason will be given (adverse event, death, lack of efficacy, lost to follow-up, protocol deviation, withdrawal by subject, non-compliance with study drug and other).
- Number and percentage of all randomized subjects by study completion status, i.e., completed 12 months on the study regardless of assigned treatment status (Yes, No). For those who did not complete the study, the number and percentage for each reason will be given (adverse event, death, lost to follow-up, protocol deviation, withdrawal by subject, non-compliance with study drug and other).

A listing of screen failures will be provided by investigative site. Subject listings will be produced by investigative site and treatment group for the following:

- Randomization information
- Treatment discontinuations
- Study discontinuations
- Dates of First and Last Evaluations
- Inclusion/Exclusion from analysis sets for subjects excluded from at least one analysis set and the reason for exclusion, if applicable.

7.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 8.1.6 Protocol Deviations) will be assessed for all randomized subjects. The number and percentage of subjects meeting any protocol deviation criteria (PD1-PD5) will be summarized for each criterion and overall, by treatment group as well as by study site. See Appendix 7 for a list of the sub-codes and their definition.

Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. A listing of the protocol deviation definitions will be provided and a listing of subjects who had protocol deviations will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

PD5 - SAE was not submitted in the required time frame.

At the time of the 3-month analysis of the primary endpoint, a summary of protocol deviations will be provided and upon completion of the study a summary for the full study period will be provided.

7.2.3 Demographic and Other Baseline Characteristics

7.2.3.1 Recipient Demographic

Recipient demographics will be summarized by descriptive statistics and compared between treatment groups using Fisher's Exact Test or a one-way ANOVA with treatment as the factor. The safety analysis set will be summarized and if different, the full analysis set will be summarized. A summary will be provided for the screen failures. Recipient demographic variables are gender, age in years, age categories (<65, ≥65 to <=75 and >75), race (white, black or African American, Asian, American Indian or Alaska native, native Hawaiian or other Pacific Islander, and other) and (African-American vs. Others), ethnicity, weight, height and BMI. Summary statistics will also be given for the total.

7.2.3.2 Baseline Characteristics Related to FSGS and the Native Kidney

Baseline characteristics related to FSGS and native kidney status will be summarized by treatment group and overall for the full analysis set, and for the safety analysis set (SAF), if different from the FAS. Duration variables are:

- duration of FSGS (Date of skin closure – Date of Primary FSGS Diagnosis)+1,
- duration of pathology-confirmed FSGS (Date of skin closure – Date of Pathology-confirmed FSGS)+1 and
- duration of End Stage Renal Disease, ESRD (Date of skin closure – Date of ESRD Diagnosis)+1.

Other variables and their categories (where applicable) are:

- panel reactive antibody (PRA in %),
- panel reactive antibody (%) categories (<=0%, >0% - 20%, >20% - 50%, >50%),
- dialysis prior to transplant (Yes, No),
- making urine prior to transplant (Yes, No),
- reason for dialysis (fluid overload, uremia, hyperkalemia, metabolic acidosis, other and other specify) and
- plasmapheresis prior to transplant (Yes, No).

The means for continuous variables will be compared between treatment groups using an analysis of variance (ANOVA) with treatment group as the factor. For categorical variables, comparisons between treatment groups will be performed using Fisher's exact test.

These variables will be listed by investigative site and treatment group.

7.2.3.3 Donor Demographic and Other Baseline Characteristics

Donor demographic data (age, sex, race, height, weight and BMI) will be summarized by treatment group and overall for the full analysis set. The source of the kidney to be transplanted (living related, living non-related or deceased donor), and specific detailed information for deceased donors will be summarized by treatment group and overall. Detailed information for deceased donors includes:

- cause of death (anoxia, cerebrovascular /stroke, head trauma, CNS tumor, other/specify),
- terminal serum creatinine (mg/dL),
- history of hypertension (yes, no)
- history of diabetes (yes, no),
- Deceased donor criteria (DCD: Donation After Cardiac Death; ECD: Expanded Criteria Donor; SCD: Standard Criteria Donor)
- ECD Donor age category (50-59, $\geq$ 60) and
- deceased donors aged 50-59 with
    - death by cerebrovascular accident (yes),
    - history (hx) of hypertension (yes),
    - terminal serum creatinine >1.5 mg/dL (yes),
- controlled DCD (yes, no, unknown).

Detailed information for the donated kidney will include:

- longest primary organ preservation method (pump, cold storage)
- cold ischemia time (hours)
- cold ischemia time (hours) for living donors
- cold ischemia time (hours) for deceased donors
- warm ischemia time (hours)
- total ischemia time (hours)

Continuous variables will be compared between treatment groups using an analysis of variance (ANOVA) with treatment group as a factor. Categorical variables will be compared between treatment groups using Fisher's exact test.

Listings will be provided by investigative site and treatment group for the variables above.

7.2.3.4 Transplant Surgery Information

Listings will be provided by investigative site and treatment for variables related to the transplant surgery, specifically,

- admission/discharge day,
- making urine prior to transplant (yes or no),
- length of surgery,
- complications, and if yes, the specific complications,
- hemodynamically unstable during surgery (yes or no),
- dialysis within 7 days following skin closure (No, Yes).

Summaries by treatment group and overall will be provided for the longest primary preservation method for the donated organ, warm ischemia time, cold ischemia time and total ischemia time using the FAS.

7.2.3.5 Crossmatch of Histocompatibility, ABO Type and Serology

7.2.3.5.1 Histocompatibility

The total number of Human Lymphocyte Antigen (HLA) mismatches between the donor and recipient will be calculated for the Full Analysis Set. The number and percent of patients with 0, 1, 2, etc. mismatches will be displayed. The broad type designations will be provided for HLA A, HLA B and HLA DR. These are 2 numeric values for each of the HLA antigens. A mismatch between a donor and a recipient exists if the donor has an antigen which doesn't appear in the recipient.

For complete details on how to determine the number of HLA mismatches, see Appendix 4.

7.2.3.5.2 ABO Type

ABO Type will be categorized as identical, compatible or not recorded. Identical is defined as the donor and recipient have the same blood type. Compatible is defined as the recipient has blood type A or B and the donor has O or the recipient is type AB and the donor is A, B or O. The number and percent of patients within each treatment group and overall will be displayed for the FAS.

7.2.3.5.3 Recipient and Donor Viral Serology

Patient and donor status (negative or positive) will be determined for each of the following serology parameters using the definitions provided below.

- Hepatitis B surface antibody (Hepatitis B Surface Antibody is positive if any of the following are positive: Hepatitis B Surface Antibody (HBSAB), Hepatitis B Surface Antibody IgG (HBSIGG) or Hepatitis B Surface Antibody IgM (HBSIGM)).
- Hepatitis B core antibody (Hepatitis B Core Antibody is positive if any of the following are positive: Hepatitis B Core Antibody (HBCOREAB), Hepatitis B Core Antibody IgG (HBCIGG) or Hepatitis B Core Antibody IgM (HBCIGM)).
- Hepatitis B surface antigen (Hepatitis B Surface Antigen (HBsAG) is a stand-alone lab result).
- Hepatitis B Virus E antigen (Hepatitis B E Antigen (HBeAG) is a stand-alone lab result.)
- Hepatitis C antibody (Hepatitis C Antibody is positive if any of the following are positive: Hepatitis C Surface Antibody (HCAB), Hepatitis C Antibody IgG (HCVIGGAB) or Hepatitis C Antibody IgM (HCVIGMAB)).

- Epstein-Barr virus antibody (Epstein Barr Virus is positive if any of the following are positive: Epstein - Barr virus Antibody (EBVAB), Epstein - Barr virus Antibody IgG (EBVIGGAB) or Epstein-Barr Virus Antibody IgM (EBVIGMAB)).
- Cytomegalovirus antibody (Cytomegalovirus is positive if any of the following are positive: Cytomegalovirus Antibody (CMVAB), Cytomegalovirus Antibody IgG (CMVIGGAQ), or Cytomegalovirus Antibody IgM (CMVIGMAB)).

Counts and percentages will be provided for each recipient/donor combination with D=Donor, R=Recipient, +=Positive, -=Negative, U=Unknown (D+/ R+, D+/R-, D+/RU, D-/R+, D-/R-, D-/RU, DU/R+, DU/R-, and DU/RU). The data will be summarized by treatment group and overall for the FAS.

7.2.3.6 Country and Investigative Site

The number and percent of subjects will be provided for the SAF by treatment group and total number for each investigative site and by country.

7.2.3.7 Medical History

Medical history and targeted medical history is coded with MedDRA. Medical history and targeted medical history will be summarized by System Organ Class and Preferred Term by treatment group and total for the SAF. The number and percent of subjects will be presented.

7.2.4 Previous, Concomitant, and other Immunosuppressant Medications

Previous, concomitant and other immunosuppressant medications will be coded with WHO-DD or WHO-DRL(immunosuppressant medications), and a table will be created for each category with summaries provided by chemical subgroup (ATC 4th level) and preferred WHO name by treatment group for the SAF. Previous medications are those initiated prior to the first dose of bleselumab for those assigned to the bleselumab regimen and those that occur prior to the first dose of MMF for those on the SOC regimen. This definition is consistent with the definition of treatment emergent.

Subjects taking the same medication multiple times will be counted once per medication. A medication, which can be classified into several chemical and/or therapeutic subgroups, will be presented in all chemical and therapeutic subgroups.

The following listings will be provided by investigative site and treatment group.

- Previous and Concomitant Medications
- Non-Medication Therapy
- Immunosuppressant Medications Other than Study Medication.

7.3 Study Drugs

Descriptive statistics will be used to characterize duration of dosing (measured in days) and exposure to drug by treatment group and overall. These summaries will be based on the SAF.

7.3.1 Extent of Exposure for Bleselumab

Duration of exposure will be summarized for bleselumab in two ways.

- Descriptive statistics of duration (days) of exposure = 'Date of last dose of study drug' – 'Date of first dose of study drug' + 1.
- Exposure time will be categorized by month according to the following categories:
    - ≤ 1month
    - > 1month, ≤ 2 months
    - > 2 months, ≤ 3 months
    - > 3 months, ≤ 4 month
    - > 4 months, ≤ 5 month
    - > 5 months, ≤ 6 month
    - > 6 months, ≤ 7 month
    - > 7 months, ≤ 8 month
    - > 8 months, ≤ 9 month
    - > 9 months, ≤ 10 month
    - > 10 months, ≤ 11 month
    - > 11 months, ≤ 12 month
    - > 12 months

Counts and percentages of subjects in each of these categories will be summarized for the SAF.

7.3.2 Treatment Compliance for Bleselumab

During the treatment period, overall compliance with the dosing schedule will be examined for subjects in the SAF whose total study drug infusion count is known. Compliance = (total number of study drug infusions received in the treatment period/total number of infusions planned for the treatment period) x 100. Patients randomized to receive bleselumab are scheduled to receive a single infusion on the following days (i.e., target days) of the study Days 0, 7, 14, 28, 42, 56, 70, 90 and monthly for months 4 through 12.

Percent overall compliance will be summarized in two ways for the SAF:

- Descriptive statistics will be presented.
- Percent compliance will be categorized according to the following categories:
    - < 50%
    - ≥ 50% to < 70%
    - ≥ 70% to < 90%
    - ≥ 90%.

A listing of study drug exposure for bleselumab will be provided by investigative site.

7.3.3 Extent of Exposure for Basiliximab, Tacrolimus, MMF and steroids

The total dose of basiliximab (mg) will be summarized by treatment group for the initial dose and for the post-transplant dose given on Day 3, 4 or 5. The duration of dosing for tacrolimus, MMF and steroids will each be summarized by treatment group for the SAF in two ways.

- Descriptive statistics of Duration (days) of exposure = 'Date of last dose of study drug' – 'Date of first dose of study drug' + 1.

- Exposure time will be categorized by month according to the following categories:
    - ≤ 1 month
    - > 1 month, ≤ 2 months
    - > 2 months, ≤ 3 months
    - > 3 months, ≤ 4 month
    - > 4 months, ≤ 5 month
    - > 5 months, ≤ 6 month
    - > 6 months, ≤ 7 month
    - > 7 months, ≤ 8 month
    - > 8 months, ≤ 9 month
    - > 9 months, ≤ 10 month
    - > 10 months, ≤ 11 month
    - > 11 months, ≤ 12 month
    - > 12 months.

Counts and percentages of subjects in each of these categories will be summarized for the SAF.

7.3.4 Exposure to Tacrolimus

7.3.4.1 Tacrolimus Dosing

Descriptive statistics will be used to summarize tacrolimus total daily dose at each scheduled visit. The summary at each visit will be for that visit only and will not be cumulative.

If multiple levels of a dose were received by a subject within a visit, the subject's mean total daily dose (including intermittent doses of 0 mg) within the visit window will be used for analysis. The mean total daily dose within a visit window will be calculated as a cumulative dose (within the window) divided by total duration (including intermittent doses of 0 mg) of tacrolimus dosing within the visit window; only the doses from first dose day through last dose day will be considered for the calculation. For a detailed description of the calculations involved, see Appendix 5, Section 9.5.

The analysis described above will be performed for both mg and mg/kg units, separately. When needed, a subject's weight assessment from the vital signs CRF that is closest to the start of a dosing stint will be used to convert from one unit to another (i.e., mg to mg/kg or mg/kg to mg). If there are two weight measurements that are equidistant from the start of the dosing stint (e.g., values on Days 2 and 4 for a dose on Day 3), the earlier weight measurement will be used.

The total daily dose, and the duration of exposure (calculated as last dose day – first dose day + 1) will also be summarized by treatment group.

7.3.5 Exposure to MMF

The total daily dose of MMF (mg/day) will be summarized using descriptive statistics at each scheduled visit. The summary at each visit will be for that visit only and will not be cumulative.

So that subjects are counted only once at each time point, each subject's mean total daily dose (including doses of 0 mg/day) within a visit window will be calculated and used for analysis. The mean total daily dose within a visit window will be calculated as cumulative dose (within the window) divided by total duration (including intermittent doses of 0 mg) of MMF dosing within the visit window; only the doses from first dose day through last dose day will be considered for the calculation. For a detailed description of the calculations involved, see Appendix 5, Section 9.5.

The duration of exposure (calculated as last dose day – first dose day +1) will also be summarized.

- For subjects that switch from MMF to Myfortic, the MMF equivalent of Myfortic (1 mg of MMF = 1000/720 mg of Myfortic) will be used in all analyses of MMF.

7.4 Analysis of Efficacy

The objective in this study is to compare the efficacy of the bleselumab regimen (Arm 2) relative to the SOC regimen (Arm 1) for the prevention of FSGS recurrence post-transplant.

All efficacy summaries for the comparison of interest will be based on the FAS. Since many analyses are performed for specific time periods (e.g., Month 3), analyses of event data by time period will first consider all visits within the defined visit window and then select the visit closest to the target day for the analysis. Displays will be cumulative unless otherwise specified. For example, a summary at 6 months will include all events up through six months. In addition, listings by investigator and treatment group will be provided for all data used in efficacy analyses.

7.4.1 Analysis of Primary Endpoint(s)

The primary endpoint is recurrence of FSGS defined by nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0g/g) through 3 months' post-transplant. Death, graft loss or lost to follow-up will be imputed as rFSGS. The percentage of subjects who have recurrence of FSGS will be computed along with a two-sided 95% confidence interval (CI) for each of the treatment groups and for the treatment difference (Arm 2 – Arm 1). A positive difference indicates a higher recurrence rate in the bleselumab regimen compared to the SOC regimen. Confidence intervals for the incidence of rFSGS for each treatment group will be obtained using the Normal Approximation $\{p \pm Z_{.025}\sqrt{p(1-p)/n}\}$.

The formula for the two-sided 95% CI for the difference is:

$$p_t - p_s \pm Z_{.025}\sqrt{p_t(1-p_t)/n_t + p_s(1-p_s)/n_s}$$

where p_t and n_t are the proportion of FSGS recurrence and the sample size in Bleselumab regimen, respectively, p_s and n_s and are the proportion of FSGS recurrence and the sample size in SOC regimen, respectively. Fishers' exact will also be used to test for treatment differences.

7.4.1.1 Subgroup Analysis of Recurrence of FSGS determined by Nephrotic Range Proteinuria

For each treatment group, incidence of FSGS recurrence will be calculated for following subgroups: age (<65, ≥ 65), gender, race (African-American vs. Others), donor types (deceased donors vs. others), and donor relationship (living related vs. living non-related). The incidence of FSGS recurrence by first or repeat transplant will be provided by treatment group.

7.4.2 Analysis of Secondary Endpoints

7.4.2.1 Recurrence of FSGS through 6 and 12 Months determined by Nephrotic Range Proteinuria

The percentage of subjects with rFSGS through 6 and 12 months' post-transplant will be analyzed as described for the primary endpoint. Death, graft loss or lost to follow-up will be imputed as rFSGS. The percentage of subjects who have rFSGS through 6 and 12 months, a 95% CI for each of the treatment-group estimates, the treatment difference (Bleselumab regimen – SOC regimen) and a 95% CI for the difference will be provided. Fishers' exact test will also be used to test for treatment differences.

7.4.2.2 Biopsy-Proven Acute Rejection

Summaries by treatment group will be given for the incidence of BPAR (Banff Grade ≥ 1, local read) through 3, 6 and 12 months. P-values comparing the two groups will be obtained using Fisher's exact. A two-sided 95% CI will be constructed for each of the treatment groups and for the treatment difference [see Section 7.4.1 for the formulas]. Subjects who drop out of the study prior to each of the defined time points (3, 6 or 12 months), if any, without having a BPAR by local review will not be counted as having a BPAR. Subjects who have met the criteria for a BPAR and drop out of the study prior to each of the defined time points will be included in the BPAR count.

In a second set of analyses, subjects who drop out of the study without having a BPAR by local review will be counted as a recurrence. The same set of summaries will be computed as described in the previous paragraph.

7.4.2.3 Efficacy Failure

Incidence of efficacy failure defined as death, graft loss, BPAR (Banff Grade ≥ 1, local read), or lost to follow up through 12 months' post-transplant will be summarized by treatment group. A two-sided 95% CI will be constructed for each of the treatment groups and for the treatment difference (see Section 7.4.1 for the formulas).

For each treatment group, Kaplan-Meier estimates will be used to estimate efficacy failure at one year. The treatment difference will be computed as Arm 2 – Arm 1. A two-sided 95% CI will be constructed for the treatment difference using Greenwood's formula for standard error. A Wilcoxon test will be used to compare survival curves.

7.4.2.4 Biopsy-Proven rFSGS through 3, 6 and 12 Months determined by Independent Blinded Review of the Biopsy Slides

Biopsy slides will be provided for all subjects after the appearance of symptoms for rejection or rFSGS, or at the Day 90/month 3 visit, if there has not been a previous biopsy indicating rFSGS in the transplanted kidney. The blinded, central reader will objectively assess podocyte changes to identify those with rFSGS. Subjects who drop out of the study and do not provide a biopsy for slide review will not be included in the analysis of biopsy-proven rFSGS. Any biopsies after 3 months are for-cause only and there are no other protocol-defined biopsies.

The percentage of subjects who have biopsy-proven rFSGS will be computed along with a two-sided 95% confidence interval (CI) for each of the treatment groups and for the treatment difference (Arm 2 – Arm 1). Fishers' exact test will also be used to test for treatment differences.

The method used to confirm rFSGS (light microscopy, electron microscopy) will be summarized, n(%), by treatment group. Summaries, n (%), will be provided for the rFSGS histologic classification (perihiliar variant, cellular variant, tip variant, collapsing variant and not otherwise specified) by treatment group. Treatment differences for rFSGS confirmation method (LM, EM) and distribution of histologic type will be assessed using Fisher's Exact Test.

7.4.3 Analysis of Exploratory Endpoints

7.4.3.1 Patient Survival and Graft Survival

Patient and graft status through 12 months' post-transplant will be summarized by treatment group. Patient status is defined as alive or deceased. Graft status is defined as graft loss determined by subject death, re-transplant, nephrectomy, or return to permanent dialysis (> 30 days) or graft survival determined as the absence of any of the above. Patient and graft status will be summarized by treatment group with a two-sided 95% CI for each treatment group and a two-sided 95% CI for the treatment difference (see Section 7.4.1 for the formulas). There will be no imputation for lost to follow-up for one display. In a second display of patient and graft survival, lost to follow-up will be counted as an event (graft loss or patient death).

Summaries (counts and percentages) will be provided by treatment for the FAS. Fisher's Exact Test will be used to compare the two treatment groups for one analysis.

In a second analysis, Kaplan-Meier estimates will be used to estimate patient survival and graft survival at one year. Any drop-outs prior to one-year will be censored at the time of drop-out. The treatment difference will be computed as Arm 2 – Arm 1. A two-sided 95% CI will be constructed for the treatment difference using Greenwood's formula for standard error. A Wilcoxon test will be used to compare survival curves. In kidney transplant studies efficacy failure tends to occur early and the Wilcoxon test is more powerful test in detecting differences early in time.

7.4.3.2 Estimated Glomerular Filtration Rate

Summaries for the mean eGFR value based on MDRD criterion will be given for Day 56, Day 90 and at 4, 5, 6 and 12 months and analyzed at each time point using an analysis of covariance (ANCOVA) with treatment as the factor and the week 4 value as a covariate. A summary and comparison of the results for the two treatment groups at three months will provide kidney function information at the time of the three-month interim analysis.

Sample SAS code is provided below.

```
PROC GLM data=dsetname;
CLASS TREAT;
MODEL MGFR = AVISITN TREAT Week4 /SOLUTION;
LSMEANS TREAT / STDERR PDIFF DIFF CL;
RUN;
```

The mean change in eGFR value from week 4 (e.g., Month 6 value minus Week 4 value) will also be similarly analyzed for each time point (Day 56, Day 90 and months 4, 5, 6 and 12).

Also, incidence of GFR < 40 mL/min and the incidence of a decrease of GFR ≥ 10% from week 4 to each time point (Day 56, 90, months 4, 5, 6, and 12) will be analyzed using Fisher's exact test. The difference from the standard of care for ASKP1240+Tac will be shown with a 95% CI.

Descriptive statistics (n, mean, sd, min, median, and max) will be provided by study visit beginning at week 4. Summaries for change will be calculated with week 4 as the baseline value.

7.4.3.3 Recurrence of FSGS with no Imputation for Death, Graft Loss or Lost to Follow-up

Incidence of rFSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g) cumulatively up to 3, 6 and 12 months post-transplant will be summarized by treatment group. There will be no imputation for death, graft loss or lost to follow-up in this display. A two-sided 95% CI will be constructed for each of the treatment group and for the treatment difference. Fishers' exact will also be used to test for treatment differences.

7.4.3.4 Time to rFSGS

For each treatment group, Kaplan-Meier estimates will be used to estimate FSGS recurrence. The treatment difference will be computed as Arm 2 – Arm 1. A two-sided 95% CI will be constructed for the treatment difference using Greenwood's formula for standard error. A Wilcoxon test will be used to compare survival curves and will be displayed on the graph. This analysis will be conducted for

- FSGS recurrence (defined by nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0g/g))
- FSGS recurrence (defined by nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0g/g) or initiation of plasmapheresis)

- FSGS recurrence (defined by nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0g/g), death graft loss or lost to follow-up
- Biopsy proven (blinded, central read) FSGS recurrence

Those who drop out of the study prematurely without sufficient information to determine recurrence will be censored at the time of withdrawal with the exception of bullet 3.

7.4.3.5 Time to First BPAR

Kaplan-Meier estimates will be used to estimate the time to first BPAR by treatment group. The treatment difference will be computed as ASKP1240+Tac - SOC. A two-sided 95% CI will be constructed for the treatment difference using Greenwood's formula for standard error. A Wilcoxon test will be used to compare survival curves and will be provided on the graph. Those who drop out of the study prematurely without sufficient information to determine recurrence will be censored at the time of withdrawal.

7.4.3.6 Urine Protein-Creatinine Ratio and the Urine Albumin-Creatinine Ratio

The urine protein-creatinine ratio, the change from week 1 (Day 7) for collections up to week 4, and the change from week 4 for collections after week 4 will be summarized for each scheduled collection time. The urine protein-creatinine ratio collected up to week 4 will be analyzed with an ANCOVA with treatment group as the factor of interest and the first available post-transplant value as the covariate. The urine protein-creatinine ratio after week 4 will be analyzed with an ANCOVA with treatment as a factor and the week 4 value as a covariate. These data are usually right-skewed and will be transformed using the natural logarithm (ln) to produce data that more closely conforms to a normal distribution. Values of 0, if any, will have 0.5 added to enable calculation of the ln transformation. The ln-transformed data will be analyzed and then back-transformed using the exponential transformation to provide the summaries.

The urine albumin-creatinine ratio will be analyzed and summarized as described for the urine protein-creatinine ratio.

7.4.3.7 Patient-Reported Outcomes

7.4.3.7.1 Short Form Health Survey

The Short Form 36-Item Health Survey Scores Version 2.0 (SF-36, v2) provides scores for each of eight health domains (physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions). The items for an individual domain are averaged to obtain a mean score. Items that are left blank are not included in the calculations. Each domain is directly transformed into a 0 - 100 scale with the assumption that each question carries equal weight. Once transformed a score represents a percentage of the total possible score for an item. Lower scores indicate greater disability (i.e., a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability).

The eight subscales are summarized into two scores, the physical component summary (PCS) and mental component summary (MCS) scores. The PCS is an average of the mean scores for

the physical domains and the MCS is an average of the mean scores for the mental domains. The PCS and MCS are transformed to norm-based scores with a mean of 50 and a SD of 10. A two-point difference in the PCS and a three-point difference in the MCS are considered clinically meaningful.

Descriptive statistics (n, mean, median, sd, min and max) will be provided for each of the eight domains and the PCS and MCS. In this study, SF-36v2 scale scores, PCS and MCS will be calculated by QualityMetric and a report of the results will be provided.

7.4.3.7.2 EuroQol-5 dimensions-5 levels

The EuroQol-5 dimensions-5 levels (EQ-5D-5L) is an international and standardized non-disease specific instrument for describing and valuing health status. This questionnaire consists of two parts:

- 5-dimensions (EQ-5D-5L): mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each dimension there are 5 levels (i.e., scores 1 to 5) to classify the severity of the dimension, ranging from no problems to extreme problems or inability to perform the specified activity
- VAS, where 0 represents the worst imaginable health state and 100 the best imaginable health state.

The number of responses (%) for each of the 5 categories within a dimension will be summarized by visit and treatment. Fisher's exact test will be used to compare the distribution of responses between the two treatment groups at each visit.

The following SAS code may be used:

```
PROC FREQ data=dataset;
   TABLE treatment * dimension / Exact;
   Output out=pvalue exact;
RUN;
```

For each dimension, the percentage of patients who respond with no issue, slight, moderate, severe, and unable to function will be graphically displayed (Appendix 6). If applicable, the percentage who do not respond will be shown on the graph. The absolute value for the VAS and the change from baseline to the Month 3, and 12/EOS Visit in the VAS score will be summarized by treatment group and visit. The change from baseline will be defined as the Month 3, 12/EOS Visit value minus the baseline value. The change from baseline for the VAS Score will be analyzed by using an analysis of covariance (ANCOVA) model with treatment group as a fixed factor and the baseline VAS score as a covariate.

The following SAS code may be used:

```
PROC GLM data=dataset;
    CLASS treat;
    MODEL VAS=visit treat base / solution;
     lsmeans treat / stderr diff cl;
run;
```

7.4.3.7.3 Kidney Transplant Questionnaire

The score for each of the five domains of the KTQ (i.e., physical symptoms, fatigue, uncertainty/fear, appearance, and emotional) is obtained by summing the values for all of the items in the dimension and dividing by the number of items in that dimension. Dimension scores range from 1 (worst possible score) to 7 (best possible score). Instructions to determine the score for each of the dimensions are given below.

- Physical Symptoms: Sum the 6 patient specific items and divide by 6.
- Fatigue: Sum items 8 (weak), 25 (low level of energy), 12 (sluggish), 23 (increased tiredness) and 14 (very little strength) and divide by 5.
- Uncertainty/Fear: Sum items 21 (protective of transplant), 15 (fear of panic related to rejection), 16 (uncertain about the future), and 17 (worried) and divide by 4.
- Appearance: Sum items 18 (excessive hair growth), 7 (excessive appetite), excessive weight (19), acne (20) and divide by 4.
- Emotional: Sum items 22 (irritable, difficult to get along with), 10 (depressed), 13 (anxious), 24 (frustrated), 11 (stubborn), 9 (impatient) and divide by 6.

  In the event that one of the items does not have a response, sum the items with a response and divide by the number of responses.

The change from baseline in the score for each of the 5 domains at 3 and 12 months will be analyzed using ANCOVA with treatment as a factor and baseline as a covariate.

7.5 Analysis of Safety

All analyses of safety will be presented by treatment group for SAF, unless otherwise specified.

7.5.1 Adverse Events

Summaries and listings of SAEs and Serious TEAEs include SAEs upgraded by the sponsor based on a review of the Sponsor's list of Always Serious terms if any upgrade was done.

The coding dictionary for this study will be the Medical Dictionary for Regulatory Activities (MedDRA v19.0). It will be used to summarize adverse events (AEs) by system organ class (SOC) and preferred term (PT). All adverse event summaries will display frequencies and percentages by treatment group.

An overview of the incidence of treatment emergent adverse events and death by treatment group will be provided for the 3- and 12-month treatment periods. Adverse events will be collected up to 30 days after the last dose and will be represented in the AE overview. The overview table will include the following details by treatment group:

- Number and percentage of subjects with TEAEs,
- Number and percentage of subjects with drug-related TEAEs
    - related to any drug,
    - related to bleselumab,

  - related to tacrolimus,
  - related to MMF, or
  - related to basiliximab,

- Number and percentage of subjects with Serious TEAEs,
- Number and percentage of subjects with Drug-related serious TEAEs,
  - related to any drug,
  - related to bleselumab,
  - related to tacrolimus,
  - related to MMF, or
  - related to basiliximab,
- Number and percentage of subjects with TEAE Leading to Death (i.e. outcome=fatal),
- Number and percentage of subjects with TEAE Leading to Permanent Discontinuation of Study Drug,
- Number and percentage of subjects with Drug-Related TEAE Permanent Discontinuation of Study Drug,
  - related to any drug,
  - related to bleselumab,
  - related to tacrolimus,
  - related to MMF, or
  - related to basiliximab,
- Deaths.

The number and percentage of subjects with TEAEs, classified by SOC and PT will be summarized by treatment group for:

- TEAEs,
- Drug-related TEAEs,
- Serious TEAEs,
- Drug-related serious TEAEs,
- TEAE Leading to Death (i.e. outcome=fatal),
- TEAE Leading to Permanent Discontinuation of Study Drug,
- Drug-Related TEAE Permanent Discontinuation of Study Drug,
- Deaths.

For each of the drug-related summaries, there will be a summary for:

  - related to any drug,
  - related to bleselumab,

- related to tacrolimus,
- related to MMF, or
- related to basiliximab.

In the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing severity or relationship, then the subject will be counted only once with the worst severity and highest degree of relationship. If any of the severity or relationship values are missing, the subject will be counted as having the greatest severity and the event will be considered to be related. If an adverse event has multiple classifications, it will be included in each classification category. All adverse events data will be displayed in a listing.

A listing of infections and post-transplant lymphoproliferative disorder (PTLD), if any, will also be provided. If there are no PTLDs, the listing will have the phrase, 'No Data Available for this Report'.

Clusters of adverse events associated with tacrolimus, MMF or bleselumab will be summarized by treatment group. These clusters are hepatic events, BK infection, cardiac events, cardiovascular events, cytomegalovirus, diarrhea, dyspepsia, gastroenteritis, G.I. disturbances, G.I. pain/ discomfort, glucose abnormality, hypertension, lipids, malignancy, MMF GI specific, MMF hematologic, MMF lower GI, MMF upper GI, MMF other GI, neurotoxicity, opportunistic infections, renal events, respiratory tract infections, upper GI complex, urinary tract infections, and viral and fungal infections.

7.5.1.1 Potentially Excessive Toxicities

The following set of defined toxicities, monitored on a continuous basis, will be summarized by treatment group. These will be provided for the DMC review:

- Deaths
- Graft Loss
- Acute Rejection (BPAR$\geq$ 2A Banff T cell and/or $\geq$ Banff 1 AMR)
- Severe Anemia (NCI-CTCAE Grade 4: Two consecutive Hemoglobin < 6.5 g/dL taken within 14 days of first detection after Day 28 post-transplantation)
- Agranulocytosis (NCI-CTCAE Grade 4: Two consecutive absolute Neutrophil Count < 100 cells/mm^3 taken within 14 days of first detection after Day 28 post-transplantation)
- BK Virus-Associated Nephropathy: (BKVAN) (excludes BK viremia or viuria alone)
- Cytomegalovirus Tissue Disease: (CMV) (excludes CMV syndrome, viremia alone, viuria alone)
- Malignancies (Excludes non-melanoma skin malignancies and PTLD)
- BK Virus Infection
- CMV Virus Infection
- Post-Transplant Lymphoproliferative Disease (PTLD)

7.5.2 Clinical Laboratory Evaluation

Clinical laboratory variables (hematology, biochemistry, urinalysis, coagulation/thrombotic pathway, hepatic profile, and fasting lipid profile) will be summarized using mean, standard deviation, minimum, maximum and median for each treatment group at each visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same manner. For renal tests (serum creatinine, blood urea nitrogen, eGFR, urine protein/creatinine ratio, urine albumin/creatinine ratio), the latest assessment in the Day 28 visit window will be serve as baseline for values collected after Day 28. For the urine/protein and urine/creatinine ratios, post-transplant changes after week 1 the first post-transplant.

Shift tables will also be used to summarize the change from baseline to worst value post-transplant for the select laboratory parameters. Table 2 lists the cut points used for these analyses.

Table 2 Cut Points Used for Laboratory Shift Tables

Laboratory Parameter	Shift Categories
Fasting glucose (mg/dL)	<70, 70-100, >100-<126, 126-200, >200 Create a shift to greatest for this parameter.
Magnesium (mg/dL)	<0.9, 0.9-<1.2, 1.2-<1.7, 1.7-2.7, >2.7-4.9, >4.9-7.0, >7.0 Create a shift to least for this parameter.
Potassium (mmol/L)	<2.5, 2.5-<3.5, 3.5-5.1, >5.1-6.5, >6.5-8, >8.0 Create a shift to least and shift to greatest for this parameter.
SGPT (U/L)	<35, 35-105, >105-175, >175-280, >280-350, >350-700, >700-1000, >1000 Create a shift to greatest for this parameter.
SGOT (U/L)	<35, 35-105, >105-175, >175-280, >280-350, >350-700, >700-1000, >1000 Create a shift to greatest for this parameter.
WBC (10^9/L)	<1.5, 1.5-3.0, >3.0-4.5, >4.5-11.0, >11.0-15.0, >15.0 Create a shift to least for this parameter.
Platelets (10^9/L)	<25, 25-<50, 50-<100, 100-<130, 130-<400, >=400 Create a shift to least for this parameter.
Hematocrit (%)	Male and female: <24, 24-<30, 30-<33, 33-<36, 36-<45, >=45 Create a shift to least for this parameter.
Hemoglobin (g/dL)	Male and female: < 8, 8-<10, 10-<11, 11-<12, 12-<15, >=15 Create a shift to greatest for this parameter.
Total cholesterol (mg/dL)	<200, 200-239, >239 Create a shift to greatest for this parameter.
LDL cholesterol (mg/dL)	<100, 100-129, 130-159, 160-189, >=190 Create a shift to greatest for this parameter.
HDL cholesterol (mg/dL)	<40, 40-60,>=60 Create a shift to least for this parameter.
Triglycerides (mg/dL)	<150, 150-199, 200-499, >=500 Create a shift to greatest for this parameter.
Table continued on next page	

Laboratory Parameter	Shift Categories
Serum creatinine (mg/dL)	<0.6, 0.6-1.2,>1.2-1.5, >1.5-2, >2-2.5, >2.5-3, >3 Create a shift to greatest for this parameter.
GFR (MDRD) ($mL/min/1.73m^2$)	<15, 15-29,>29-59, >59-89, >89 Create a shift to least for this parameter.
Blood urea nitrogen (mg/dL)	<8, 8-18, >18-50, >50-75, >75 Create a shift to greatest for this parameter.
Total bilirubin (mg/dL)	0.3-1.0, >1.0-2.0, >2.0 Create a shift to greatest for this parameter.
Alkaline phosphatase (U/L)	<35, 35-105, >105-175, >175-280, >280-350, >350-700, >700-1000, >1000
ANC (cells/µL)	<500, 500-<1000, 1000-<2000, 2000-<8000, >=8000 Create a shift to lowest for this parameter.

7.5.2.1 Liver Enzymes and Total Bilirubin

The following potentially clinically significant criteria for liver tests – defined as Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The subject's highest value during the post-transplant period will be used.

Parameter	Criteria
ALT	> 3xULN
	> 5xULN
	> 10xULN
	> 20xULN
AST	> 3xULN
	> 5xULN
	> 10xULN
	> 20xULN
ALT or AST	> 3xULN
Total Bilirubin	> 2xULN
ALP	> 1.5xULN
ALT and/or AST AND Total Bilirubin(*)	(ALT and/or AST > 3xULN) and total bilirubin > 2xULN

(*) Combination of values measured within same sample

The number and percentage of subjects with potentially clinically significant values in liver enzyme and total bilirubin tests during the post-transplant period will be presented by treatment group.

The following data will be presented graphically by treatment group:

- eDISH Plot of Peak AST/ALT (xULN) against Peak Total Bilirubin (xULN)

7.5.2.2 Potentially Clinical Significant Values in Select Laboratory Tests

The number and percentage of subjects with potentially clinically significant (PCS) values in select laboratory tests will be summarized by treatment group using the cutoffs in both sets of units given below. For each laboratory parameter, the incidence of patients that met the relevant criteria will be tabulated and treatment group will be compared using Fisher's exact test. Table 3 describes the laboratory parameter and PCS criteria to be used in analyses.

Table 3 Potentially Clinically Significant (PCS) Criteria for Analyses of Select Laboratory Parameter

Laboratory Parameter	PCS Criteria	PCS Criteria in SI Units
Fasting glucose	>200 mg/dL	>11.0 mmol/L
SGOT/AST	>175 U/L	>175 U/L
SGPT/ALT	>175 U/L	>175 U/L
WBC	<1.5 10^9/L	< 1500 10^6/L
Platelets	<100 10^9/L	<100 10^9/L
Hematocrit	<24%	0.24 (fraction of 1)
Hemoglobin	<8.0 g/dL	<80 g/L
Total cholesterol	>239 mg/dL	>6.19 mmol/L
LDL cholesterol	≥190 mg/dL	≥4.92 mmol/L
Triglycerides	≥500 mg/dL	≥5.65 mmol/L
Serum creatinine	Female: >2.0 mg/dL, Male: >2.5 mg/dL	Female: > 176.8 µmol/L; Male >221 µmol/L
eGFR (MDRD)	≤ 29 mL/min/1.73m^2	≤ 29 mL/min/1.73m^2
Total bilirubin	> 2.0 mg/dL	> 34.21 µmol/L

7.5.3 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure and pulse rate) will be summarized using mean, standard deviation, minimum, maximum and median by treatment group and visit. Additionally, a within-subject change will be calculated by visit as the post-baseline measurement minus the baseline measurement and summarized by treatment group and visit. The baseline value will be obtained at screening.

7.5.3.1 Potentially Clinically Significant Values in Select Vital Signs

The number and percentage of subjects with potentially clinically significant vital signs will be summarized by treatment group.

Tables for potentially clinically significant vital signs will be generated using the baseline value and highest value obtained post baseline for each subject for each treatment group.

The following potentially clinically significant criteria are defined for each parameter:

Vital Sign Variable	Criteria
SBP	≥160 mmHg AND ≥20 mmHg change from baseline
DBP	≥100 mmHg AND ≥15 mmHg change from baseline
Pulse Rate	≥100 bpm AND ≥15 bpm change from baseline

7.5.3.2 Clustered Safety Events

The following clusters of safety events, based on adverse events, laboratory values, and vital sign values will be summarized: BK infection, cardiac, cardiovascular, cytomegalovirus, diarrhea, dyspepsia, gastrointestinal (GI) disturbances, gastroenteritis, GI pain/discomfort, glucose abnormality, hepatic events, hypertension, lipids, malignancy, neurotoxicity, opportunistic infections, renal events, respiratory tract infections, upper GI complex, urinary tract infections, infections and infestations. Details of the specific adverse events, vital values and laboratory values that compose each cluster are described in Section 9.2. The final set of preferred terms for each cluster will be updated based on the actual reported terms for the study. The subset of the infections and infestations that were determined to be viral infections or fungal infections will each be analyzed as separate clustered safety events.

The incidence of treatment emergent clustered safety events will be summarized by treatment group and overall.

7.5.4 Electrocardiograms (ECGs)

A 12-lead ECG will be performed as part of screening, month 3 and 12. Number and percentage of subjects with normal, not clinically significant abnormal and clinically significant abnormal results as assessed by the investigator for the 12 lead ECG will be tabulated by treatment group at each treatment visit and time point.

7.5.5 Viral Load Testing

The cumulative number and percentage of subjects with a positive test result for CMV, EBV and BKV will be summarized by visit. Absolute non-zero serum viral loads (log10 IU/ml) for CMV, EBV and BKV and urine BK viral loads (copies/ml) will be summarized by visit and treatment group. Results for subjects who are negative at baseline will be shown in a second set of tables (cumulative positive by visit, viral loads).

The cumulative number and percentage of subjects with a CMV, EBV and BKV infections will be tabulated. The categories and sub-categories to be tabulated by visit, if they occur, are shown below:

- CMV Infection
    - CMV Active Infection
    - CMV Disease
        - CMV Syndrome Symptoms

  - Pneumonia
  - Gastrointestinal Disease
  - Hepatitis
  - CNS Disease
  - Retinitis
  - Other Tissue Invasive Disease
- EBV Infection
  - EBV Infection
  - EBV Disease
- BK Virus Infection
  - BKVAN

7.5.6 Anti-Bleselumab Antibodies

The number of and percentage of subjects with Anti-Bleselumab antibodies will be summarized for treatment arm 2 by visit (Days 0, 14, 28, 90, months 6, 9, 12/EOS) and a total will be provided. The results of the screening assay and the confirmation assay will be tabulated. Descriptive statistics will be used to summarize anti-Bleselumab titers at each scheduled visit (n, GM, GSD, Min, Max). Subjects with anti-bleselumab antibodies will have an additional test to determine if the antibodies are neutralizing. The number and percentage of subjects with neutralizing antibodies will be provided by visit.

7.5.7 Bleselumab bi-specific antibody

The Bleselumab bi-specific antibody measures whether a portion of the Bleselumab molecule has formed a new antibody with the endogenous anti-CD40 antibody. Antibody concentration levels (ng/mL) will be summarized (n, GM, GSD, Min, Max,) by visit. The LLOQ for the assay is 100 ng/mL.

7.5.8 Incidence of New-onset Diabetes Mellitus after transplantation (NODAT)

Subjects who are at risk for experiencing NODAT are those without diabetes at skin closure. For these analyses, subjects will be considered at risk if they did not have diabetes (type I or II, or NODAT with prior transplant) present at skin closure, and did not have any pre-transplant (lab Day < 0) fasting glucose value > 200 mg/dL. In addition, subjects on antidiabetic medication (e.g. insulin or oral hypoglycemic) for ≥ 30 pre-transplant days that did not end that stint more than 7 days prior to transplant will not be considered at risk. These subjects should be noted as having a history of diabetes on the Targeted Medical History CRF.

For at-risk subjects, any of the following events constitutes a NODAT event within the post-transplant period.

- Two, post-transplant, high (≥ 126 mg/dL) fasting plasma glucose ≥ 30 days apart. If the subject had a major event (died, experienced graft loss, was lost to follow-up, or discontinued study) but didn't have two high values ≥ 30 days apart he/she will still be counted as a NODAT event if the last fasting plasma glucose value was high.
- Use of insulin for ≥ 30 consecutive days. If a subject had a major event, he will be counted as a NODAT event if he was on insulin at the time of the major event.
- Use of oral hypoglycemics for ≥ 30 consecutive days during the study. If a subject had a major event, he will be counted as a NODAT event if he was on an oral hypoglycemic agent at the time of the major event.
- Use of other antidiabetic medications for ≥ 30 consecutive days during the study. If a subject had a major event, he will be counted as a NODAT event if he was on another antidiabetic medication at the time of the major event.

Antidiabetics and high laboratory (fasting glucose) values prior to skin closure are not considered. In addition, high laboratory values and antidiabetic medications that started after a major event are not considered. All at-risk subjects who do not have an event as described above will be counted as non NODAT.

The number and percentage of patients with NODAT through Study Months 3, 6, and 12 will be summarized by treatment group. The percentage will be calculated from the at risk population (patients with no history of diabetes mellitus) and compared among treatment groups using Fisher's exact test.

7.6 Analysis of PK

7.6.1 Tacrolimus Trough Concentration

Descriptive statistics will be used to summarize tacrolimus trough concentration (ng/ml) by treatment group and scheduled collection visit. The serum concentration at trough (C_{trough}) (Day 1: 11-13 hours post-dose, 4, 7, 14, 28, 42, 56, 70, 90, months 4 – 12, EOS) for tacrolimus will be listed and summarized using descriptive statistics (n, mean, SD, %CV, Min, Median, Max, GM, Geo %CV) at each scheduled collection time point for subjects in both regimens.

For the purpose of analyses, the trough concentration within each visit window that is closest to the target scheduled collection day will be used. If there are two concentration values within a specified visit window that are equidistant from the target day (e.g., values on Days 2 and 4 for collection Day 3), the latter will be used.

7.6.2 Bleselumab Concentrations

The serum concentration at peak (C_{max}) (Day 0, 7, 14, 28), trough (C_{trough}) (Day 0, 7, 14, 28, 42, 56, 70 90, months 6, 9, 12) and the peak to trough ratio for bleselumab will be listed and summarized using descriptive statistics (n, mean, SD, %CV, Min, Median, Max, GM, Geo %CV) at each scheduled collection time point for subjects in bleselumab regimen.

7.7 Analysis of anti-CD40 auto-antibodies

Titers for the anti-CD40 auto-antibodies will be provided for both treatment groups and summarized for the FAS. Titers below the LLOQ will be assigned ½ LLOQ. This antibody data will be analyzed after normalizing the data using a natural log transformation (SAS LOG function). Summaries for this data will include n, the geometric mean, geometric standard deviation and the minimum and maximum values. After obtaining the summary statistics for the log transformed values, the mean and standard deviation will be exponentiated to obtain the geometric mean and the geometric standard deviation.

Log-transformed anti-CD40 auto-antibody titers will be compared between the treatment groups at each post-baseline visit (Day 7, Day 14, Day 28, Day 56, Day 90, Month 6, 9 and 12) using a mixed model repeated measures analysis with the baseline value as the covariate. The variability of antibody values usually decreases with increasing values of antibody levels (heteroscedasticity). The model will assume heteroscedasticity and that the regression lines for the two treatment groups are parallel (no baseline by treatment group interaction). The SAS code for this model is shown below:

```
proc mixed;
model postCD40=trtgrp baseCD40 / solution;
repeated / local=exp(baseCD40  baseCD40^2);
run;
```

7.8 Subgroups of Interest

The primary efficacy endpoint will be summarized by the treatment group for the subgroups as defined in Section 7.4.1.1.

7.9 Interim Analysis (and Early Discontinuation of the Clinical Study)

7.9.1 Interim Data Reviews and the Interim Analysis

Interim data reviews by a DMC (Data Monitoring Committee) were originally planned as follows:

- 50% of the subjects have been enrolled, completed and cleaned through Month 3
- 100% of subjects have been enrolled, completed and cleaned through Month 3 (Interim Analysis),
- 100% of subjects have been enrolled, completed and cleaned through Month 6.

An interim analysis was planned when all subjects completed 3 months' post-transplant follow-up. The purpose of the interim analysis was to evaluate treatment differences for the recurrence of FSGS to support strategic decision making for future project development and study design. Instead, due to slow enrollment, the first 50 subjects transplanted and dosed will be analyzed and the results used to support strategic decisions.

The first subject was enrolled in May 2017 with 50 subjects transplanted and dosed as of mid July 2019. The additional 10 subjects are planned to be enrolled. Due to the slow enrollment

Astellas and the development partner, Kyowa Kirin Co., Ltd. (KKC) plan to follow these 50 subjects for three months (the time of the primary endpoint), and conduct an interim analysis to evaluate response in the two treatment groups. This interim analysis will serve as the foundation for a Briefing Document to support a Type C meeting with the FDA, if the results merit a go forward decision. TLFs from this interim analysis will be discussed in an open session with the members of the DMC.

7.9.2 Data Monitoring Committee (DMC) and Data Analysis Center (DAC)

A Data Monitoring Committee (DMC) and an independent Data Analysis Center (DAC) will be established. A charter for the DMC (Data Monitoring Committee) has been created and contains all of the definitions of the outputs that will be provided. A charter for the DAC will be created.

The DAC will provide the aggregated by-treatment summaries using the correct treatment assignment to the DMC members. The displays will initially be created by the study programmer(s) and provided to the study team using a dummy randomization. The study team will review for format and content and the study programmer will make any requested modifications. Once finalized, the DAC will use the programs and datasets created by the study programmer(s) and populate the TLFs using the actual treatment randomization. The displays will be kept in a secure directory on the Astellas Unix until the study has been locked. Once the study has been locked the security controls will be removed for the sub-directory.

For the interim analysis of the 50 subjects transplanted, dosed and followed through at least three months, the unblinded TLFs will be produced by a representative of Astellas rather than by the independent DAC.

7.9.3 DMC Open and Closed Sessions

There will be an open and closed session for the DMC (Data Monitoring Committee) meetings. The open session will be attended by members of the DMC and Astellas study team members. Aggregated by-treatment data summaries for disposition, baseline characteristics, recipient and donor demographics, recipient and donor baseline characteristics and baseline characteristics related to FSGS and kidney transplantation will be available to the study team and presented during the open session. All other displays described in the DMC charter will be provided by the DAC to the DMC using the treatment randomization and discussed during the closed session. Aggregated efficacy and safety data before the interim analysis at three months and after the interim analysis at three months will not be available to the study team until the data has been locked following completion of the study.

The display(s) for the planned interim analysis at three months and other aggregated efficacy and safety results for data through 3 months post-transplantation will be provided to the study team and shared with the DMC. These results will be discussed during the open session between members of Astellas and the DMC.

For the interim analysis of the 50 subjects transplanted, dosed and followed through three months, there will be a single open session since the TLFs with the treatment assignment can be viewed by the study team after database cutoff. A discussion of the results with the experts on the DMC will help the study team to understand the results of this study. The results will not be shared with the sites until the study has been completed and the database locked.

7.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information

7.10.1 Missing Data

A subject will be considered lost to follow up (i.e., unknown outcome) if the subject has not had the event of interest and does not have a study assessment within 30 days prior to the target day (see Section 7.10.3) for analysis.

Imputation for missing start and stop dates and times for adverse events and concomitant medications should use the following algorithm. If time is missing, then 00:00 will be assigned for start time and 24:00 for stop time. If day is missing, then the first day of the month will be assigned for a start day and the last day of the month for stop day. If month is missing, then the first month of the year will be assigned for start month and the last month of the year as the stop month. However, if the imputation rules lead to impossible dates, then the algorithm may be revised. The imputed data will be used to determine whether or not an adverse event is treatment emergent, whether or not a medication is concomitant. Listings of adverse events and concomitant medications will present the actual dates; imputed dates will not be shown.

For PK analyses, if at least half of the individual data in a group are 0, the standard deviation and %CV will not be calculated. If one or more values are below the LLOQ (lower limit of quantitation), the geometric mean will not be calculated.

Any additional consideration for handling missing data is addressed in relevant sections.

7.10.2 Outliers

Unless otherwise specified, analyses will use all available data.

7.10.3 Visit Windows

For the purpose of data presentation and analyses, study Day is defined relative to the day of skin closure (Day 0) and unless specifically stated otherwise, the term baseline will refer to the last assessment/evaluation up to and including Day 0.

The visit windows defined in the table below will apply for analyses by visit. For data collected at every visit the following visit windows will apply.

Visit Name (time period)	Week	Target Day	Visit Window (study Day)	Target Window (Day) for ASKP1240 Infusion
Screening		-	≤ 0	
Baseline		0	≤ 0	
Day 0	1	0	0	0
Day 1	1	1	1 – 2	
Day 4	1	4	3 – 5	
Day 7	1	7	6 – 10	6-8
Day 14	2	14	11 – 21	13-15
Day 28	4	28	22 – 35	26-30
Day 42	6	42	36 – 49	40-44
Day 56	8	56	50 – 63	54-58
Day 70	10	70	64 – 80	68-72
Day 90/Month 3	12	90	81 – 115	88-92
Month 4	16	120	116 – 135	117-123
Month 5	20	150	136 – 166	147-153
Month 6	24	182	167 – 197	179-185
Month 7	28	212	198 – 227	205-219
Month 8	32	242	228 – 257	235-249
Month 9	36	272	258 – 287	265-279
Month 10	40	302	288 – 317	295-309
Month 11	44	332	318 – 347	325-339
Week 48/ Month 12	48	362	348 – 377	358-372
Week 52/ EOS	52	392	378-407	No dosing

8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.00	24-JAN-2018	NA	Document finalized
2.00	19-NOV-2019	Description of interim analyses was updated.	Specifications of the timing of an interim analysis were changed. The procedures of interim analysis were revised.
		Definition of Full Analysis Set was updated.	Subjects who enroll in the study but don't have primary FSGS, will not be included in the FAS, since they are not included in the population of interest, primary FSGS, and are not at risk for recurrence of their primary FSGS.
		Definition of primary efficacy endpoint was updated.	Subjects with a protein-creatinine ratio (≥ 3.0 g/g) on Day 0 only (day of skin closure) will not be considered to have a recurrence if this is the only day with the elevated ratio and subsequent values do not meet this limit.
		Pharmacodynamic Analysis Set was removed.	Per team decision.
		Added descriptions for analyses of several endpoints.	Added detailed analysis for Anti-bleselumab antibodies, anti-bleselumab neutralizing antibodies, bleselumab bi-specific antibodies, and anti-CD40 auto-antibodies.
		Added analysis of New Onset of Diabetes after Transplant (NODAT)	Per DSMB request.
		Additional changes to correct typographical errors or add clarity	To easily understand the text in the document.

9 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

Laupacis A, Pus N, Muirhead N, Wong C, Ferguson B, Keown P. Disease-Specific Questionnaire for Patients with a Renal Transplant. Nephron. 1993; 64: 226-231.

9.1 Appendix 1: Grading of Acute Kidney Allograft Rejection

2007 Update to the Banff 97 Diagnostic Categories for Renal Allograft Biopsies

Category	Global Assessment	Histopathological Findings
1	**Normal**	
2	**Antibody-mediated changes** (may coincide with categories 3, 4 and 5 and 6)	Due to documentation of circulating anti-donor antibody, and C4d or allograft pathology C4d depletion without morphologic evidence of active rejection Cd4+, presence of circulating anti-donor antibodies, no signs of acute or chronic TCMR or ABMR (i.e., g0, cg0, ptc0, no ptc lamination). Cases with simultaneous borderline changes or ATN are considered indeterminate
	Acute antibody-mediated rejection[1]	Cd4+, presence of circulating anti-donor antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade):
	Grade I	ATN-like minimal inflammation
	Grade II	Capillary and/or glomerular inflammation (pct/g >0) and/or thromboses
	Grade III	Arterial – v3
	Chronic active antibody-mediated rejection[1]	Cd4+, presence of circulating anti-donor antibodies, morphologic evidence of chronic tissue injury, such as glomerular double contours and/or peritubular capillary basement membrane multi-layering and/or interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening in arteries
3	**Borderline** (may coincide with categories 2 and 5 and 6)	"Suspicious" for acute T-cell-mediated rejection This category is used when no intimal arteritis is present, but there are foci of tubulitis (t1, t2, or t3) with minor interstitial infiltrate (i0 or i1) or interstitial infiltrate (i2, i3) with mild (t1) tubulitis
4	**T-cell mediated rejection** (TCMR, may coincide with categories 2 and 5 and 6)	
	Acute T-cell-mediated rejection (Type/Grade)	
	Grade IA	Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)
	Grade IB	Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)
	Grade IIA	Cases with mild-to-moderate intimal arteritis (v1)
	Grade IIB	Cases with severe intimal arteritis comprising >25% of the luminal area (v2)
	Grade III	Cases with "transmural" arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)
	Chronic active T-cell-mediated rejection	"Chronic allograft arteriopathy" (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)

Category	Global Assessment	Histopathological Findings
5	**Interstitial fibrosis and tubular atrophy**	No evidence of specific etiology (may include nonspecific vascular and glomerular sclerosis, but severity graded by tubulointersitial features)
	Grade I	Mild interstitial fibrosis and tubular atrophy (<25% cortical area)
	Grade II	Moderate interstitial fibrosis and tubular atrophy (26-50% of cortical area)
	Grade III	Severe interstitial fibrosis and tubular atrophy/loss (>50% of cortical area)
6	**Other**	Changes not considered to be due to rejection-acute and/or chronic (for diagnosis see full article Table 14; may include isolated g, cg or cv lesions and coincide with categories 2, 3, 4 and 5)

[1] Suspicious for antibody-mediated rejection if C4d (in the presence of antibody) or alloantibody (C4d+) not demonstrated in the presence of morphologic evidence of tissue injury.

For complete description, please refer to the below reference.

Reference:

Solez K, Colvin RB, Racusen LC, et al. Banff '07 classification of renal allograft pathology: updates and future directions. Am J Transplant 2008;8: 753-60.

9.2 Appendix 2: Clustered Safety Events

Adverse Events, Laboratory Values, and Vital Sign Values That Constitute Clusters

Example

Cluster	**Events (adverse events‡, lab values, and vitals) that compose the cluster**	
BK Infection	BK virus infection Polyomavirus associated nephropathy	
Cardiac	Acute myocardial infarction Angina pectoris Aortic valve incompetence Arrhythmia Atrial fibrillation Atrioventricular block first degree Bradycardia Cardiac arrest Cardiac failure congestive Cardiac murmur Cardiomegaly Chest discomfort Chest pain Coronary artery disease Dyspnoea exertional Electrocardiogram change Endocarditis	Extrasystoles Heart rate increased Labile blood pressure Mitral valve stenosis Myocardial infarction Myocardial ischaemia Palpitations Sinus bradycardia Sinus tachycardia Supraventricular tachycardia Tachycardia Troponin increased Ventricular extrasystoles Ventricular tachycardia
Cardiovascular	Arterial thrombosis limb Arteriosclerosis Arteriovenous fistula Arteriovenous fistula site haemorrhage Arteriovenous fistula thrombosis	Deep vein thrombosis Dyslipidaemia Pelvic venous thrombosis Peripheral vascular disorder Pulmonary embolism Pulmonary oedema Vasodilatation
Cytomegalovirus	Cytomegalovirus colitis Cytomegalovirus infection Cytomegalovirus test positive Cytomegalovirus viraemia	
…	…	…

‡ The complete list of adverse events that define each cluster will be finalized after the final data review. The list of potential adverse event terms for the defined clusters is greater than 1200 and will not be listed here. There is a dataset that has been created with the targeted terms and is periodically updated. A set of programs references this dataset with a standard set of terms and provides the adverse events within each cluster for an individual study.

9.3 Appendix 3: Liver Safety Monitoring and Assessment

If laboratory testing for a subject enrolled in study and receiving study drug reveals an increase of serum aminotransferases (AT) to > 3X ULN, or bilirubin > 2X ULN, at least all four of the usual serum hepatic measures (ALT, AST, ALP, and TBL) should be repeated. Testing should be repeated within 48-72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and marked liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and marked where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3 x ULN	or	> 2 x ULN
Marked	> 3 x ULN	and	> 2 x ULN

In addition, the subject should be considered to have marked hepatic abnormalities for any of the following:

- ALT or AST > 8X ULN
- ALT or AST > 5X ULN for more than 2 weeks
- ALT or AST > 3X ULN and INR > 1.5
- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or marked abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and marked abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) or an appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Marked hepatic liver function abnormalities, in the absence of another etiology, may be considered an important medical event and reported as a Serious Adverse Event (SAE). The sponsor should be contacted and informed of all subjects for whom marked hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'adverse events' on the AE page of CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, should be entered on the concomitant medication page of CRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents
- Based on the subject's history, other testing may be appropriate including:
    - acute viral hepatitis (A,B, C, D, E or other infectious agents).
    - ultrasound or other imaging to assess biliary tract disease
    - other laboratory tests including INR, direct bilirubin
- Consider gastroenterology or hepatology consultations
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFTs, such as viral hepatitis, pre-existing or acute liver disease or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST > 8X ULN
- ALT or AST > 5X ULN for more than 2 weeks
- ALT or AST > 3X ULN and (TBL > 2X ULN or INR > 1.5)
- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring for a subject with moderate or marked hepatic laboratory tests is not possible, drug should be discontinued.

References

(1) Guidance for Industry titled “Drug-Induced Liver Injury: Premarketing Clinical Evaluation” issued by FDA on July 2009.

(2) Ware JE Jr, Kosinski M, Dewey JE. How to Score Version Two of the SF-36 Health Survey. Lincoln, RI: Quality Metric, Incorporated, 2000.

(3) Ware JE Jr, Bjorner JB, Kosinski M. SF-36 Health Survey: Manual and Interpretation Guide. 2nd ed. Lincoln, RI: Quality Metric, 2007.

9.4 Appendix 4: Handling of the Human Leukocyte Antigen (HLA) Mismatching

The HLA antigens are located on the cell surface. The genes encoding the HLA antigens are on chromosome 6 and have co-dominant expression: both alleles of one gene locus result in a surface HLA antigen. HLA class I antigens consist of a heavy chain and a β2m unit and include the HLA-A, HLA-B and HLA-C antigens, while HLA class II antigens are constituted by two heavy chains and include the HLA-DR, HLA-DP and HLA-DQ antigens. All HLA genes (loci) are very polymorphic: each has various alleles (variants) that can be distinguished by DNA sequencing of gene DNA or by serological techniques for detection of the gene products (the HLA antigens on the cell surface): HLA typing.

The HLA types for HLA-A, HLA-B and HLA-DR are entered in the eCRF. Broad HLA types comprise of several fine specificities, the narrow types, but it is only the broad type codes (roughly equivalent to the serologically defined antigen or serotype (allotype)) that are entered into the eCRF.

Example:

	HLA A		HLA B		HLA DR	
Donor:	A11	A66	B5	-	DR5	DR6

	HLA A		HLA B		HLA DR	
Recipient:	A25	A32	B12	B5	DR5	DR7

Both codes for a locus will be considered identical (homozygote) if only one code is entered. In this case, the investigator will either enter the code twice or put a dash for the second entry (or leave the second entry blank). The order of the entries is unimportant. A mismatch between a donor and a recipient exists if the donor has an antigen which doesn't appear in the recipient.

Calculation of the number of HLA mismatches:

For the comparison of the HLA types between the donor and the recipient, the following steps should be done to calculate the number of HLA mismatches:

1. If the entry for a locus is a numeric code and a dash (or missing), then the dash for that locus is to be replaced (for calculation only) by the numeric code (homozygote).

2. The following rules should be applied when calculating the number of mismatches within a HLA A, B, and DR locus:

- If both codes are missing in either the donor or recipient, the number of mismatches is unknown (missing)

- If the two codes are non-missing and identical for the recipient and the donor (without regard to the order) or the donor is homozygote and the donor code matches either one of the recipient's codes, then the number of mismatches is 0.

Examples:

Donor	Recipient	Mismatch
A1 A2	A2 A1	0
A2 A2	A2 A1	0

- If one code from the donor exists in the recipient but the other code is different between the donor and recipient or the donor has identical codes (homozygote) but they do not match either code in the recipient, then the number of mismatches is 1.

Examples:

Donor	Recipient	Mismatch
A2 A3	A2 A1	1
A2 A3	A2 A2	1
A2 A2	A3 A4	1
A2 A2	A1 A1	1

- If the donor is not homozygote and all codes are different between the donor and the recipient, then the number of mismatches is 2.

Example:

Donor	Recipient	Mismatch
A1 A2	A3 A4	2

3. If the number of mismatches from any of the three loci is missing, then total number of HLA mismatches is missing. Otherwise, the total number of HLA mismatches is the sum of the mismatches from the three loci.

An example following rules 1-4 above is provided below:

	HLA A		HLA B		HLA DR	
Donor: (broad types)	A11	A10	B5	B5	DR5	DR6

	HLA A		HLA B		HLA DR	
Recipient: (broad types)	A10	A19	B12	B5	DR5	DR7

	HLA A	HLA B	HLA DR	Total
Mismatch:	1	0	1	2

9.5 Appendix 5: Calculation of Dose when Dose Varies within a Visit Interval

Here are 3 examples for the Day 90 visit which has a window from 81 to 115.

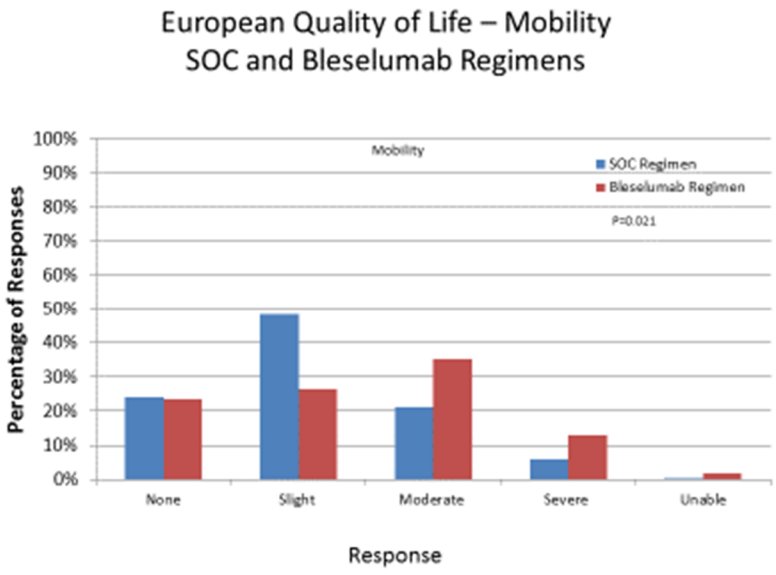
	Last Dose	--------Dose---------		
			Start	Stop
Pt#	Day	Level	Day	Day
1	110	5	1	100
1	110	0	101	105
1	110	10	106	110
2	500	5	1	100
2	500	0	101	105
2	500	10	106	500
3	500	5	1	100
3	500	0	101	105
3	500	10	106	110
3	500	0	107	120
3	500	7	121	500

Mean dose for Pt 1 at Day 90 is calculated as:
[5mg*(100-81+1) + 0mg*(105-101+1)+ 10mg*(110-106+1)]/[110-81+1]=5mg/day

Mean dose for Pt 2 at Day 90 is calculated as:
[5mg*(100-81+1) + 0mg*(105-101+1)+ 10mg*(115-106+1)]/[115-81+1]=5.71mg/day

Mean dose for Pt 3 at Day 90 is calculated as:
[5mg*(100-81+1) + 0mg*(105-101+1)+ 10mg*(110-106+1)+0mg(115-111+1)]/[115-81+1]=4.29mg/day

9.6 Appendix 6: Example for Presenting Results for EQ-5D-5L



This example was created using excel. The final graphs will be created using SAS and the legend will be contained within the graph rather than located to the right of the graph.

9.7 Appendix 7: Protocol Deviation Codes and Sub-codes

Deviation Code	Deviation sub-code	Deviation
PD1	PD1	Entered into the study even though they did not satisfy entry criteria.
PD1	IN01	Inclusion 1
PD1	IN02	Inclusion 2
PD1	IN03	Inclusion 3
PD1	IN04	Inclusion 4
PD1	IN05	Inclusion 5
PD1	IN06	Inclusion 6
PD1	IN07	Inclusion 7
PD1	IN08	Inclusion 8
PD1	IN09	Inclusion 9
PD1	IN10	Inclusion 10
PD1	IN11	Inclusion 11
PD1	EX01	Exclusion 1
PD1	EX02	Exclusion 2
PD1	EX03	Exclusion 3
PD1	EX04	Exclusion 4
PD1	EX05	Exclusion 5
PD1	EX06	Exclusion 6
PD1	EX07	Exclusion 7
PD1	EX08	Exclusion 8
PD1	EX09	Exclusion 9
PD1	EX10	Exclusion 10
PD1	EX11	Exclusion 11
PD1	EX12	Exclusion 12
PD1	EX13	Exclusion 13
PD1	EX14	Exclusion 14
PD1	EX15	Exclusion 15
PD1	EX16	Exclusion 16
PD1	EX17	Exclusion 17
PD1	EX18	Exclusion 18
PD1	EX19	Exclusion 19
PD1	EX20	Exclusion 20
PD1	EX21	Exclusion 21
PD2		Developed withdrawal criteria during the study and was not withdrawn.
PD3		Received wrong treatment or incorrect dose.
PD3	OOW3	Visit missed.
PD3	OOW4	Bleselumab missed dose.
PD3	TAC1	Subject received tacrolimus but not randomized to receive tacrolimus.
PD3	TAC2	Subject received wrong dose of tacrolimus.
PD3	MMF1	Subject received MMF but was not randomized to receive MMF.
PD3	MMF2	Subject received wrong dose of MMF.

PD3	ASP1	Subject received Bleselumab but not randomized to receive Bleselumab.
PD3	ASP2	Subject received wrong dose of Bleselumab.
PD3	ASP3	Subject received wrong vial of Bleselumab.
PD3	ASP5 .	Flush not given post dosing following Bleselumab administration.
PD3	ASP 7	Subject received an incorrect preparation of Bleselumab.
PD3	STE2	Steroids completely withdrawn.
PD4		Received excluded concomitant treatment.
PD5		SAE was not submitted in the required time frame

9.8 Appendix 8: Key Contributors and Approvers

List of Key Contributors and Approvers

Key Contributors

The following contributed to or reviewed this Statistical Analysis Plan as relevant to their indicated discipline or role.

Primary author (s)

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Author and Approver Signatories

PPD Global Data Science was the study statistician for this study.

PPD Global Data Science was the biostatistics peer reviewer of this Statistical Analysis Plan

This Statistical Analysis Plan was approved by:

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This Statistical Analysis Plan was approved by:

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