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

Protocol for Phase 2a Study of Bleselumab (ASKP1240)

ISN/Protocol 7163-CL-3201

Version 3.1

Incorporating Nonsubstantial Amendment 2 [See Attachment 1]

02 February 2018

IND 100686

Sponsor:

Astellas Pharma Global Development, Inc. (APGD)
1 Astellas Way
Northbrook, IL 60062

Protocol History:
Version 1.0 [08Jul2016]
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Version 2.0 [10May2017]
Version 3.0 [23Jan2018]

Investigator:
Investigator information is on file at Astellas

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I. SIGNATURES

1. SPONSOR'S SIGNATURE

Required signatures (e.g., Protocol authors, Sponsor's reviewers and contributors, etc.) are located in Section 13, Sponsor Signatures; e-signatures (when applicable) are located at the end of this document.

2. COORDINATING INVESTIGATOR'S SIGNATURE

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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02 February 2018

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: _____ _____
<Insert name, department/affiliation, name of institution> Date (DD Mmm YYYY)

Printed Name: _____

Address: _____

_____

3. INVESTIGATOR'S SIGNATURE

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02 February 2018

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that sub-Investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: _____

<Insert name and qualifications of the Investigator> Date (DD Mmm YYYY)

Printed Name: _____

Address: _____

_____

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) **See Section 5.5.5**	PPD **Please fax the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Medical Safety Pharmacovigilance** **Fax number: 1-888-396-3750** **Email: Safety-US@astellas.com**
Clinical Research Contacts:	PPD PPD
Medical Monitors:	PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

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
APC	Antigen-presenting cell
APGD	Astellas Pharma Global Development, Inc.
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the plasma concentration‑time curve
AUC_{inf}	Area under the concentration-time curve from time 0 to infinity
AUC_{336}	Area under the concentration-time curve at 336 hours
$AUC_{0\text{-}168h}$	Area under the concentration-time curve from baseline to 168 hours
$AU_{0\text{-}336h}$	Area under the concentration-time curve from baseline to 336 hours
AUST	Astellas US Technologies, Inc.
BKV	BK virus
BKVAN	BK virus associate nephropathy
BPAR	Biopsy-proven acute rejection
BUN	Blood urea nitrogen
CD	Cluster of differentiation
CD40L	CD40 ligand (CD154)
CI	Confidence interval
CIT	Cold ischemia time
C_{max}	Maximum concentration
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CNS	Central nervous system
CRO	Contract research organization
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
eCRF	Electronic case report form
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
e/PRO	Electronic/Patient Reported Outcomes
EOT	End of Treatment
EQ-5D-5L	European quality of life – 5 dimensions – 5 levels

Abbreviations	Description of abbreviations
ESRD	End stage renal disease
FcR	Fc receptor
FIH	First-in-human
FSGS	Focal segmental glomerulosclerosis
GC	Germinal centers
GCP	Good clinical practice
GFR	Glomerular filtration rate
GMP	Good manufacturing practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IC_{50}	Half-maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IgG	Immunoglobulin G
IL	Interleukin
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
IVIG	Intravenous immunoglobulin
KTQ	Kidney transplant questionnaire
LA-CRF	Liver abnormality case report form
LDH	Lactate dehydrogenase
LFT	Liver function test
MCS	Mental component summary
MDRD	Modification of Diet in Renal Disease
MFI	Mean fluorescence intensity
MMF	Mycophenolate mofetil
MST	Mean survival time
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHP	Non-human primate
NOAEL	No-observed-adverse-effect level
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PCS	Physical component summary
pFSGS	Primary focal segmental glomeruloscerosis
PGx	Pharmacogenetics
PKAS	Pharmacokinetic analysis set
PTLD	Post-transplant lymphoproliferative disorder

Abbreviations	Description of abbreviations
rFSGS	Recurrent focal segmental glomerulosclerosis
rTAC	Reduced tacrolimus
SAE	Serious adverse event
SAF	Safety analysis set
sCD154	Soluble CD154
SF-36s	Short form 36-item health survey score version 2.0
SOC	Standard of care
SOP	Standard operating procedure
SPC	Summary of product characteristics
Tac	Tacrolimus
t_{max}	Time to attain C_{max}
$t_{1/2}$	Terminal elimination half-life
TB	Tuberculosis
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TLF	Tables, listings and figures
TNF	Tumor necrosis factor
ULN	Upper limit of normal
VAS	Visual analogue scale
WFI	Water for injection

Definition of Key Study 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 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.
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.
Cold Ischemia Time	Time between initiation of cold preservation to final unclamping in the recipient.
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 subject-reported outcome that is collected by electronic methods.
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.
Enroll	The point in time when a subject signs the informed consent.
Hepatic enzymes	Also called Liver enzymes: Aspartate aminotransferase, (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP).
Interim Analysis	Analysis comparing intervention groups at any time before the formal completion of the trial.
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).

Terms	Definition of terms
Liver Function Test	Includes aspartate aminotransferase, (AST), alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) and/or total bilirubin, and/or prothrombin time (PT/INR).
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 21/month 12/EOS). See EOS term.
Total ischemia time	Time from circulatory arrest in donor to final unclamping of the kidney in the recipient.
Warm Ischemia Time	Time between circulatory arrest in donor to initiation of cold preservation.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	02 February 2018, Version 3.1
Sponsor: Astellas Pharma Global Development, Inc. (APGD)	**Protocol Number:** 7163-CL-3201
Name of Study Drug: Bleselumab (ASKP1240)	**Phase of Development:** 2a
Title of Study: 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	
Planned Study Period: From October 2016 to May 2020	

Study Objective(s):

Primary Objective

- 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 (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.

Secondary Objectives

- 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 (rFSGS) through 3, 6 and 12 months post-transplant.
- To assess the safety of the bleselumab regimen compared with the SOC regimen.

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 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).
- 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 nephrotic-range proteinuria with protein-creatinine ratio (≥ 3 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 auto-anti-cluster of differentiation (CD)40 antibody 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]).
Planned Total Number of Study Centers and Location(s): Approximately 45 investigative centers in North America.
Study Population: Male and female subjects 18 years of age or older who are de novo, living or deceased donor kidney recipients and have biopsy-proven primary focal segmental glomerulosclerosis (pFSGS)
Number of Subjects to be Enrolled/Randomized: 60 (30 subjects in each arm [Arm 1: SOC regimen (basiliximab induction, tacrolimus, steroids and MMF)] and [Arm 2: Bleselumab regimen (basiliximab induction, tacrolimus, steroids and bleselumab)])
Study Design Overview: This is a Phase 2a, randomized, open-label, active control, multi-center study to assess the efficacy and safety of bleselumab in preventing the rFSGS in de novo kidney transplant subjects. The study will consist of the following periods: • Screening (days -21 to -1) • Transplant (day 0 [zero]) • Post-transplant (day 0/post-skin closure through 12 months post-transplant) Prior to any study-related assessments, the Informed Consent Form (ICF)/Authorization will be signed by the subject (visit 1). All subjects will enter into a screening period (days -21 to -1 prior to transplant), undergo a transplant (day 0), and are then to 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 and stratified by previous kidney transplant status (no or yes) to open-label treatment of 1 of 2 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 will receive induction therapy with basiliximab (Simulect® [the first dose as a 20 mg bolus injection prior to transplantation or intra-operatively before revascularization, and the second a 20 mg bolus injection on day 3 or 4 or 5 post-transplant]). For subjects randomized to Arm 2, bleselumab 200 mg will be given intravenously over 30 minutes on day 0, to be initiated intra-operatively prior to revascularization of the allograft, and then at 200 mg per infusion on days 7, 14, 28, 42, 56, 70 and 90/month 3, and once per month through month 12.

The initial dose of tacrolimus (Prograf®) must be anticipated to be administered orally within 48 hours post-transplant at 0.1 mg/kg/day (two equally divided doses at 0.05 mg/kg/day every 12 hours with a target trough level of 4 – 11 ng/mL for the duration of the study). Tacrolimus may be given intravenously IF medically indicated (only early post-transplant when oral is not tolerated, and should be discontinued as soon as the subject can tolerate oral administration, usually within 2-3 days post-transplant).

For subjects randomized to Arm 1, the initial dose of MMF at 1 g bid may be given up to 12 hours preoperatively, or before revascularization. MMF may be given orally or intravenously.

After the initial doses of tacrolimus and MMF, dose adjustments in the post-transplant period are allowed.

Corticosteroids will be administered as an intravenous bolus of 500, 250, 125 and 60 mg of methylprednisone (or equivalent oral/intravenous corticosteroid dose), on days 0 and 1 and 2 and 3, respectively.

Oral prednisone is to be tapered according to the following schedule, and continue through 12 months post-transplant:

Days Post-transplant	Prednisone Equivalent (mg)
Days 4 - 14	20 – 30
Days 15 - 28	10 – 20
Day 29 and on	5 – 10

Steroid withdrawal is not allowed.

Subjects are to return to the study center in the post-transplant period (visits 2 – 21) in order to assess efficacy and safety, completion of clinical assessments, collection of pharmacokinetic samples, and to complete electronic patient reported outcome (ePRO) measurements.

Only subjects in Arm 2 are to provide pharmacokinetic samples. On day 0, pharmacokinetic samples are to be collected within 30 minutes or less pre-initial, and post-initial, intraoperative, bleselumab administration. 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 the day 28 visit. 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.

All subjects who have not had a biopsy with a diagnosis of recurrent FSGS (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 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.

A Data Monitoring Committee (DMC) will be responsible for data evaluation and will meet as defined in the DMC charter.

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

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.

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.

Inclusion/Exclusion Criteria

Inclusion:

A subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulation (e.g., Health Insurance Portability and Accountability Authorization for US sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Male or female subject must be ≥ 18 years of age.
3. Subject is a recipient of a de novo kidney from a living or deceased donor and has biopsy-proven, pFSGS as a cause of ESRD in their native kidneys (initial diagnosing biopsy report is required). A subject who has biopsy-proven pFSGS as a cause of ESRD, and their most current graft failure(s) is due to biopsy-proven, recurrent FSGS, is eligible.
4. Subject is anticipated to receive first oral dose of tacrolimus within 48 hours of transplant procedure.
5. Female subject must either:
    - Be of non-child bearing potential:
        - Post-menopausal (defined as at least 1 year without any menses) prior to screening, or
        - Documented surgically sterile
    - Or, if of childbearing potential,
        - Agree not to try to become pregnant during the study and for 90 days post-last dose,
        - And have a negative serum pregnancy test at screening,
        - And, if heterosexually active, agree to consistently use two forms of highly-effective birth control* (at least one of which must be a barrier method) starting at screening, throughout the study and for 90 days post-last dose.
6. Female subject must agree not to breastfeed starting at screening, throughout the study and for 90 days post-last dose.
7. Female subject must not donate ova starting at screening, throughout the study and for 90 days post-last dose.
8. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective form of contraception consisting of two forms of birth control* (at least one of which must be a barrier method) starting at screening, throughout the study and for 90 days post-last dose.
9. Male subject must not donate sperm starting at screening, throughout the study and for 90 days post-last dose.
10. Subject must be willing and able to comply with the study requirements including prohibited concomitant medication restrictions.
11. Subject agrees not to participate in another interventional study while on treatment.

*Highly effective forms of birth control include:
- Consistent and correct usage of established oral contraception
- Injected or implant hormonal methods of contraception
- Established intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: condom or occlusive cap (diaphragm ore cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
- Any male partner that has undergone effective surgical sterilization
- Any female partner that has undergone effective surgical sterilization

Waivers to the inclusion criteria will NOT be allowed.

Exclusion:

A subject will be excluded from participation if any of the following apply:

1. Subject has Induction therapy, other than study-assigned basiliximab, planned as part of initial immunosuppressive regimen.
2. Subject has a diagnosis of secondary FSGS (familial, virus associated, medication, etc., protocol Appendix 12.5) or a defined genetic cause of FSGS.
3. Subject has previously received any organ transplant including a kidney and the most current graft failure(s) is not due to the recurrence of FSGS.
4. Subject will receive a kidney as part of a multi-organ transplant.
5. Subject will receive a dual kidney transplant from a deceased donor.
6. Subject will receive a kidney with an anticipated cold ischemia time of > 30 hours.
7. Subject will receive a kidney that meets **BOTH** Extended Criteria Donor (ECD) and Donation after Cardiac Death (DCD) criteria. (A kidney that meets either ECD **OR** DCD criteria may be eligible for inclusion.)
8. Subject will receive a blood group system (A, AB, B, O, ABO) incompatible (including A_2 into B or O) donor kidney.
9. Recipient or donor is known to be seropositive for human immunodeficiency virus (HIV).
10. Subject has a current calculated panel reactive antibody (cPRA) level > 50%.
11. Subject has a current malignancy or a history of malignancy (within the past 5 years), except non-metastatic basal or squamous cell carcinoma of the skin that has been treated successfully, or a renal cell carcinoma that has been treated successfully more than 2 years prior to transplantation.
12. Subject has significant liver disease, defined as having during the past 21 days consistently elevated aspartate aminotransferase (SGOT) (AST) and/or alanine aminotransferase (SGPT) (ALT) levels greater than 1.5 times the upper value of the normal range of the investigational site.
13. Subject is known to have a positive test for latent tuberculosis (TB) and has not previously received adequate anti-microbial therapy/or would require TB prophylaxis after transplant.
14. Subject has an uncontrolled concomitant infection or any other unstable medical condition that could interfere with the study objectives.
15. Subject is concurrently participating in another drug study or has received an investigational drug up to 30 days or 5 half-lives (depending on medication) prior to transplant.

16. Subject is currently receiving or has received up to 8 weeks prior to transplant an immunologic

biologic compound (i.e., tumor necrosis factor inhibitors, [e.g., etanercept, adalimumab], intravenous immunoglobulin). A subject who has previously received a kidney organ transplant and is currently on an immunosuppression regimen that includes MMF, or any of its components, must discontinue MMF.

17. Subject has previously received bleselumab or participated in a clinical study with bleselumab.
18. Subject has a known hypersensitivity to tacrolimus, MMF, basiliximab, corticosteroids, or any of their components.
19. Subject has any form of substance abuse, psychiatric disorder, or a condition that in the opinion of the Investigator could invalidate communication with the Investigator.
20. Subject has a clinically significant abnormal electrocardiogram (ECG) at screening.
21. Subject is unlikely to comply with the visits scheduled in the protocol, in the opinion of the Investigator.

Waivers to the exclusion criteria will NOT be allowed.

Investigational Product(s):

Bleselumab (ASKP1240) – Immunosuppression

Bleselumab will be provided by the Sponsor for up to 12 months post-transplant and the subject is then to be placed on a SOC regimen of the Investigator's choice.

Dose(s)

Up to a total of 17 doses, at 200 mg per dose

Mode of Administration

Intravenous infusion

Duration

Up through 12 months (day 0 [initiated intra-operatively, prior to revascularization of the allograft and may continue during reperfusion]; and, days 7, 14, 28, 42, 56, 70 and 90/month 3, and once per month through month 12 as a single, 30-minute infusion).

Comparative Drug(s):

Mycofenolate Mofetil (MMF) – Immunosuppression

The oral formulations (capsules and/or tablets) will be provided by the Sponsor through 12 months post-transplant and is then to be sourced by the site and provided via commercial supply.

MMF for intravenous administration is allowed but will not be supplied by the Sponsor.

A switch from MMF to mycophenolic acid (Myfortic®) will be allowed for medical reasons but will not be supplied by the Sponsor.

Dose(s)

Initial dose at 1 g bid may be given up to 12 hours preoperatively, or before revascularization. Post-initial dose, adjustments in the post-transplant period are allowed.

Mode of Administration

Oral or intravenously

Duration

Post-initial dose, daily through 12 months post-transplant.

Other Regimen Component(s):

Basiliximab (Simulect®) – Induction, Immunosuppression

Basiliximab will be sourced by the site and provided via commercial supply.

Dose(s)

20 mg

Mode of Administration

Bolus injections

Duration

Up through day 5 (1st dose on day 0 [prior to transplant or intra-operatively prior to revascularization], and 2nd dose on day 3 or 4 or 5 post-transplant).

Tacrolimus Capsules (Prograf®) – Immunosuppression

Tacrolimus will be provided by the Sponsor through 12 months post-transplant and is then to be sourced by the site and provided via commercial supply.

Dose(s)

Initial dose at 0.1 mg/kg/day (two equally divided doses at 0.05 mg/kg/day every 12 hours) on day 0. Post-initial dose, adjustments with a target trough level of 4 – 11 ng/mL in the post-transplant period are allowed.

Mode of Administration

Oral or intravenous IF medically indicated (only during early post-transplant when oral is not tolerated, and should be discontinued as soon as the subject can tolerate oral administration, usually within 2 – 3 days post-transplant).

Duration

Post-initial dose, daily through 12 months post-transplant.

Corticosteroids (methylprednisone, or equivalent oral/iv corticosteroid dose) – Immunosuppression

Corticosteroids will be sourced by the site and provided via commercial supply.

Dose(s)

500, 250, 125 and 60 mg methylprednisone (or equivalent oral/intravenous corticosteroid dose)

Mode of Administration

Oral or intravenous bolus

Duration

Days 0 and 1 and 2 and 3, respectively, and through 12 months post-transplant.

Oral prednisone is to be tapered according to the following schedule, and continue through 12 months post-transplant:

Days Post-transplant	Prednisone Equivalent (mg)
Days 4 - 14	20 – 30
Days 15 - 28	10 – 20
Day 29 and on	5 – 10

Steroid withdrawal is not allowed.

Concomitant Medication Restrictions or Requirements:

Cytomegalovirus Prophylaxis

All subjects (with the exception of those in whom both the donor and recipient are serologically negative [D-/R-] for Cytomegalovirus (CMV) must receive prophylaxis with valganciclovir that will be dosed consistent with the package insert. Duration of therapy should be approximately 200 days in D+/R- combinations, and approximately 100 days in the remaining subjects.

For leukopenia, the recommended approach is to adjust doses of other drugs that may be associated with leukopenia prior to making changes in the valganciclovir dose.

Pneumocystis jiroveci Pneumonia Prophylaxis

Pneumocystis jiroveci pneumonia prophylaxis must be administered to all study participants according to the standard institutional protocol and applied uniformly to all enrolled subjects regardless of treatment group. If there is no institutional protocol, the investigator must decide on appropriate *Pneumocystis jiroveci* pneumonia prophylaxis.

Fungal Prophylaxis

A standard antifungal prophylactic regimen per institutional protocol must be given uniformly to all enrolled subjects regardless of treatment group. If there is no institutional protocol, the Investigator must decide on appropriate fungal prophylaxis.

Bacterial Prophylaxis

Peri-operative bacterial prophylaxis must be given per institutional protocol and should be given uniformly to all enrolled subjects regardless of treatment group. If there is no institutional protocol, the Investigator must decide on appropriate bacterial prophylaxis.

Duration of Treatment:

Up to 12 months.

Bleselumab will be provided for up to 12 months, after which subjects are to be placed on a SOC regimen of the Investigator's choice.

Formal Stopping Rules:

Subject Level

Subjects must discontinue bleselumab per below, but are allowed to continue on the protocol-defined visit schedule for the collection of safety and clinical assessment information:

- Subjects whose liver function tests meet one of the following criteria, verified by 2 consecutive measurements, and in the absence of other etiologies (e.g., biliary stenosis or obstruction, viral hepatitis other than CMV, etc.):
  - ALT or AST > 8 x upper limit of normal (ULN)
  - ALT or AST > 5 x ULN for more than 2 weeks
  - ALT or AST > 3 x ULN and (total bilirubin [TBL] > 2 x ULN or international normalized ratio [INR] > 1.5 x ULN)
  - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- BK nephropathy confirmed by renal biopsy (Section 5.5.1.1.5)
- CMV End Organ Disease (Appendix 12.6)
- Subjects who develop severe bone marrow suppression as defined by the following in the absence of other etiologies (e.g., bleeding, other established causes of neutropenia) and have been verified by two (2) consecutive results within 14 days of the first detection that occur after Day 28 post-transplant:

- Anemia: Hemoglobin < 6.5 g/dL graded National Cancer Institute Common Terminology Criteria for Adverse Events criteria (NCI-CTCAE) Grade 4 and/or
- Agranulocytosis: Absolute Neutrophil Count (ANC) < 100 cells/mm^3 graded NCI-CTCAE Grade 4

- Subjects who require plasmapheresis for any reason post-initial bleselumab treatment
- In the subjects' best interest per Investigator discretion

Endpoints for Evaluation:

Primary:

- Recurrence of FSGS 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.

Secondary:

- Recurrence of FSGS defined as 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.
- Biopsy-proven acute rejection (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.

Exploratory:

Efficacy

- Graft and patient 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).
- Time to rFSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g).
- Time to rFSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g) or initiation of plasmapheresis.
- Time to rFSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g), death, graft loss or lost to follow-up.
- Time to recurrence of biopsy-proven (blinded, central read) FSGS.
- Time to first BPAR (Banff Grade ≥ 1, local read).
- Urine protein-creatinine ratio through 6 and 12 months post-transplant.
- Urine albumin-creatinine ratio through 3, 6 and 12 months post-transplant.
- Change in auto-anti-CD40 antibodies from baseline.
- Change in patient-reported outcomes from baseline (SF-36s, EQ-5D-5L, and KTQ).

Safety

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

Statistical Methods

Sample size justification

The primary variable is rFSGS defined by 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.	

It has been estimated from the literature that the expected FSGS recurrence rate for the SOC group is between 30 and 50% following a first kidney transplant and up to 80% for re-transplant with most occurring by three months post-transplant. In the previous study with these same treatments in kidney transplant patients, there were 3 of approximately 50 patients who experienced death, graft loss, or loss to follow-up in each of the two planned treatment arms. Thus, imputing death, graft loss or lost-to-follow-up as rFSGS is not expected to have a sizeable and differential impact on the rFSGS estimates. Literature estimates of FSGS recurrence were used to examine the precision 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 2-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 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)
Difference and 95% CI (2-sided)	0.233 -0.039 to 0.505	0.20 -0.06 to 0.46	0.133 -0.112 to 0.355
40% Reduction from SOC	0.30 (9/30)	0.267 (8/30)	0.20 (6/30)
Difference and 95% CI (2-sided)	0.20 -0.068 to 0.434	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 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 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

General Considerations

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 is a sufficient number of patients with more than one kidney transplantation. Endpoints analyzed with Fisher's Exact test may be analyzed with a CMH test stratifying by previous kidney transplant status (no or yes) if there is a sufficient number of patients with more than 1 kidney transplantation. For time-to-event endpoints, Cox regression will be used comparing the 2 treatment groups and will include previous kidney transplantation (no, yes) in the model provided there are sufficient multi-transplant patients.

Efficacy

The percentage of subjects who have a rFSGS, defined by nephrotic range proteinuria or death, graft loss or loss to follow-up, by 3, 6 and 12 months will be computed along with a 95% CI for each estimate and the treatment difference (Arm 2 – Arm 1). Similar summaries will be created for the biopsy-proven rFSGS by a blinded, central read at 3, 6 and 12 months. Treatment differences (Arm 2 – Arm 1) in BPAR incidence (T- or B-cell) through 3, 6 and 12 months will be calculated. A 2-sided 95% confidence interval will be constructed for the treatment differences

Efficacy failure, defined as BPAR, death, graft loss or lost to follow-up will be analyzed as described for rFSGS.

The mean estimated glomerular filtration rate (eGFR) value based on MDRD criterion at 12 months will be compared between the control and experimental groups using an analysis of covariance (ANCOVA) with treatment as a factor and the week 4 value as a covariate.

Graft survival is defined as an absence of all of the following: subject death, re-transplant, nephrectomy, or return to permanent dialysis (> 30 days). Incidence of graft survival will be provided and compared between the treatment groups using Fisher's exact test. A 95% CI will be constructed for the treatment difference (Arm 2 – Arm 1) in incidence of graft survival at one year. If there are subjects with an unknown outcome, they will be treated as having a graft loss in one analysis and excluded in the second analysis. Patient survival will be analyzed in a like manner.

Kaplan-Meier estimates of FSGS recurrence, biopsy-confirmed FSGS, BPAR, efficacy failure rate, graft survival, and patient survival at one year will be calculated. The treatment difference will be computed as Arm 2 - Arm 1. A positive difference indicates a higher failure rate in the test group and a negative difference indicates a higher failure rate in the standard of care arm. A 2-sided 95% confidence interval will be constructed for the treatment difference from the normal approximation using Greenwood's formula. 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 a more powerful test in detecting differences early in time. Recurrence of FSGS generally occurs early post-transplant.

Subjects with unknown outcome, if they exist, will be treated as having the event in one analysis and will be counted as censored in a second analysis.

There will be no adjustment for multiplicity in this proof-of-concept study.

The urine protein-creatinine ratio, albumin-creatinine ratio will be summarized over time. The urine-protein creatinine ratio and the urine albumin-creatinine ratio collected up to week 4 will be analyzed with an ANCOVA model with treatment group as a factor and the post-transplant value as the covariate. The urine-protein creatinine ratio and the urine albumin-creatinine ratio after week 4 will be analyzed with an ANCOVA with treatment as a factor and the week 4 value as a covariate.

The eGFR at 3, 6 and 12 months, the change from week 4 will be analyzed using an ANCOVA with the week 4 value at the covariate.

Auto-anti-CD40 antibodies (present or absent), antibody level and change from baseline will be summarized by treatment group.

For the EuroQol-5 dimensions-5 levels (EQ-5D-5L), the percentage of patients in each treatment arm who report problems (dichotomized to no, yes) for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) will be tabulated and graphically displayed. For each dimension, the percentage of patients who respond with no issue, slight issue, moderate issue, severe issue, and unable to function will be provided. The percentage of patients who report 'yes' for each of the EQ-5D-5L dimensions will be compared between the treatment groups at each visit using Fisher's Exact test. The change from baseline for the Visual Analogue Scale (VAS) Score, part of the EQ-5D-5L, will be analyzed by using an ANCOVA with treatment group as a fixed factor and the baseline VAS score as a covariate.

The change from baseline in the Kidney Transplant Questionnaire (KTQ) score for each of the 5 domains (physical symptoms, fatigue, uncertainty/fear, appearance, and emotional) at 3 and 12 months will be analyzed using an ANCOVA with treatment as a factor and baseline as a covariate.

QualityMetric will calculate SF-36v2 scale scores, and the Physical Component Summary (PCS) and Mental Component Summary (MCS). By-treatment group summaries of the 8t domains and the PCS and MCS will be provided at each visit using descriptive statistics (n, mean, median, sd, min and max). Between-group comparisons of the scores will be completed with an ANOVA with treatment group as the factor.

Pharmacokinetics

Descriptive statistics will be used to summarize bleselumab concentrations for Arm 2 at the trough and peak concentrations over the course of the study (ng/mL) by scheduled collection visit. Bi-specific bleselumab antibodies and anti-bleselumab antibodies (present or absent) will be listed and summarized using descriptive statistics.

Safety

For each treatment arm, the frequencies and percentages will be displayed for the following treatment emergent adverse events (coded using MedDRA) by system organ class and preferred term:

- Overall
- Serious
- Related (considered by the Investigator to be possibly or probably related) to study drug
- Leading to the permanent discontinuation of study drug

Descriptive statistics for each laboratory test (e.g., hematology, biochemistry, urinalysis) and its change from baseline (month 1 for renal tests) and vital signs will be tabulated by treatment group and scheduled time point.

Presence of CMV, EBV and BKV and the viral load data for each, if present, will be summarized by scheduled visit and treatment group.

Interim Analysis

An interim analysis is planned once all subjects have completed the 3 months post-transplant follow-up to assess treatment differences for rFSGS. The purpose of this analysis is to support strategic decision making for future project development and study design. The result will aid in determining if this compound will continue development for rFSGS.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart

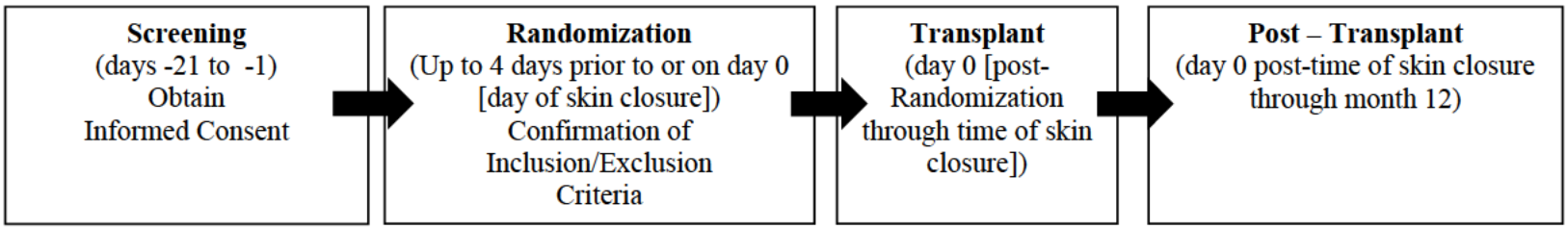


Table 1 Schedule of Assessments – Screening Through 12 Months Post-Transplant

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**									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 crossmatch	X																				
Pregnancy test [7]	X						X		X		X	X	X	X	X	X	X	X	X	X	X
Laboratory tests (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

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**									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																					
Anti-bleselumab antibody sampling [12]		X				X	X				X			X			X				X
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 continued on 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 during the screening/transplant period 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 and 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 continued on next page

9. Transplant information to be collected includes: donor demographics (age, sex, race), donor viral serology (HBV, HCV, CMVand 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. Randomization will be stratified by previous kidney transplant status (no or yes).
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. If a subject is not able to provide an answer to the question(s), it is not a requirement to complete the rest of the ePRO assessment(s) at the respective visit.
18. EQ-5D-5L. The baseline EQ-5D-5L is to be completed by the subject at screening, day 90/month 3, and month 12/EOS. If a subject is not able to provide an answer to the question(s), it is not a requirement to complete the rest of the ePRO assessment(s) at the respective visit.
19. KTQ subjects are to complete the KTQ at screening, days 14 and 90/ month 3, and months 6 and 12/EOS. If a subject is not able to provide an answer to the question(s), it is not a requirement to complete the rest of the ePRO assessment(s) at the respective visit.
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.

1 INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is an important cause of glomerular disease in children and adults where approximately 40 to 60% of subjects will progress to ESRD in 10 to 20 years [Cravedi et al, 2013]. In the US, primary focal segmental glomerulosclerosis (pFSGS) is the leading glomerular disease in dialysis subjects. In pFSGS subjects who receive kidney transplants, the rate of developing recurrent focal segmental glomerulosclerosis (rFSGS) ranges from 6 to 55% [Trachtman et al, 2015] and patients with rFSGS who are re-transplanted experience disease recurrence with a higher frequency [Delville, et al, 2014]. With no approved pharmacologic therapy and limited effectiveness with other treatment options such as plasmapheresis, many subjects with rFSGS suffer the consequences of the recurrence within 3 months in the form of nephrotic syndrome and its sequelae [Canaud et al, 2010].

1.1 Background

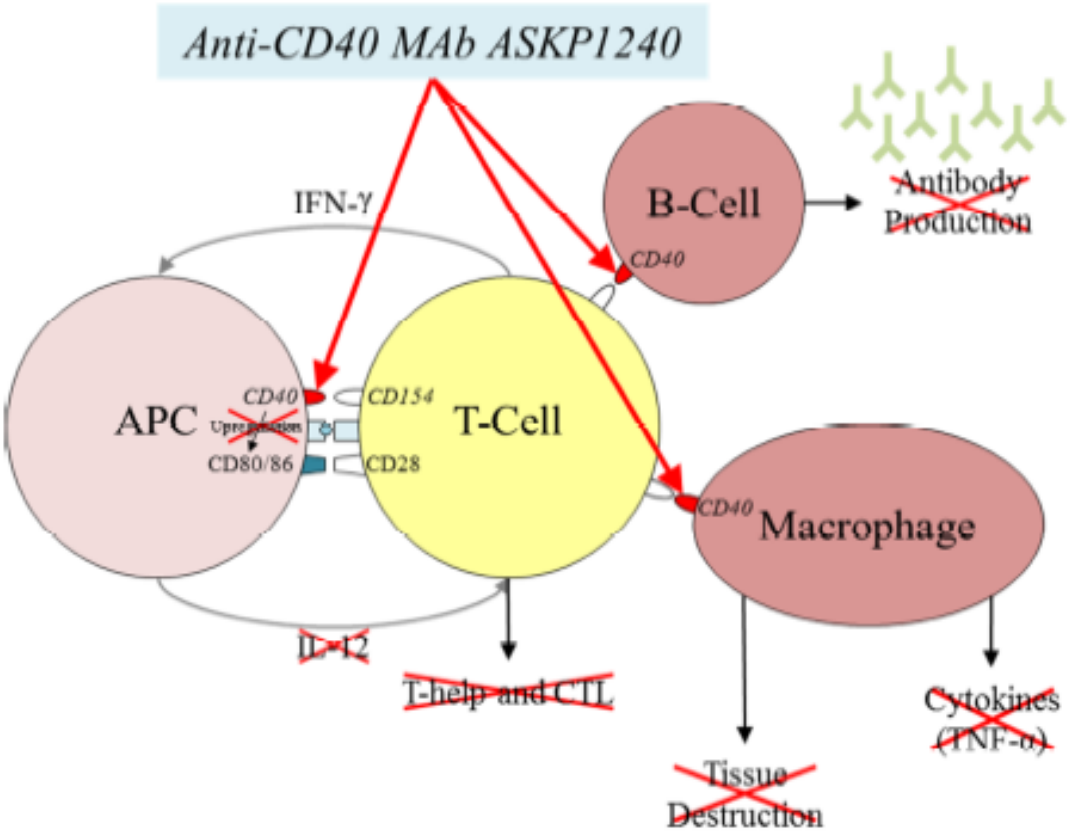
Although the pathogenesis of FSGS is not fully understood, cluster of differentiation (CD)40 is reported to overexpress on podocytes from rFSGS subjects [Delville et al, 2014]. In addition, anti-CD40 autoantibodies are present in the serum of rFSGS subjects; and pre-transplant elevation of anti-CD40 antibody is reported to correlate with the risk of rFSGS post-transplant. Bleselumab, a fully human immunoglobulin (IgG)4 anti-CD40 antagonistic monoclonal antibody, may block the interaction of the anti-CD40 autoantibodies with CD40 expressed on podocytes, thereby reducing antibody-mediated cytotoxicity. Alternatively, in an adriamycin-induced FSGS animal model, an increase in CD40 expression was observed in the podocytes, and renal injury was reduced by the administration of the murine anti-CD40 ligand monoclonal antibody MR1; the authors suggest that MR1 might have inhibited the interaction of CD40 ligand (CD154, CD40L) expressing inflammatory cells with CD40 present on the podocytes thereby reducing renal damage [Kairaitis et al, 2003]. Whichever mechanism is responsible for renal injury in FSGS, bleselumab could have a therapeutic effect by either preventing the binding of CD40 autoantibodies to the podocytes or by blocking the interaction of CD40L expressing inflammatory cells with the podocytes.

1.2 Non-clinical and Clinical Data

1.2.1 Mechanism of Action

Bleselumab is a fully human anti-CD40 monoclonal antibody (IgG4) antagonist that inhibits both humoral (immunoglobulin production) and cellular immune responses by blocking the CD40/CD154 interaction between T cells, B cells, and antigen-presenting cells.

Bleselumab inhibits peripheral blood mononuclear cell (PBMC) proliferation, up-regulation of B cell activation marker, and dendritic cell cytokine production (interleukin [IL]-12 and tumor necrosis factor [TNF]-alpha) induced by soluble CD154 (sCD154). Collectively, these results suggest that bleselumab will have an immunosuppressive effect.



1.2.2 Summary of Nonclinical Pharmacology

An in vitro flow cytometry study confirmed that bleselumab binds to CD40 on human and monkey B lymphocytes (Study 7163-PH-0001). Geometric mean half-maximal inhibitory concentration (IC_{50}) values for human and cynomolgus monkey B cells were 18.1 and 43.8 ng/mL, respectively.

Two pilot and one pivotal in vitro validation studies were performed to determine the effect of varying concentrations of bleselumab in human whole blood on CD40 surface antigen occupancy (Studies 7163-PH-0002 [pilot], 7163-PH-0014 [pilot] and 7163-PH-0015 [pivotal]). All three studies showed that the level of cell surface CD40 antigen occupancy on human B cells (CD20+ cells) was concentration dependent. In the pivotal validation study, the mean IC_{50} was determined to be 22.2 ng/mL.

The results from in vitro studies with cynomolgus monkey B cells were very similar to those seen with human B cells, suggesting that the cynomolgus monkey is the most appropriate species for further investigation of bleselumab. The pharmacodynamics of bleselumab in the monkey was related to the serum bleselumab concentration.

Bleselumbab monotherapy in a kidney transplantation model in cynomolgus monkeys showed that the mean survival time (MST) for the minimum dose level (1 mg/kg twice weekly) during the induction phase of the study was 54.7 days compared to a MST of 6.0 days for the control group (Study 7163-PH-0005). These results together with the results from the delayed-type

hypersensitivity model (Study 7163-PH-0011) suggest that the minimum effective dose of bleselumab is 1 mg/kg. When bleselumab was used alone or in combination with other immunosuppressants in a cynomolgus monkey kidney transplantation study, bleselumab prolonged median survival time in a dose-dependent manner, and showed an additive effect when combined with tacrolimus (FK506; 1 mg/kg) or mycophenolate mofetil (MMF; 15 mg/kg) plus steroid (Study 7163-PH-0004). In a kidney transplantation study in cynomolgus monkeys evaluating the relationship between pharmacokinetics and pharmacodynamics, bleselumab serum concentrations and antigen occupancy were correlated, with high antigen occupancy dependent on high serum bleselumab concentrations (Study 7163-PH-0017).

1.2.3 Summary of Toxicology

A single-dose intravenous toxicity study of bleselumab was conducted in cynomolgus monkeys (Study 7163-TX-0001). Seven animals per group were administered intravenous bleselumab at doses of 0 (saline or vehicle), 1, 10, and 100 mg/kg. There were no deaths or toxicologic findings related to bleselumab administration. Immunophenotypic and histopathologic changes related to the pharmacologic effect of bleselumab were noted. $CD40^{+}CD45^{+}$ cell counts decreased over time, most noticeably at 10 and 100 mg/kg. A decrease in $CD3^{-}CD20^{+}$ cells was noted in 1 male at 100 mg/kg. Atrophy of the germinal center in the spleen was noted with all doses. Atrophy of the germinal center in the mesenteric lymph node was observed at 10 and 100 mg/kg, and occurred in the submandibular lymph node only at the 100 mg/kg dose level. No anti-bleselumab antibody was detected in any animal.

A 4-week intermittent repeated dose toxicity study of bleselumab with a 4-week recovery period was conducted in the cynomolgus monkey (Study 7163-TX-0002). Bleselumab was evaluated in groups of 3 males and 3 female monkeys at dose levels of 0 (control), 1, 10 and 100 mg/kg per week for 4 weeks. An additional 3 males and 3 females were added to each treatment group to assess the reversibility of findings during the recovery period. There were no deaths and no toxicological changes related to bleselumab administration with respect to clinical observations, body weight, food consumption, hematology, immunophenotyping, blood chemistry, urinalysis, organ weights, gross pathology, ophthalmology, electrocardiogram (ECG), blood gas analysis, respiration rate and body temperature [Investigator Brochure, 2016]. No anti-bleselumab antibodies were detected in any animal at any time point.

Changes in histopathology and immunohistochemistry related to the pharmacological effect of bleselumab were noted at all dose levels of bleselumab. Histopathology findings included atrophy of the germinal center of the spleen, submandibular and mesenteric lymph nodes, and Peyer's patches. Corresponding to these histopathologic findings, weak reaction to anti-CD20 antibody was observed in the germinal center area of the spleen and lymph nodes in immunohistochemistry evaluations. These findings were almost completely reversed at the end of the 4-week recovery period in the 1 mg/kg treatment group and were partially reversed in the 10 mg/kg dose group. The 100 mg/kg dose group showed no attenuation in the findings at the end of the 4-week recovery period.

A 13-week intermittent repeated dose toxicity study of bleselumab with a 13-week recovery period was conducted in the cynomolgus monkey (Study 7163-TX-0005). Bleselumab was administered intravenously once weekly for 4 weeks and once every 2 weeks, thereafter, from the 6th dosing, for a total of 9 dose administrations, at dose levels of 0 (control), 1, 10, and 100 mg/kg to 3 male and 3 female cynomolgus monkeys per group in order to investigate its toxicity. Three males and three females were added to each group in order to assess the reversibility of any toxicity observed during the dosing period in a subsequent 13-week recovery period. The animals in the control group received bleselumab placebo. Systemic exposures to bleselumab and anti-bleselumab antibody production were also evaluated. Clinical signs, body weight, food consumption, body temperature, respiratory rate, blood pressure, electrocardiography, ophthalmology, urinalysis, hematology, immunophenotyping, blood chemistry, serum cytokine, gross pathology, organ weights, and histopathology were conducted. A progressive decline in erythrocyte count was noted in 1 female in the 100 mg/kg group from week 9 of dosing, and reticulocyte ratio also decreased. Erythrocyte count continued to decline and the animal was sacrificed in a moribund state on recovery day 47. Histopathology of the bone marrow showed only slight hematopoietic cell degeneration; however, electron microscopy showed presence of virus-like particles. It was hypothesized that the death of this female was due to an infectious process, possibly viral, secondary to the immunosuppressive activity of the test article.

The histopathology changes described below during or after the dosing period were considered to be results of a pharmacological effect. In the 1 mg/kg group, atrophy of the germinal center was observed in the spleen in 1 male and in the submandibular lymph nodes in 1 other male. In the 10 mg/kg group, atrophy of the germinal center was observed in the spleen, submandibular, and mesenteric lymph nodes in all males and females, and in the Peyer's patches in 2 males and 2 females. In the 100 mg/kg group, atrophy of the germinal center was observed in the spleen, submandibular and/or mesenteric lymph nodes, and in the Peyer's patches in all males and females. These histopathology changes were completely reversed by the end of the 13 week recovery period.

Immunophenotypic changes were observed in both male and female monkeys administered bleselumab at the 10 or 100 mg/kg dose levels. At the 10 mg/kg dose level, $CD3^{-}CD20^{+}$ cell count decreased by more than 50% in 4 males and 1 female at weeks 9 and/or 13 of dosing. Two of the four male animals showed $CD3^{-}CD20^{+}$ cell counts that were below the lower limit of the predose level. At the 100 mg/kg dose level, $CD3^{-}CD20^{+}$ cell count decreased by more than 50% in 5 males and 2 females at Weeks 5, 9 and/or 13 of dosing. In addition, one male and three females had $CD3^{-}CD20^{+}$ cell counts that were below the lower limit of the predose level.

In toxicokinetic studies, C_{max} showed a dose-proportional increase, but increases in $AUC_{0\text{-}168h}$ and $AUC_{0\text{-}336h}$ tended to be greater than dose proportional at the higher dose levels. C_{max} increased gradually with weekly dosing until the fifth dosing, but then gradually decreased after changing the dose interval to bi-weekly administration and appeared to reach a steady state after the seventh dose. No sex difference was noted in the serum bleselumab profile.

At 1 mg/kg, anti-bleselumab antibody was detected in 1 male and 3 females, and these animals showed a decrease in bleselumab exposure.

The no-observed-adverse-effect level (NOAEL) was established (excluding the intended pharmacologic effect) for the 13-week repeated dose toxicity study was determined to be 10 mg/kg.

A 52-week intermittent repeated dose toxicity study of bleselumab with a 13-week recovery period was conducted in the cynomolgus monkey (Study 7163-TX-0006). Bleselumab was administered intravenously once weekly for 4 weeks and once every 2 weeks, thereafter, from the 6th dosing, for a total of 29 dose administrations, at dose levels of 0 (control), 1, 10, 30, and 100 mg/kg to 4 male and 4 female cynomolgus monkeys per group in order to investigate its toxicity. Two males and two females were added to each group in order to assess the reversibility of any toxicity observed during the dosing period in a subsequent 13-week recovery period. The animals in the control group received bleselumab placebo. Systemic exposures to bleselumab and anti-bleselumab antibody production were also evaluated. Clinical signs, body weight, food consumption, body temperature, respiratory rate, blood pressure, electrocardiography, ophthalmology, urinalysis, hematology, immunophenotyping, blood chemistry, serum cytokine, gross pathology, organ weights, and histopathology were conducted.

At the 100 mg/kg and the 30 mg/kg dose levels, 3 males (100 mg/kg) and 4 males (30 mg/kg) were euthanized in a moribund state near the end of the dosing period or in the early stage of the recovery period. Hematologic findings indicate that at least 4 of 6 male animals in the 30 mg/kg group and 3 of 6 male animals in the 100 mg/kg group developed anemia as defined as a > 15% decrease in red blood cells (RBCs) compared to baseline. These findings became apparent on or after 39 weeks and eventually animals required termination for moribundity. Immunophenotypic changes were observed in both male and female monkeys administered bleselumab at the 10, 30, and 100 mg/kg dose levels. At the 10 mg/kg dose level, $CD3^{-}CD20^{+}$ cell count decreased by more than 50% in 4 of 6 males on both weeks 27 and 39 while 3 females showed a 50% decrease in $CD3^{-}CD20^{+}$ cells on week 27 and 4 females at 39 weeks. At the 30 mg/kg dose level, 3 to 4 males and the same number of females showed 50% decreases in CD3-CD20+ cells on weeks 27, 39, and/or 53. Finally, at the 100 mg/kg dose level, CD3-CD20+ cells declined by more than 50% in 3 to 4 males on weeks 9 through 53, while a similar decline was observed in 4 to 5 females on weeks 13 through 53.

The following changes were considered related to a pharmacological action of bleselumab: decreased CD3-CD20+ cell count and CD40+CD45+ cell count in peripheral blood at 10 mg/kg and greater; homogeneous immunohistochemical reaction to anti-CD20 antibody in the follicles in the spleen and/or lymph nodes and disappearance of immunohistochemical reactivity to anti-CD3 and anti-CD4 antibodies in the germinal center area of the spleen at 1 mg/kg and greater; germinal center atrophy in the spleen and/or lymph node; basophilic change in the follicles in the spleen at 1 mg/kg and greater; and follicular hypertrophy in the spleen, lymph node and/or Peyer's patches at 10 mg/kg and greater. After the 13-week recovery period, changes due to the pharmacological effects of bleselumab recovered. Some histopathological changes remained after the recovery period, but the extent of the changes was reduced.

In toxicokinetic studies, C_{max} and $AUC_{0\text{-}168h}$ increased dose-proportionally. After the fifth dosing, C_{max} tended to be greater and $AUC_{0\text{-}168h}$ was greater than after the first dosing. Except for some animals at 1 mg/kg, the C_{max}, $AUC_{0\text{-}168h}$, and $AUC_{0\text{-}336h}$ were constant from the fifth dose until the final (29th) dosing. No sex difference was noted in the serum bleselumab profile. bleselumab non-binding cell ratio in B-cells and mean fluorescence intensity (MFI) of labeled-bleselumab-binding B-cells decreased at 1 mg/kg group and greater. At 1 mg/kg, anti-bleselumab antibody was detected in 1 male and 3 females. These animals also showed decreases in bleselumab systemic exposure and in the bleselumab non-binding cell ratio and MFI.

The NOAEL was established (excluding the intended pharmacologic effect) for the 52-week repeated dose toxicity study was determined to be 1 mg/kg.

The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals. There is no indication that bleselumab would require a special approach to evaluate genotoxicity.

No carcinogenicity studies of bleselumab have been conducted.

A reproductive toxicity study of bleselumab (embryo-fetal development) in cynomolgus monkeys was performed (Study 7163-TX-0003). Bleselumab was administered intravenously once weekly over 6 weeks, to 12 pregnant cynomolgus monkeys per group at dose levels of 0, 1, 10, and 100 mg/kg during the organogenesis period (on days 20, 27, 34, 41, 48, and 55 of gestation). No dam died in any group. No significant differences were noted in body weight or food consumption in any group. No significant differences were noted between groups in fetal sex, fetal or placental weight, external or placental measurement parameters, amniotic fluid volume, organ weights, number of vertebral centrum, length of ossified long bone, or external, placental, visceral or skeletal findings. Embryo-fetal loss was not seen in the 0 (control) or 1 mg/kg bleselumab dose groups. In the 10 and 100 mg/kg bleselumab dose groups embryo-fetal loss was seen in 2 of 12 and 3 of 12 animals, respectively. Based on these data, the NOAEL for in the dams was 100 mg/kg while the NOAEL for embryo-fetal loss was 1 mg/kg. The historical average rate of embryo-fetal development at the facility that performed the embryo-fetal toxicology study is 8.6% with a range of 0 to 20%.

Anti-bleselumab antibody was detected in 3 dams in the 1 mg/kg group on treatment day 55 of gestation and/or at cesarean sectioning. Serum bleselumabconcentrations in these dams were decreased and/or disappeared by repeated dosing. No anti-bleselumab antibody was detected in the other dams or in any fetus in the 1 mg/kg group, or in any dam or fetus in the 100 or 10 mg/kg group.

In toxicokinetic studies, C_{max} and AUC of bleselumab in dams increased with ascending dose, and on treatment day 55 of gestation were higher than on treatment day 20 of gestation in all test article groups. On the day of cesarean sectioning, serum bleselumab concentrations were detected for all dams and fetuses in the 100 mg/kg group, and for 4 dams and 2 fetuses in the 10 mg/kg group; however, bleselumab concentration was not detected for any dam or fetus in the 1 mg/kg group.

Local tolerance of bleselumab was assessed as part of the 4-week and 13-week repeated dose toxicity study in cynomolgus monkeys (Studies 7163-TX-0002 and 7163-TX-0005). No noteworthy findings were noted in the animals dosed with bleselumab following macroscopic and histopathologic examination of the injection site. Based on these findings, the local tolerance NOAEL was determined to be 100 mg/kg.

1.2.4 Clinical Data

1.2.4.1 Study 7163-CL-0101

Study 7163-CL-0101 was a first-in-human (FIH) phase 1, randomized, double-blind, placebo-controlled study of single intravenous doses at escalating dose levels in 108 healthy subjects with 36 subjects receiving placebo and 72 subjects receiving bleselumab in 12 dose groups (0.00003, 0.0001, 0.0003, 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, or 10 mg/kg). Treatment-emergent adverse events (TEAEs) were reported by 47.2% (17/36) of subjects in placebo and 52.8% (38/72) of subjects who received any dose of bleselumab. The most common TEAEs were headache, upper respiratory tract infection, cough, and dermatitis contact. There were no clinically significant drug-related ECG abnormalities or safety laboratory findings in any of the dose groups. No subjects experienced cytokine release syndrome.

For bleselumab dose levels between 0.1 to 10 mg/kg, AUC_{inf} and c_{max} increased more than dose proportionality. The maximal concentration of bleselumab (t_{max}) was achieved at approximately 1.5 hours after administration while the $t_{1/2}$ increased with increasing dose levels of bleselumab, which was approximately 8 days at dose levels ranging from 1 to 10 mg/kg.

The primary pharmacodynamic variable was B cell CD40 occupancy over time (binding of bleselumab-biotin to B cells). At dose levels ranging from 0.03 to 10 mg/kg, the percent change from baseline (i.e., percent occupancy) ranged from approximately 67% to 85% starting at 0.5 hours after dosing. B cell CD40 occupancy was sustained above 50% for 1 day at 0.1 mg/kg bleselumab, for 4 days at 0.3 mg/kg bleselumab, for 7 days at 1 mg/kg bleselumab, for 29 days at 3 mg/kg bleselumab, and for 60 days at 10 mg/kg bleselumab. No meaningful percent change from baseline was noted for total lymphocyte counts or peripheral lymphocyte subsets (CD16, CD19, CD3, CD4, CD8).

Over the course of the study, a total of 5 subjects in the bleselumab 1 mg/kg group and 1 subject in the bleselumab 10 mg/kg group seroconverted from anti-bleselumab antibody negative to anti-bleselumab antibody positive. No coagulation abnormalities were noted.

1.2.4.2 Study 7163-CL-0103

Study 7163-CL-0103 was a phase 1b, randomized, double-blind, parallel group, placebo-controlled, single-dose, pharmacokinetic, pharmacodynamic, safety and tolerability study of bleselumab in de novo kidney transplant recipients. A total of 46 subjects were randomized and received study drug in one of 5 treatment groups: placebo (n = 8), bleselumab 50 mg (n = 10), bleselumab 100 mg (n = 9), bleselumab 200 mg (n = 10) or bleselumab 500 mg (n = 9).

Treatment emergent adverse events (TEAEs) occurred in 100% of subjects. Incidences of TEAEs were not bleselumab dose dependent. BK infection occurred in 12.5% of placebo, 40.0% of bleselumab 50 mg, 0.0% of bleselumab 100 mg, 10.0% of bleselumab 200 mg and 22.2% of bleselumab 500 mg treatment groups. Cytomegalovirus (CMV) infection occurred in a single subject in each of the placebo, bleselumab 100 mg and bleselumab 500 mg treatment groups. There were no thromboembolic events, myocardial infarctions or malignancies reported in the subjects receiving bleselumab. Serious adverse events (SAE) occurred in 37.5% of placebo, 60.0% of bleselumab 50 mg, 11.1% of bleselumab 100 mg, 0.0% of bleselumab 200 mg and 33.3% of bleselumab 500 mg treatment groups. No subjects experienced cytokine release syndrome.

Both AUC and C_{max} increased more than dose proportionally suggesting that bleselumab showed nonlinear pharmacokinetics. Mean maximal B cell CD40 receptor occupancy (> 85%) was achieved initially in all dose groups, except the 500 mg dose group (> 70%). In general, there was a dose dependent duration of maximum B cell CD40 receptor occupancy.

Only one subject had treatment emergent anti-bleselumab antibodies formation. This subject was on bleselumab50 mg treatment group. No adverse events (AEs) attributable to anti-bleselumab antibodies were reported.

1.2.4.3 Study 7163-CL-0107

This was a phase 2a, multi-center, randomized, double-blind, placebo-controlled, sequential dose group, multiple-dose escalation intravenous dose study to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of bleselumab administered in subjects with moderate to severe plaque psoriasis. The subjects were randomized to receive multiple doses of either placebo or ASKP1240 at 0.1, 0.3, 1.0, or 3.0 mg/kg. The pharmacokinetics showed AUC_{336} and C_{max} increased more than dose proportionally, suggesting bleselumab demonstrated nonlinear pharmacokinetics after single and multiple doses in the dose range tested in subjects with psoriasis.

Although the study was not powered to demonstrate statistical differences in bleselumab treatment from placebo, there was evidence of pharmacologic activity at the 3.0 mg/kg bleselumab dose relative to placebo as measured by classic and linear PASI score.

There were no clinically significant infusion reactions and no cytokine release syndrome or thromboembolic events. Reversible elevated liver function tests (LFTs) were observed but only in the high dose bleselumab cohorts (1.0 and 3.0 mg/kg). In general, a favorable safety profile with bleselumab was observed.

1.2.4.4 Study 7163-CL-0108

The 7163-CL-0108 Study is a phase 2a, randomized, open-label, active control, multi-center study to assess the efficacy and safety of bleselumab in de novo kidney transplant recipients. A total of 139 subjects were randomized and received study drug in one of 3 treatment groups: standard of care (SOC; Tacrolimus [Tac] + MMF + steroids), calcineurin inhibitor (CNI)

avoidance (bleselumab + MMF + steroids), and CNI minimization-MMF avoidance (bleselumab + reduced Tac (rTac) + steroids).

The primary study duration of 7163-CL-0108 is 6 months after kidney transplantation, followed by a long term extension period of up to 3 years. The results showed bleselumab + rTac regimen demonstrated similar efficacy for the prevention of acute rejection at the pre-specified 6-month end point and at the previously unplanned 12-month analysis (4/44, 9.1%; 4/44, 9.1%) compared to SOC (3/48, 6.3%; 6/48, 12.5%), respectively. The difference (bleselumab + rTac – SOC) with the 95% CI at 6 and 12 months was 2.8% [-8.1%, 13.8%] and -3.4% [-16.0%, 9.2%]. The upper limit of the non-inferiority margin was less than 20%, the pre-specified limit, indicating similar efficacy.

The bleselumab + MMF group did not achieve non-inferiority compared to SOC at both the 6- and 12-month analyses with the incidence of biopsy-proven acute rejection (BPAR) in bleselumab + MMF group statistically higher than SOC. Subjects and graft survival were similar in all three treatment groups.

The higher rate of AEs in the bleselumab + MMF group in the various categories is predominantly driven by the higher rate of acute rejection in that group. Other AEs were generally consistent with those seen in renal transplant subjects. The elevated LFTs were observed in all three groups but the subjects in the ASKP1240 + rTac group had higher incidences of elevated transaminases or total bilirubin than the SOC and ASKP1240 + MMF groups; however, the elevated LFTs seemed transient and reversible regardless of whether the subjects discontinued or continued ASKP1240 treatment.

BK virus (BKV) infection occurred more commonly in the bleselumab + rTac group (27.3%) compared to SOC (10.2%) and bleselumab + MMF (15.2%) groups. Also BK virus associated nephropathy (BKVAN) occurred at 6.8% in the bleselumab + rTac group compared to SOC (4.1%) and bleselumab + MMF (4.3%) groups. No subject had graft loss due to BK infection/nephropathy by 12 months. Cytomegalovirus (CMV) infection was reported in all three treatment arms as follows, SOC (4.1%), bleselumab +MMF (6.5%) and bleselumab + rTac (6.8%). By month 12, the accumulated occurrence of CMV infection was reported for SOC (6.1%), bleselumab +MMF (10.9%) and ASKPK1240 + rTac (13.6%) treatment arms.

During the six month study period, three malignancies were reported; one renal cell carcinoma and one squamous cell carcinoma in bleselumab + MMF. A single subject in bleselumab + rTac had a squamous cell carcinoma of skin. Between the 6 to 12 month period, there were two more malignancies reported, both in bleselumab + rTac, one basal cell carcinoma and one polycythemia vera. There was no case of post-transplant lymphoproliferative (PTLD) reported during the study to-date.

Two subjects died during the six month study period. A death was reported in the bleselumab + rTac group on day 45 primarily due to sepsis following an inadvertent injury to the appendix during the transplant procedure. Another death reported in the bleselumab + MMF group on day 4 was due to cardiac arrest and was considered not related to any of the study

drugs. During the 6 to 12 months study period, one additional subject in the bleselumab + rTac group was reported dead at home on day 420 due to unknown reason.

Two subjects experienced graft loss during the six month study period. One subject in SOC group underwent allograft nephrectomy on day 18 due to thrombosis. The second subject in the bleselumab + rTac treatment arm underwent placement of a donor kidney that was immediately removed due to poor perfusion. During the same procedure the mate donor kidney was then implanted and continues to function well. The first donor kidney has been counted as a graft loss. There was no graft loss during the 6 to 12 months follow-up period.

Overall, the study showed bleselumab + rTac regimen demonstrated similar efficacy in the prevention of acute rejection at both six months end point and 12 months analysis. A favorable safety profile with ASKP1240 was consistently observed in the subjects with kidney transplantation.

1.3 Summary of Key Safety Information for Study Drugs

Cross-reactivity studies of human tissues demonstrated specific binding of bleselumab to lymphocytes in lymphoid tissues as well as binding to infiltrating lymphocytes in non-lymphoid human tissues. Non-lymphoid staining of bleselumab was seen in membranes of sinusoidal lining cells in the liver and in glandular epithelium in the prostate, thyroid, kidney and parathyroid. Bleselumab also specifically stained human lymphocytes, monocytes, and platelets in peripheral blood.

Bleselumab inhibited sCD154-induced IL-12 and TNF-alpha release from dendritic cells. bleselumab inhibited human and cynomolgus monkey PBMC proliferation induced by sCD154 in a concentration-related manner. A correlation was observed between serum concentration of bleselumab and % binding to CD40 on B cells. Bleselumab did not inhibit collagen-induced platelet aggregation.

In non-human primates (NHP), bleselumab inhibited delayed type hyper-sensitivity reaction and antigen-specific antibody production at a dose of ≥ 1 mg/kg. Bleselumab exhibited a potent immunosuppressive effect and prolonged renal allograft survival when administered as induction and/or maintenance therapy in the cynomolgus monkey.

Further examinations of the effects of bleselumab on major physiologic systems were examined in a 4-week, 13-week and 52-week toxicity studies in the monkey. No treatment-related effects were noted on the cardiovascular, respiratory, renal, or central nervous systems. Anemia has been noted in 1 animal in the 13-week repeat dose toxicology study and in 4 of 5 animals beginning at the 39-week time point of the 52-week toxicology study. In the 52-week study some animals were euthanized due to moribundity in the 30 mg/kg and 100 mg/kg dose groups. Histologic change in lymphoid organs has been observed following repeated dose administration of bleselumab to cynomolgus monkeys. Specifically in the nonhuman primate studies of bleselumab, germinal centers (GC) were shown to be either small or they could not be observed. Signs of toxicity (degeneration, necrosis, and apoptosis) were not observed in the follicular tissue with small or absent GC. No toxicological changes were observed in the cells or tissue in the regions other than the GC atrophy of follicle. These findings indicate an

impairment of B cell maturation to be the primary cause of the GC atrophy. This would be consistent with the mechanism of action of bleselumab. The findings were reversible following cessation of drug administration. Decreases in peripheral blood $CD3^{-}CD20^{+}$ B cells also occurred and are considered to reflect the pharmacological action of bleselumab on B cell maturation in lymphoid tissues. The decreased peripheral circulatory B cell counts were also reversible on cessation of drug administration. Given the coincidence of the reformation of GC, the peripheral blood B cell counts may be a correlate of alterations in the germinal center morphology.

Reproductive toxicity studies are completed. Effects of bleselumab may result embryo-fetal loss at doses higher than 1 mg/kg.

The FIH healthy volunteer study (Study 7163-CL-0101) described above showed that a single dose of bleselumab was well tolerated. No evidence of cytokine release syndrome was seen. Activation of the coagulation cascade was not seen. Drug infusions were relatively well tolerated with a single occurrence of a drug related skin rash suggesting that cutaneous reactions may be seen following administration of bleselumab. Over the course of the study, a total of 6 subjects in bleselumab dose groups seroconverted from anti-bleselumab antibody negative to anti-bleselumab antibody positive.

Study 7163-CL-0103 described above showed that a single dose of bleselumab was well tolerated by de novo renal transplant subjects. No evidence of cytokine release was seen and there were no thromboembolic events observed. One subject in the bleselumab 50 mg treatment group developed treatment emergent anti-bleselumab antibodies.

Study 7163-CL-0107 in subjects with psoriasis and study 7163-CL-0108 in de novo renal transplant subjects also showed multiple doses of bleselumab was well tolerated with no evidence of cytokine release and no thromboembolic events observed.

The CD40-CD40L interaction has been targeted in humans previously [Pree and Wekerle, 2006; Kirk et al, 2001]. Two humanized anti-CD40L antibodies have been investigated in the setting of various autoimmune disorders and renal transplantation. Anti-CD40L antibody (hu5C8, monoclonal antibody against CD154 [ligand for CD40]), was effective in NHPs in preventing renal allograft rejection and prolonging survival [Kirk et al, 1999] but was associated with thrombotic events in humans [Kirk et al, 2001]. The other agent, IDEC-131, was evaluated in a variety of autoimmune disorders, and treatment was complicated by a thromboembolic event in a patient with Crohn's Disease [Pree and Wekerle, 2006]. The thromboembolic events involved both venous and arterial vasculature. The exact mechanisms for these events are not clear at present and may represent effects on platelets and/or vascular endothelium [Sidiropoulos and Boumpas, 2004; Kirk et al, 2001]. The absence of CD40L has been shown to affect the stability of ex vivo-generated thrombi in high shear flow conditions and arterial thrombi in in vivo nonclinical models. Animals and platelets deficient for CD40 had a phenotype similar to wild type in these studies [Andre et al, 2002].

Antagonistic and agonistic anti-CD40 antibodies have been administered clinically [Hussein et al, 2010; Advani et al, 2009; Vonderheide et al, 2007; Kasran et al, 2005]. For example, an

antagonistic anti-CD40 IgG1 was administered to subjects with non-Hodgkin's lymphoma [Hussein et al, 2010; Advani et al, 2009]. Although well tolerated clinically in the 16 subjects, depletion of B cells was noted. An antagonistic anti-CD40 IgG4 was also administered to subjects with moderate-to-severe Crohn's disease and single-dose administration was clinically well tolerated [Kasran et al, 2005]. Transient decreases of B cells were also noted.

Although bleselumab is not a CD40 agonist, it is important to note that the administration of agonistic CD40 monoclonal antibodies has also been performed. Vonderheide et al [2007] reported that following the administration of an agonistic anti-CD40 IgG2 to subjects with various advanced solid organ tumors, cytokine release syndrome occurred in 16 of 29 subjects; however, the cytokine release syndrome was generally mild and resolved within 24 hours following dosing. Lymphocytopenia, thrombocytopenia, and dose-related transient elevations in serum liver transaminases were also noted. Hypersensitivity or antibody-dependent cellular cytotoxicity was not considered to be involved. To date, no subjects have experienced cytokine release syndrome in any previous clinical studies.

1.4 Risk-Benefit Assessment

Results from nonclinical studies with bleselumab have not identified significant safety issues that would preclude clinical development of bleselumab. As noted above anemia has been observed in NHPs dose with bleselumab 30 mg/kg and 100 mg/kg for more than 4 weeks. Histologic change in lymphoid organs and reductions of $CD3^{-}CD20^{+}$ cell counts have also been observed in NHPs dosed at 10 mg/kg, 30 mg/kg and 100 mg/kg. Whether these findings constitute an unacceptable risk to subjects in the study is unclear. GC atrophy, including severe lymphoid depletion, has also been observed pre-clinically with a number of commercial products (e.g., rituximab, belimumab, atacicept, methotrexate and abatacept) in association with varying degrees of reduction in peripheral $CD3^{-}CD20^{+}$ cells.

In populations of subjects with rheumatoid arthritis and/or SLE where comparative data is available, abnormalities of germinal center histology alone do not result in an incremental risk of infectious complications. Moreover, neither isolated profound peripheral blood total B cell depletion nor depletion of specific subsets of B cells are associated with clinically meaningful differences in incidence of infection.

The results of the FIH study (7163-CL-0101) indicated that a single dose of bleselumab was well tolerated. Anemia and reductions in CD3-CD20+ cell counts were not observed following a single dose of bleselumab at any dose. In addition, bleselumab has been evaluated following a single dose in kidney transplant recipients (Study 7163-CL-0103). Although the study was not designed to assess efficacy bleselumab showed mean maximal B cell CD40 receptor occupancy (> 85%) achieved in all dose groups and was found to be well tolerated. In the ongoing 3-year long multiple-dose study in kidney transplant recipients (Study 7163-CL-0108), the 6-month and 12-month preliminary results showed that bleselumab was found to be well tolerated and bleselumab + Tac group also showed non-inferiority to the SOC in the prevention of rejection.

There is a known risk of cytokine release syndrome, characterized by rapid induction of pro-inflammatory cytokines and accompanied by headache, myalgias, nausea, diarrhea, erythema, vasodilatation, and hypotension, with subsequent life-threatening lung injury, renal failure, and disseminated blood clots [Suntharalingam et al, 2006] following administration of monoclonal antibodies in man. Immunoreactivity appears to be related in part to Fc receptor (FcR) binding and antibody dependent cellular cytotoxicity and/or complement dependent cytotoxicity. Bleselumab is an IgG4 isotype that has been genetically modified with the intent to decrease binding to FcR, thereby reducing antibody dependent cellular cytotoxicity potential. In addition, IgG4 has lower complement activating potential than other IgG isotypes. Additionally in the nonclinical studies, bleselumab related cytokine release was not observed in vivo in cynomolgus monkeys at doses up to 100 mg/kg or in vitro in human blood at concentrations up to 200 mcg/mL. Finally cytokine release syndrome was not observed in the FIH (Study 7163-CL-0101) single dose study or the single dose study in kidney transplant recipients (Study 7163-CL-0103), as well as the multiple dose study in kidney transplant recipients (Study 7163-CL-0108).

Most biologic therapies elicit some level of antibody response which may contribute to AEs or loss of efficacy of the therapeutic agent. As bleselumab is a fully human antibody, the potential for human anti-human antibodies is relatively low. Treatment emergent antibodies to bleselumab following single doses have been seen in 6.9 to 11.1% of subjects receiving bleselumab; however less events were reported in the 7163-CL-0108 study where other immunosuppressants were concomitantly used. There have been no AEs attributed to anti-bleselumab antibodies reported.

Bleselumab is intended to be an immunosuppressive agent and, therefore, the potential to increase the risk of infection and reactivate latent, chronic infections is expected.

Animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women; therefore, the risk to the development of the fetus in humans is unknown. Women who are able to become pregnant must use contraception during treatment with bleselumab and during any protocol-defined treatment period. If a woman becomes pregnant, while taking bleselumab, she should be informed of the potential hazards to the fetus and bleselumab treatment must be discontinued immediately. If a man impregnates his partner while taking bleselumab, both parties should be informed of the potential hazards to the fetus. Additionally, sperm donation is prohibited during and for 90 days post-last study drug dosing.

Subjects will be closely monitored by the Principal Investigator for signs and symptoms of anemia, infection, cytokine release, and thromboembolic events. In addition to being closely monitored by the Investigator, the Sponsor Medical Monitor and the Sponsor Medical Safety Pharmacovigilance physician/designee will periodically review the safety data. A full range of safety data will be assessed, including but not limited to, hematology, biochemistry, vital signs, and AEs.

Multiple doses of bleselumab monotherapy showed evidence of efficacy in a psoriasis study and the bleselumab and tacrolimus combination regimen demonstrated a similar rate of acute

rejection compared to SOC in renal transplant subjects. Two important identified risks are hepatic toxicity and viral infections. The blood chemical findings in preclinical studies showed isolated elevations of alanine phosphatase (SGPT) (ALP), aspartate aminotransferase (SGOT) (AST), alkaline aminotransferase (ALT) and lactate dehytdrogenase (LDH) that were not dose-related and in some cases returned to lower values with continued dosing; in phase I completed studies TEAEs related to abnormal LFTs (e.g., ALT) were not clinically significant. In both phase II studies (one complete and one ongoing) elevated liver chemistries are transient and reversible regardless of bleselumab continuation or discontinuation and have not been associated with significant clinical findings. The occurrences of BK infection are of concern but have not resulted in significant impairment of renal survival and no graft loss.

The Sponsor is continuously monitoring safety in the ongoing clinical study and has instituted mitigating measures for this study. The Sponsor believes that the risks recognized with bleselumab are acceptable and do not preclude further clinical investigations. A DMC that will be responsible for the evaluation of data is to be organized and meet periodically.

There is no approved pharmacologic therapy and limited effectiveness with other treatment options such as plasmapheresis. Many subjects with rFSGS suffer the consequences of the recurrence in the form of nephrotic syndrome and its sequelae. Based on this unmet medical need and the safety and efficacy results from previous and ongoing clinical studies with bleselumab, the Sponsor believes bleselumab may have potential benefit in the prevention of rFSGS.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

- To assess the efficacy of the bleselumab regimen (basiliximab induction, tacrolimus, steroids and bleselumab) compared with the SOC regimen (basiliximab induction, tacrolimus, steroids and MMF) in the prevention of the recurrence of focal segmental glomerulosclerosis (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.

2.1.2 Secondary Objectives

- 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) rFSGS through 3, 6 and 12 months post-transplant.
- To assess the safety of the bleselumab regimen compared with the SOC regimen.

2.1.3 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 auto-anti-CD40 antibodies 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]).

2.2 Study Design and Dose Rationale

2.2.1 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 rFSGS in de novo kidney transplant subjects.

The study will consist of the following periods:

- Screening (days -21 to -1)
- Transplant (day 0 [zero])
- Post-transplant (day 0/post-skin closure through 12 months post-transplant)

Prior to any study-related assessments, the informed consent form (ICF)/authorization will be signed by the subject (visit 1). All subjects will enter into a screening period (days -21 to -1 prior to transplant), undergo a transplant (day 0), and are then to 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 and stratified by previous kidney transplant status (no or yes) to open-label treatment of 1 of 2 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 will receive induction therapy with basiliximab (Simulect® [the first dose as a 20 mg bolus injection prior to transplantation or intra-operatively before revascularization, and the second a 20 mg bolus injection on day 3 or 4 or 5 post-transplant]).

For subjects randomized to Arm 2, bleselumab 200 mg will be given intravenously over 30 minutes on day 0, to be initiated intra-operatively prior to revascularization of the allograft, and then at 200 mg per infusion on days 7, 14, 28, 42, 56, 70 and 90/month 3, and once per month through month 12]).

The initial dose of tacrolimus (Prograf®) must be anticipated to be administered orally within 48 hours post-transplant at 0.1 mg/kg/day (2 equally divided doses at 0.05 mg/kg/day every 12 hours with a target trough level of 4 – 11 ng/mL for the duration of the study). Tacrolimus may be given intravenously IF medically indicated (only early post-transplant when oral is not tolerated, and should be discontinued as soon as the subject can tolerate oral administration, usually within 2-3 days post-transplant).

For subjects randomized to Arm 1, the initial dose of MMF at 1 g bid may be given up to 12 hours preoperatively, or before revascularization. MMF may be given orally or intravenously.

After initial doses of tacrolimus and MMF, dose adjustments in the post-transplant period are allowed.

Corticosteroids will be administered as an intravenous bolus of 500, 250, 125 and 60 mg of methylprednisone (or equivalent oral/intravenous corticosteroid dose), on days 0 and 1 and 2 and 3, respectively.

Oral prednisone is to be tapered according to the following schedule, and then continue through 12 months post-transplant:

Days Post-transplant	Prednisone Equivalent (mg)
Days 4-14	20–30
Days 15-28	10–20
Day 29 and on	5–10

Steroid withdrawal is not allowed.

Subjects are to return to the study center in the post-transplant period (visits 2-21) in order to assess efficacy and safety, completion of clinical assessments, collection of pharmacokinetic samples, and to complete electronic patient reported outcome (ePRO) measurements.

Only subjects in Arm 2 are to provide pharmacokinetic samples. On day 0, pharmacokinetic samples are to be collected within 30 minutes or less pre-initial, and post-initial, intraoperative, bleselumab administration. 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 the day 28 visit. 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.

All subjects who have not had a biopsy with a diagnosis of recurrent FSGS (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/month 3 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) 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.

A Data Monitoring Committee (DMC) will be responsible for data evaluation and will meet as defined in the DMC charter.

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 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 21/month 12) procedures are to be completed within 30 days post-last treatment.

2.2.2 Dose Rationale

Although the pathogenesis of FSGS is still not fully understood, literature suggests that auto-anti-CD40 antibody is potentially associated with rFSGS. In cultured human podocytes, a monoclonal CD40-blocking antibody partially reversed the podocyte depolarization and shrinking seen after treatment with purified anti-CD40 antibody from the sera of subjects who developed rFSGS, indicating that blocking the interaction of the CD40 auto-antibody with the CD40 on podocytes may be a potential therapeutic target in the treatment of rFSGS.

Bleselumab, a fully human IgG4 anti-CD40 antagonistic monoclonal antibody, could have a therapeutic effect for the prevention of FSGS following renal transplantation by either preventing the binding of CD40 autoantibodies to the podocytes or by blocking the interaction of CD40L expressing inflammatory cells with the podocytes. None of the 6 subjects from the 7163-CL-0108 study with a medical history of FSGS treated with bleselumab (6 subjects, 5 treated with bleselumab + MMF and 1 treated with bleselumab + rTac) had a rFSGS while the SOC arm had recurrence in 2 of 2 subjects.

The dosing regimen proposed in this study is as same as the 7163-CL-0108 study, which demonstrated efficacy in preventing acute rejection with manageable safety profiles. The dosing rationale for this study is to ensure the sufficient immunosuppression to prevent acute rejection and to assess the efficacy in the prevention of rFSGS.

2.3 Endpoints

2.3.1 Primary Endpoint

- Recurrence of FSGS 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.

2.3.2 Secondary Endpoints

- Recurrence of FSGS defined as 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.
- 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.

2.3.3 Exploratory Endpoints

Efficacy

- Graft and patient 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).
- Time to rFSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g).
- Time to rFSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g) or initiation of plasmapheresis.
- Time to rFSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g), death, graft loss, or lost to follow-up.
- Time to recurrence of biopsy-proven (blinded, central read) FSGS.
- Time to first BPAR (Banff Grade ≥ 1, local read).
- Urine protein-creatinine ratio through 6 and 12 months post-transplant.

- Urine albumin-creatinine ratio through 3, 6 and 12 months post-transplant.
- Change in auto-anti-CD40 antibodies from baseline.
- Change in patient-reported outcomes from baseline (SF-36s, EQ-5D-5L and KTQ).

Safety

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

3 STUDY POPULATION

3.1 Selection of Study Population

Male and female subjects 18 years of age or older who are de novo, living or deceased donor kidney recipients and have biopsy-proven pFSGS.

3.2 Inclusion Criteria

A subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulation (e.g., Health Insurance Portability and Accountability Act [HIPAA] Authorization for US sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Male or female subject must be ≥ 18 years of age.
3. Subject is a recipient of a de novo kidney from a living or deceased donor and has biopsy-proven, pFSGS as a cause of ESRD in their native kidneys (initial diagnosing biopsy report is required). A subject who has biopsy-proven pFSGS as a cause of ESRD, and their most current graft failure(s) is due to biopsy-proven, recurrent FSGS, is eligible.
4. Subject is anticipated to receive first oral dose of tacrolimus within 48 hours of transplant procedure.
5. Female subject must either:
    - Be of non-child bearing potential:
        - Post-menopausal (defined as at least 1 year without any menses) prior to screening, or
        - Documented surgically sterile

- Or, if of childbearing potential,
  - Agree not to try to become pregnant during the study and for 90 days post-last dose,
  - And have a negative serum pregnancy test at screening,
  - And, if heterosexually active, agree to consistently use two forms of highly-effective birth control* (at least one of which must be a barrier method) starting at screening, throughout the study and for 90 days post-last dose.

6. Female subject must agree not to breastfeed starting at screening, throughout the study and for 90 days post-last dose.
7. Female subject must not donate ova starting at screening, throughout the study and for 90 days post-last dose.
8. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective form of contraception consisting of two forms of birth control* (at least one of which must be a barrier method) starting at screening, throughout the study and for 90 days post-last dose.
9. Male subject must not donate sperm starting at screening, throughout the study and for 90 days post-last dose.
10. Subject must be willing and able to comply with the study requirements including prohibited concomitant medication restrictions.
11. Subject agrees not to participate in another interventional study while on treatment.

*Highly effective forms of birth control include:

- Consistent and correct usage of established oral contraception
- Injected or implant hormonal methods of contraception
- Established intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
- Any male partner that has undergone effective surgical sterilization
- Any female partner that has undergone effective surgical sterilization

Waivers to the inclusion criteria will NOT be allowed.

3.3 Exclusion Criteria

A subject will be excluded from participation if any of the following apply:

1. Subject has Induction therapy, other than study-assigned basiliximab, planned as part of initial immunosuppressive regimen.
2. Subjects with a diagnosis of secondary FSGS (familial, virus associated, medication, etc., Appendix 12.5) or a defined genetic cause of FSGS.
3. Subject has previously received any organ transplant including a kidney and the most current graft failure(s) is not due to the recurrence of FSGS.

4. Subject will receive a kidney as part of a multi-organ transplant.
5. Subject will receive a dual kidney transplant from a deceased donor.
6. Subject will receive a kidney with an anticipated cold ischemia time of > 30 hours.
7. Subject will receive a kidney that meets **BOTH** Extended Criteria Donor (ECD) and Donation after Cardiac Death (DCD) criteria. (A kidney that meets either ECD **OR** DCD criteria may be eligible for inclusion.)
8. Subject will receive a blood group system (A, AB, B, O, ABO) incompatible (including A_2 into B or O) donor kidney.
9. Recipient or donor is known to be seropositive for human immuno-deficiency virus (HIV).
10. Subject has a current calculated panel reactive antibody (cPRA) level > 50%.
11. Subject has a current malignancy or a history of malignancy (within the past 5 years), except non-metastatic basal or squamous cell carcinoma of the skin that has been treated successfully, or a renal cell carcinoma that has been treated successfully more than 2 years prior to transplantation.
12. Subject has significant liver disease, defined as having during the past 21 days consistently elevated AST (SGOT) and/or ALT (SGPT) levels greater than 1.5 times the upper value of the normal range of the investigational site.
13. Subject is known to have a positive test for latent tuberculosis (TB) and has not previously received adequate anti-microbial therapy/or would require TB prophylaxis after transplant.
14. Subject has an uncontrolled concomitant infection or any other unstable medical condition that could interfere with the study objectives.
15. Subject is concurrently participating in another drug study or has received an investigational drug up to 30 days or 5 half-lives (depending on medication) prior to transplant.
16. Subject is currently receiving or has received up to 8 weeks prior to transplant an immunologic biologic compound (i.e., TNF inhibitors, [e.g., etanercept, adalimumab], intravenous immunoglobulin [IVIG]). A subject who has previously received a kidney organ transplant and is currently on an immunosuppression regimen that includes MMF, or any of its components, must discontinue MMF.
17. Subject has previously received bleselumab or participated in a clinical study with bleselumab.
18. Subject has a known hypersensitivity to tacrolimus, basiliximab, MMF, corticosteroids, or any of their components.
19. Subject has any form of substance abuse, psychiatric disorder, or a condition that in the opinion of the Investigator could invalidate communication with the Investigator.

20. Subject has a clinically significant abnormal ECG at screening.
21. Subject is unlikely to comply with the visits scheduled in the protocol, in the opinion of the Investigator.

Waivers to the exclusion criteria will NOT be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Test Drug(s)

Bleselumab (ASKP1240) is manufactured by Kyowa Hakko Kirin Co., Ltd. in partnership with Astellas.

Bleselumab is formulated at 100 mg/mL insterile Water for Injection (WFI). Bleselumab drug product for intravenous injection will be supplied as 1 mL solution (1.350 mL: ~ 30% overfill).

The clinical material is a clear or slightly opalescent, colorless to light brownish-yellow liquid product provided in 3 mL glass, single-use vials.

Product should be stored refrigerated between 2 and 8°C (36 and 46°F); do not freeze and protect from light.

Instructions for handling and preparation/dilution of the study drug can be found in the Pharmacy Manual.

4.1.2 Comparative Drug(s)

4.1.2.1 Basiliximab

Basiliximab (Simulect®) will be provided via commercial supply.

For manufacturing, formulation, storage, handling and preparation details please refer to the package insert, summary of product characteristics (SPC), or local product information supplied by the manufacturer.

4.1.2.2 Tacrolimus

Prograf® (Tacrolimus) is manufactured by Astellas Pharma Inc., Toyama, Japan.

Prograf is available for oral administration as capsules (tacrolimus capsules) containing the equivalent of 0.5, 1.0 or 5.0 mg of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 0.5 mg capsule shell contains gelatin, titanium dioxide and ferric oxide, the 1 mg capsule shell contains gelatin and titanium dioxide, and the 5 mg capsule shell contains gelatin, titanium dioxide and ferric oxide.

Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

Only the oral formulations of 0.5, 1.0 and 5.0 mg capsules will be supplied by the Sponsor through 12 months post-transplant, and is then to be sourced by the site and provided via commercial supply.

Product should be stored at 25°C (77°F), controlled room temperature;excursions permitted 15 to 30°C (59 to 86°F).

For further manufacturing and formulation details please refer to the package insert, SPC, or local product information supplied by the manufacturer.

Tacrolimus for intravenous administration will not be provided by the Sponsor.

4.1.2.3 Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is a white to off-white crystalline powder. It is slightly soluble in water (43 μg/mL at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.6). It is freely soluble in acetone, soluble in methanol, and sparingly soluble in ethanol. The apparent partition coefficient in 1-octanol/water (pH 7.4) buffer solution is 238. The pKa values for MMF are 5.6 for the morpholino group and 8.5 for the phenolic group.

Mycophenolate mofetil hydrochloride has a solubility of 65.8 mg/mL in 5% Dextrose Injection USP (D5W). The pH of the reconstituted solution is 2.4 to 4.1.

Only the oral formulations of 250 and 500 mg capsules and tablets, respectively, will be provided by the Sponsor through 12 months post-transplant, and is then to be sourced by the site and provided via commercial supply.

Inactive ingredients in MMF 250 mg capsules include croscarmellose sodium, magnesium stearate, povidone (K-90), microcrystalline cellulose, hydroxyl propyl cellulose and talc. The capsule shells contain black iron oxide, FD&C blue #2, gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide. The imprinting ink contains shellac, iron oxide and potassium hydroxide.

Inactive ingredients in MMF 500 mg tablets include iron oxide black, croscarmellose sodium, FD&C blue #2 aluminum lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, povidone (K-90), iron oxide red, talc and titanium dioxide.

Product should be stored at 25°C (77°F), controlled room temperature; excursions permitted 15 to 30°C (59 to 86°F).

For further manufacturing and formulation details please refer to the package insert, SPC, or local product information supplied by the manufacturer.

MMF for intravenous administration will not be provided by the Sponsor.

A switch from MMF to mycophenolic acid (Myfortic®) will be allowed for medical reasons but will not be supplied by the Sponsor.

4.1.2.4 Corticosteroids

Corticosteroids will be sourced by the site and provided via commercial supply.

For manufacturing, formulation, storage, handling and preparation details please refer to the package insert, SPC, or local product information supplies by the manufacturer.

4.2 Packaging and Labeling

Bleselumab, tacrolimus and MMF will be prepared, packaged, and labeled under the responsibility of a qualified person at Astellas Pharma Global Development, Inc. (APGD) and Astellas US Technologies, Inc. (AUST) in accordance with APGD - AUST Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonization (ICH) Good Clinical Practices (GCP) guidelines, and applicable local laws/regulations.

Bleselumab will be packaged as a carton of 8 vials. Each vial will be assigned an identification number.

Tacrolimus and MMF will be packaged as 100 capsules and/or tablets per bottle. Each bottle will be assigned an identification number.

Each carton and bottle will bear a label conforming to regulatory guidelines, GMP, and local laws and regulations, which identifies the contents as investigational drug. Each carton label must remain affixed to the carton and must not be concealed by any over-labeling.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the Sponsor are received by the Investigator/designee and

- that such deliveries are recorded
- that study drug is handled and stored according to labeled storage conditions
- that study drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol
- that any unused study drug is returned to the Sponsor

Drug inventory and accountability records for the study drugs will be kept by the Investigator. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The Investigator agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The Investigator will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- A study drug inventory will be maintained by the Investigator. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.

- At the conclusion or termination of this study, the Investigator agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the person responsible.
- The site must return study drug to the Sponsor at the end of the study or upon expiration.

Detailed instructions for the handling of study drug can be found in the Pharmacy Manual.

4.4 Blinding

This section is not applicable as this is an open label study.

4.5 Assignment and Allocation

All subject numbers will be assigned using the Interactive Response Technology (IRT) starting at screening. All subjects will have a unique, ten-digit subject id. The first 5 digits of this number will be the site's protocol-specific number. The second 5 digits assigned will represent the subject's accession number. This will be the number that identifies a subject during the course of the study.

All baseline procedures will be performed prior to Randomization. Only subjects who meet all inclusion criteria and exhibit none of the exclusion criteria (Section 3, Study Population) will be randomly assigned to one of the two treatment arms in a 1:1 ratio and stratified by previous kidney transplant status (no or yes). There will be a central randomization with treatment assignments balanced between the 2 study arms and previous kidney transplant.

Randomization is to be performed via IRT. If a patient is assigned a subject number and transplanted, but does not receive the assigned treatment regimen, the subject number will not be used again. If a patient is assigned a subject number but not transplanted nor receives the assigned treatment regimen within the screening period, the subject may be rescreened and is to receive a new subject number.

Patients that are randomized (assigned a subject number), but are not transplanted and not dosed per assigned regimen will be replaced to ensure that 60 evaluable subjects are dosed.

The randomization schedules that determine subject treatment will be computer-generated by Astellas Pharma US Research Data Science department (or designee) before the beginning of the study.

Specific procedures for randomization through the IRT are contained in the study-specific IRT manual.

The Randomization list will be maintained in the IRT.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

All subjects will receive induction therapy with basiliximab (Simulect® [the first dose as a 20 mg bolus injection prior to transplantation or intra-operatively before revascularization, and the second a 20 mg bolus injection on day 3 or 4 or 5 post-transplant]).

Bleselumab (ASKP1240) will be administered as a 200 mg, 30 minute intravenous infusion. Two (2) vials of bleselumab (2 mLs total containing 200 mg of ASKP1240) are to be used per infusion. Two (2) mLs of bleselumab are to be injected into a PVC OR B. Braun OR Hospira non-PVC 100 mL normal saline infusion bag. The diluted solution must be kept at room temperature and must be administered completely within 8 hours of preparation.

Bleselumab will be administered by designated investigational site staff. The start and stop time of the infusion and the volume infused will be recorded on the eCRF. Dosing and administration instructions will be provided in the pharmacy manual.

The initial dose of tacrolimus (Prograf®) must be anticipated to be administered orally within 48 hours post-transplant at 0.1 mg/kg/day (two equally divided doses at 0.05 mg/kg/day every 12 hours with a target trough level of 4 - 11 ng/mL for the duration of the study). Tacrolimus may be administered intravenously IF medically indicated (only early post-transplant when oral is not tolerated, and should be discontinued as soon as the subject can tolerate oral administration, usually within 2 – 3 days post-transplant).

For subjects randomized to Arm 1, the initial dose of MMF at 1 g bid may be given up to 12 hours preoperatively, or before revascularization. MMF may be given orally or intravenously.

After the initial doses of tacrolimus and MMF, dose adjustments in the post-transplant period are allowed.

Corticosteroids will be administered as an intravenous bolus of 500, 250, 125 and 60 mg of methylprednisone (or equivalent oral/intravenous corticosteroid dose), on days 0 and 1 and 2 and 3, respectively, and continue through 12 months post-transplant.

Oral prednisone is to be tapered according to the following schedule and continue through 12 months post-transplant:

Days Post-transplant	Prednisone Equivalent (mg)
Days 4 - 14	20 - 30
Days 15 - 28	10 - 20
Day 29 and on	5 - 10

Steroid withdrawal is not allowed.

5.1.2 Increase or Reduction in Dose of the Study/Drug(s)

5.1.2.1 Bleselumab

Increases or reductions of bleselumab **ARE NOT** allowed.

5.1.2.2 Basiliximab

Increases or reductions of basiliximab **ARE NOT** allowed.

5.1.2.3 Tacrolimus

Increases and reductions of tacrolimus **ARE** allowed, where medically indicated.

5.1.2.4 Mycophenolate Mofetil

Increases and reductions of MMF **ARE** allowed, where medically indicated.

5.1.3 Previous and Concomitant Treatment (Medication and Non-medication Therapy)

Previous, recent or concomitant use of hepatotoxic medications such as: drugs, toxins, and herbs, will be collected at screening, each visit and in case of liver related AE. All medications (type and route) will be recorded in the electronic Case Report Forms (eCRFs), included in case narratives and used for analysis of hepatotoxicity related cases as necessary.

Refer to Appendix 12.1.1 List of Known Drug-Induced Hepatotoxicity, for the list of possible hepatotoxic medications.

All concomitant medications, immunosuppressive agents and therapies administered during treatment period through month 12/EOS will be recorded at each study visit on the eCRF. Subjects should be instructed not to take any new medications or change the dose and frequency of their ongoing medications throughout the study period without consulting the investigator.

Medications used for anesthesia purposes, with the exception of immunosuppressive agents and blood products, will not be recorded.

Any medication and therapies taken to treat an AE during the 12-month treatment period are to be captured on the Concomitant Medication, Other Immunosuppressant, or Non-medication eCRFs.

All investigational medication administered as part of another clinical study are prohibited and must be discontinued up to 30 days or 5 half-lives (depending on medication) prior to initiating study drug.

Any immunologic biologic compound will be prohibited and must be discontinued at least 8 weeks prior to transplant.

5.1.3.1 Other Immunosuppressant Medications

A subject who has previously received a kidney organ transplant and is currently on an immunosuppression regimen that includes MMF, or any of its components, must discontinue MMF.

A switch from MMF to mycophenolic acid (Myfortic®) will be allowed for medical reasons but will not be supplied by the Sponsor.

All other immunosuppressant medication substitutions must be discussed with the medical monitor to determine continuation of bleselumab infusions as applicable.

Any additional immunosuppressive medications used throughout the study are to be recorded on the appropriate eCRF.

5.1.3.2 Cytomegalovirus Prophylaxis

All subjects (with the exception of those in whom both the donor and recipient are serologically negative [D-/R-] for CMV) must receive prophylaxis with valganciclovir that will be dosed consistent with the package insert. Duration of therapy should be approximately 200 days in D+/R- combinations, and approximately 100 days in the remaining subjects.

For leukopenia, the recommended approach is to adjust doses of other drugs that may be associated with leukopenia prior to making changes in the valganciclovir dose.

5.1.3.3 Pneumocystis jiroveci Pneumonia Prophylaxis

Pneumocystis jiroveci pneumonia prophylaxis must be administered to all study participants according to the standard institutional protocol and applied uniformly to all enrolled subjects regardless of treatment group. If there is no institutional protocol, the investigator must decide on appropriate *Pneumocystis jiroveci* pneumonia prophylaxis.

5.1.3.4 Fungal Prophylaxis

A standard antifungal prophylactic regimen per institutional protocol must be given uniformly to all enrolled subjects regardless of treatment group. If there is no institutional protocol, the investigator must decide on appropriate fungal prophylaxis.

5.1.3.5 Bacterial Prophylaxis

Peri-operative bacterial prophylaxis must be given per institutional protocol and should be given uniformly to all enrolled subjects regardless of treatment group. If there is no institutional protocol, the investigator must decide on appropriate bacterial prophylaxis.

5.1.4 Treatment Compliance

Study subjects should be counseled on the need to be compliant with their study drug regimen.

5.1.5 Restrictions During the Study

Subjects must discontinue bleselumab per below, but are allowed to continue on the protocol-defined visit schedule for the collection of safety and clinical assessment information:

- Subjects whose liver function tests meet one of the following criteria, verified by two (2) consecutive measurements, and in the absence of other etiologies (e.g., biliary stenosis or obstruction, viral hepatitis other than CMV, etc.):
    - ALT or AST > 8 x upper limit of normal (ULN)
    - ALT or AST > 5 x ULN for more than 2 weeks
    - ALT or AST > 3 x ULN and (total bilirubin [TBL] > 2 x ULN or international normalized ratio [INR] > 1.5 x ULN)
    - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- BK nephropathy confirmed by renal biopsy (Section 5.5.1.1.5)
- CMV End Organ Disease (Appendix 12.6)
- Subjects who develop severe bone marrow suppression as defined by the following in the absence of other etiologies (e.g., bleeding, other established causes of neutropenia) and have been verified by two (2) consecutive results within 14 days of the first detection that occur after Day 28 post-transplant:
    - Anemia: Hemoglobin < 6.5 g/dL graded National Cancer Institute Common Terminology Criteria for Adverse Events criteria (NCI-CTCAE) Grade 4 and/or
    - Agranulocytosis: Absolute Neutrophil Count (ANC) < 100 cells/mm^3 graded NCI-CTCAE Grade 4
- Subjects who require plasmapheresis for any reason post-initial bleselumab treatment
- In the subjects' best interest per Investigator discretion

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

The following demographic information will be collected during screening: date of birth, sex, race and ethnicity.

5.2.2 Medical History

Site personnel will collect and record information regarding the subject's medical history during the screening period and any changes between screening and randomization are to be captured. Medical history includes: diagnosis for renal failure, duration and severity of renal disease at randomization, previous kidney transplant (no or yes), date of previous kidney transplant, graft failure due to rFSGS (no or yes), date of transplant failure, and screening medications (30 days prior to transplant). Additionally, the following information will be obtained: type of transplant (living related, living non-related, or deceased donor), total ischemia time in hours and minutes; length of transplant surgery, and panel reactive antibody testing (most recent cPRA level). A copy of the donor kidney biopsy report is to be collected where available.

Donor viral serology information (HBV, HCV, CMV, and EBV), if available, will be collected and recorded.

5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

Medical/surgical history including de novo kidney recipient and has biopsy-proven, pFSGS as a cause of ESRD in their native kidneys at randomization will be collected at screening.

5.3 Efficacy | Pharmacokinetics | Immunogenicity Assessment

The last value prior to the first study drug dose will be used as the baseline to which post-study drug dosing values will be compared.

5.3.1 Efficacy

5.3.1.1 Recurrence of Focal Segmental Glomerulosclerosis

The primary efficacy variable rFSGS is defined as nephrotic range proteinuria with a 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 definition and imputation rule will be used to define the secondary variables and the rFSGS through 6 and 12 months post-transplant.

5.3.1.2 Blinded, Central Read for Recurrence of Focal Segmental Glomerulosclerosis

All episodes of kidney dysfunction based on clinical signs and symptoms will be evaluated by a biopsy at the local pathological laboratory for recurrence of FSGS and for possible rejection. The same slides and images of the biopsy will also be sent to a central pathology lab and read by an independent pathologist to determine recurrence of FSGS. The central pathology lab will not be provided the subject's treatment regimen.

Subjects who have not had a biopsy with a diagnosis of recurrent FSGS 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. All other biopsies conducted will be 'for cause' only.

5.3.1.3 Biopsy-proven Acute Rejection

All episodes of kidney dysfunction based on clinical signs and symptoms will be evaluated for possible rejection. All subjects should have biopsy confirmation of rejection before treatment is begun or within 48 hours of initiation of treatment for acute rejection. The pathologist at the clinical site will grade all biopsies using the 2007 Banff criteria (Appendix 12.8, Grading of Acute Kidney Allograft Rejection). Biopsy-proven acute rejection (BPAR, T- or B-cell) will be determined by local review. All biopsies should be evaluated for presence of C4d.

Subjects who receive immunosuppressive medications for the treatment of suspected or biopsy-confirmed acute rejection are considered to have a clinically-treated acute rejection. The rejection treatment start date will be used to denote the start for the clinically treated acute rejection. If the subject has an acute rejection, allowable rejection therapy may include, but is not limited to, steroid pulse, thymoglobulin, basiliximab, OKT3, or alemtuzumab.

Subjects may remain on their assigned treatment regimen following treatment of acute rejection. If subjects permanently discontinue bleselumab, tacrolimus or MMF treatment, they are to continue with the protocol-defined visit schedule (Table 1, Schedule of Assessments) for the collection of safety and clinical assessment information.

5.3.2 Exploratory Efficacy Variables

The following exploratory efficacy variables will be assessed:

- Graft and patient 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)
- Time to rFSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g)
- Time to rFSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g) or initiation of plasmapheresis
- Time to rFSGS defined as nephrotic range proteinuria with protein-creatinine ratio (≥ 3.0 g/g), death, graft loss or lost to follow-up
- Time to recurrence of biopsy-proven (blinded, central read) FSGS
- Time to first BPAR (Banff Grade ≥ 1, local read)
- Urine protein-creatinine ratio through 6 and 12 months post-transplant
- Urine albumin-creatinine ratio through 3, 6 and 12 months post-transplant
- Change in auto-anti-CD40 antibodies from baseline
- Change in patient-reported outcomes from baseline (SF-36s, EQ-5D-5L and KTQ)

5.3.3 Pharmacokinetics

Further details on sample collection, processing, labeling, storage, and shipment procedures will be provided in the laboratory manual.

5.3.3.1 Bleselumab

Sample collection for bleselumab pharmacokinetics for subjects **in Arm 2 ONLY** is to occur at the times shown in Table 1, Schedule of Assessments. The timing of blood collections will take priority over all other scheduled study assessments except for study drug dosing.

Pharmacokinetic 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.

5.3.3.2 Anti-Bleselumab and Bleselumab Bi-Specific Antibodies

Sample collection for anti-bleselumab and bleselumab bi-specific antibodies for subjects **in Arm 2 ONLY** is to occur at the times shown in Table 1, Schedule of Assessments. The timing of blood collections will take priority over all other scheduled study assessments except for study drug dosing.

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.

5.3.3.3 Auto-Anti-CD40 Antibody

Sample collection for auto-anti-CD40 antibodies for subjects **in BOTH Arms 1 and 2** is to occur at the times shown in Table 1, Schedule of Assessments. The timing of blood collections will take priority over all other scheduled study assessments except for study drug dosing.

Samples are to be collected at screening, and prior to infusion at baseline (day 0), visit days 7, 14, 28, 56, 90/month 3, and months 6, 9 and 12/EOS.

5.4 Safety Assessment

The safety assessments include the following:

- AEs graded by NCI CTCAE criteria
- Vital sign measurements
- Clinical laboratory tests
- Bleselumab pharmacokinetics (including anti-bleselumab and bleselumab bi-specific antibodies)
- Viral serology (HBV, HCV CMV and EBV)
- Viral load testing (CMV, BKV and EBV)

Unscheduled assessments will be performed if clinically warranted. Refer to Table 1, Schedule of Assessments, for the visit assessment collection schedule.

5.4.1 Vital Sign Measurements

Vital sign measurements are to be collected as shown in Table 1, Schedule of Assessments.

Vital signs, including body temperature, systolic and diastolic blood pressure and pulse rate will be collected at all study visits. When vital signs are to be collected at the same time as a blood sample, vital signs are to be taken prior to the blood draw.

5.4.2 Adverse Events

See Section 5.5, Adverse Events and Other Safety Aspects, for information regarding AE collection and data handling.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See Appendix 12.2, Liver Safety Monitoring and Assessment, for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in LFTs, bilirubin, hepatic enzyme increased (e.g., AST, ALT) or is suspected to be due to hepatic dysfunction.

Subjects with AE's of hepatic origin accompanied by LFT abnormalities should be evaluated and carefully monitored.

Please review the requirements related to the evaluation, reporting and analysis of Drug-Induced Liver Injury (DILI) information found in Appendix 12.2, Liver Safety Monitoring and Assessment. In the event of a confirmed, marked hepatic abnormality as defined in Section 12.2, it is the Investigator's responsibility to ensure contact with the Sponsor/delegated contract research organization (CRO) by telephone or fax immediately (i.e., within 24 hours of awareness).

5.4.3 Laboratory Assessments

Below are the local and central laboratory assessments that will be performed during the conduct of the study. Refer to Table 1, Schedule of Assessments, for study visit collection days.

Clinical significance of out-of-range laboratory findings is to be determined and documented by the Investigator/sub-Investigator who is a qualified physician.

Screening safety laboratory tests may be repeated in order to confirm eligibility.

5.4.3.1 Local Laboratory Testing

Blood and urine will be collected for the following local laboratory assessments:

- Histocompatibility and crossmatch
  - Record prior results at screening
- ABO compatibility
  - Record prior results at screening
- Hematology (hemoglobin, hematocrit, RBCs, white blood cells [WBCs] with differential [including bands, if available] and platelet count)
- Biochemistry (phosphorus, total protein, serum creatinine, blood urea nitrogen [BUN], albumin, creatine phosphokinase [CPK], LDH, amylase, electrolytes [sodium, potassium, calcium, magnesium, bicarbonate, chloride], and fasting glucose)
- Coagulation/thrombotic pathway (prothrombin time, activated partial thromboplastin time and INR)
- Hepatic profile (total and direct bilirubin, AST, ALT and ALP)
- Lipid profile (total cholesterol [including low-density lipoprotein (LDL), high density lipoprotein [HDL] and triglycerides])
  - Blood specimen for the lipid profile should be drawn after the subject has fasted for at least 8 hours

- Urinalysis (pH, specific gravity, protein, glucose, ketones, bilirubin, blood and microscopic evaluation)
- Urine protein-creatinine ratio and urine albumin-creatinine ratio via a spot collection
- Serum pregnancy testing for females of child bearing potential
    - Post-initial serum pregnancy test (collected on admission to the hospital or within 7 days prior to transplant), all subsequent pregnancy tests are via urine and are to be collected prior to continued treatment
    - If a urine pregnancy test is positive at any time, a serum pregnancy test is to be performed and MUST be negative for the subject to continue participation in the study
- Recipient viral serologies (i.e., antibodies [e.g., HBV, HCV, CMV and EBV])
    - Those 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 visit day 90/month 3, and month 12/EOS
- Viral load testing (CMV, BKV [serum and urine] and EBV)
    - 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
- Tacrolimus whole blood trough level specimens
    - 11 - 13 hours post-initial dose, and immediately prior to all subsequent infusions

5.4.3.2 Central Laboratory Testing

Blood will be collected for the following central laboratory assessments:

- Bleselumab pharmacokinetic levels
- Anti-bleselumab antibodies
- Bleselumab bi-specific antibodies
- Auto-anti-CD40 antibodies

Refer to the laboratory manual for detailed instructions on sample collection, processing, labeling, storage and shipment procedures.

Refer to Appendix 12.2 for additional DILI laboratory testing requirements and timing.

5.4.4 Physical Examination

The subject will be examined by a medically qualified person, at the times specified in Table 1. Schedule of Assessments.

A complete physical examination consisting of an examination of general appearance, eyes, nose throat, neck (including thyroid), lymph nodes, chest, lungs, cardiovascular, abdomen, skin, extremities, musculoskeletal, and neurological system including mental status is to be conducted at screening, day 90/month 3 and month 12/EOS. A symptom-directed physical exam may be performed at any of the other visits, if necessary.

Height will be measured one time at screening only. Weight will be collected at all visits.

The screening physical examination also includes significant, ongoing medical conditions. Any changes between screening and randomization are to be captured in the medical/surgical history.

Any abnormal finding(s) at screening must not be exclusionary per the eligibility criteria and must be assessed and documented as not clinically significant if a subject is to be enrolled in the study. Post-initial study drug dosing, new abnormal findings or a worsening of an ongoing abnormal condition must be recorded as an AE.

5.4.5 Electrocardiogram

Standard 12-lead electrocardiogram (ECG) recordings will be used for the purposes of safety assessment and subject management by the Investigator.

A 12-lead, resting ECG is to be recorded at each timepoint as indicated in Table 1, Schedule of Assessments. Subjects should remain supine for at least 5 minutes prior to all ECGs being performed. Dates and times may be generated by the machine's internal clock and are considered source data. The results are to be interpreted by qualified personnel in real time for the management of the subjects' clinical condition. The principal investigator (PI)/designee will initial and date, and provide his/her clinical interpretation on each report. The results (normal, abnormal not clinically significant, abnormal clinically significant) are to be recorded in the eCRFs.

The ECG recorded during screening will be used to determine eligibility for study participation. Subjects who have a clinically significant abnormal ECG will not be eligible for the study. The interpretation of the ECG from screening will be the baseline to which post-study drug dosing ECGs will be compared.

Unscheduled ECGs will be performed if clinically indicated.

ECGs should be performed before the scheduled pharmacokinetic blood draws.

If a machine-read QTc exceeds 500 msec, this should be reported as an AE.

The original print-out and an electronic copy of all scheduled and unscheduled ECG tracings should be maintained on site as source data.

5.4.6 Imaging

A chest radiograph (x-ray) is to be performed in two views – lateral and anterior-posterior will be used for the purposes safety assessment and subject management by the Investigator.

Chest x-rays are to be performed as indicated in Table 1, Schedule of Assessments. The results are to be interpreted by qualified personnel in real time for the management of the subjects' clinical condition. The PI/designee will initial and date, and provide his/her clinical interpretation on each report. The results (normal, abnormal not clinically significant, abnormal clinically significant) are to be recorded in the eCRF.

Subjects who have x-ray findings suggestive of acute or chronic lung disease may be eligible for the study and must be discussed with the Sponsor Medical Monitor before the subject is enrolled in the study.

Subjects who have had a normal chest x-ray within 3 months of screening are not required to have x-rays performed at screening, per Investigator discretion.

The interpretation of the chest x-ray from screening will be the baseline to which post-study drug dosing x-rays will be compared.

Unscheduled chest x-rays will be performed if clinically indicated.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

All AEs will be recorded in the eCRF from the time of consent through 30 days post-last dose. For ALL subjects this is to conclude at the month 12/EOS visit. (The transplant that occurs on day 0 is not considered an AE or an SAE).

Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to an SAE. In these cases, it is the investigator’s responsibility to ensure these AEs or other reporting requirements are followed and the information is appropriately recorded in the eCRF accordingly.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

5.5.1.1 Definitions of Specific Adverse Events

5.5.1.1.1 Infection

Bacterial, fungal and viral infections are to be reported as an AE or an SAE.

Except for CMV, EBV and BK, infection is defined as any of the following:

- Treatment with a antimicrobial agent for a specific clinical syndrome (not prophylaxis)
- Positive cultures, pathologic identification of microbial agents or significant serological changes related to clinical symptoms
- Typical clinical presentation documented by investigator or appropriate consultant
- Other infectious hepatitis to be considered as differential diagnosis in case of LFT abnormalities

5.5.1.1.2 Definition of Cytomegalovirus

Cytomegalovirus (CMV) active infection:

- Replicative infection can be diagnosed by growing the virus *in vitro*, finding evidence of viral infection by intra-cytoplasmic or intra-nuclear inclusions or by antibody-based staining techniques for CMV in histopathologic sections or finding evidence of replication using nucleic acid based assays or antigenemia studies.

CMV disease:

- CMV disease is defined by evidence of CMV infection with attributable symptoms. CMV disease can be subclassified into CMV viral syndrome or tissue invasive disease. Definitions are listed in **Appendix 12.6. Definition of CMV Disease in Solid Organ Transplant Recipients.**

5.5.1.1.3 Definition of Epstein-Barr Virus

Epstein-Barr Virus (EBV) infection:

- Active, asymptomatic EBV infection is defined by the presence of a detectable EBV viral load as measured by a nucleic acid amplification assay. Asymptomatic infection may also be identified in lymphoid rich histopathologic specimens.

EBV disease:

- EBV disease is defined by the presence of active EBV infection with symptoms or signs attributable to the virus.

5.5.1.1.4 BK Virus Infection

BK virus (BKV) infection (replicative infection) defined as quantitative BK viral DNA load, in blood or urine above the detection threshold for the given laboratory's assay. BK infection should be classified as either BK viruria or BK viremia or both. While the presence of decoy cells in urine on cytology is suggestive of BK infection, confirmation with a specific test (e.g., polymerase chain reaction [PCR]) is required.

5.5.1.1.5 BK Virus Associate Nephropathy

Proven BKVAN is defined by evidence of BKV infection and the presence of:

- Renal biopsy associated with:
  - an acute tubular necrosis-like picture *or*
  - interstitial nephritis mimicking acute rejection *or*
  - chronic allograft nephropathy with confirmation of the presence of BKV by electron microscopy, immunohistochemistry or *in-situ* hybridization for BKV. Although intra-nuclear viral inclusions are usually seen, their presence is not mandatory for a diagnosis of BKVAN.

For purposes of this study, subjects with presumptive BKVAN diagnosed in the presence of renal allograft dysfunction and a positive BKV DNA PCR result from blood in a subject with no viral inclusions at light microscopy and negative immunohistochemistry/*in-situ* hybridization should be classified as BKV infection (i.e., BK viremia rather than BKVAN).

5.5.1.1.6 Malignancy

All malignancies are to be captured as AEs.

5.5.1.1.7 Post-transplant Lymphoproliferative Disorder

Diagnosis of PTLD should be made following review of tissue specimens. The anatomic staging of PTLD will be captured, specifically if the allograft or if the central nervous system (CNS) is involved. PTLD will be classified according to the criteria in Appendix 12.7. Additionally, if available, ancillary pathologic information related to cell phenotype, clonality, presence of EBV in the tissue specimen, and donor vs. recipient origin will be collected.

Tissue samples should be interpreted by a hematopathologist or pathologist who is familiar with the histopathologic features of PTLD. If as a matter of the subject's routine medical evaluation tissues are examined for the presence of EBV by *in situ* hybridization, the cell of origin (B, T, null, mixed) is determined or radiographic evaluation is performed to document the extent of disease (e.g., computed tomography scans) this information will be captured on the eCRF.

5.5.2 Definition of Serious Adverse Events)

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect

- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Special situation events on the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s)
- Suspected abuse/misuse of the medicinal product(s)
- Inadvertent or accidental exposure to the medicinal product(s)
- Medication error involving the medicinal product(s) (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)

All of the special situation events noted above should be recorded on the eCRF. Any situation involving these special situation events that also meets the criteria for an SAE should be reported as an SAE, recorded on the AE page of the eCRF and marked ‘serious’ on the SAE worksheet.

All the special situation events will be recorded from the time of consent through 30 days post-last dose.

The Sponsor has a list of events that they classify as “always serious” events. If an AE is reported that is considered to be an event per this classification as “always serious,” additional information on the event may be requested, those events should be reported as an SAE.

If a subject or a subject’s partner becomes pregnant during the study, this should be reported as if it were an SAE (Section 5.5.8, Procedure in Case of Pregnancy).

5.5.3 Criteria for Causal Relationship to the Study Drug

Adverse events that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship to the study drugs could not be ruled out." Relationship to study drug will be assessed using the following criteria:

Causal relationship to the study drug	Criteria for causal relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).

5.5.4 Criteria for Defining the Severity of an Adverse Event

Adverse events, including abnormal clinical laboratory values, will be graded using the NCI CTCAE guidelines (Version 4.03). The items that are not stipulated in the NCI CTCAE Version 4.03 will be assessed according to the criteria below and entered into the eCRF:

Grade	Assessment Standard
1 - Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations noted; intervention not indicated.
2 - Moderate	Local or noninvasive intervention indicated.
3 - Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization.
4 - Life Threatening	Life threatening consequences, urgent intervention indicated.
5 - Death	Death related to AE.

5.5.5 Reporting of Serious Adverse Events (SAEs)

SAEs will be captured for all subjects from the time the subject signs the informed consent. If a subject signs the informed consent but never receives study drug or is deemed a screen failure, any SAEs reported from the time of consent until determination of screen failure should be reported to the Sponsor via an SAE worksheet and followed until resolution. For subjects who are randomized, SAEs will be captured from the time of consent 30 days post-last dose. For ALL subjects this is to conclude at the month 12/EOS visit.

In the case of a SAE, the Investigator must contact the Sponsor by telephone, fax or email immediately (within 24 hours of awareness).

The Investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the Sponsor by fax or email immediately (within 24 hours of awareness). If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

For contact details, see Section II Contact Details of Key Sponsor's Personnel. Please fax or email the SAE Worksheet to:

Astellas Pharma Global Development, Inc.
Medical Safety Pharmacovigilance
Fax number: 1-888-396-3750
Email: safety-us@astellas.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Director (Section II, Contact Details of Key Sponsor's Personnel).

Follow-up information for the event should be sent promptly (within 7 days if the initial notification) as necessary.

Full details of the SAE should also be recorded on the medical records and on the eCRF.

The following minimum information is required:

- ISN/Study number
- Subject number (for randomized subjects only), sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug
- Batch number of study medication

The Sponsor or Sponsor's designee will submit expedited safety reports (i.e., IND Safety Reports) to the regulatory agencies (i.e., FDA) as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their IRB/IEC within timelines set by regional regulations (i.e., EU, (e)CTD, FDA). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

The Sponsor will notify all Investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements to their IRB/IEC.

The Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor.

You may contact the Sponsor's Medical Monitor/Expert for any other problem related to the safety, welfare, or rights of the subject.

5.5.6 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If during AE follow-up, the AE progresses to an ″SAE,″ or if a subject experiences a new SAE, the investigator must immediately report the information to the Sponsor.

Please refer to Appendix 12.2, Liver Safety Monitoring and Assessment**,** for detailed instructions on DILI.

5.5.7 Monitoring of Common Serious Adverse Events

Common SAEs are anticipated to occur in the study population independent of drug exposure. SAEs classified as "common" are provided in Appendix 12.3, Common Serious Adverse Events. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs" as specified in Appendix 12.3. The Sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in Section 5.5.5, Reporting of Serious Adverse Events.

5.5.8 Procedure in Case of Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 30 days from the discontinuation of dosing, the Investigator should report the information to the Sponsor as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated contraception date, pregnancy result and neonatal data etc., should be included in this information.

The Investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the Investigator should respond in accordance with the report procedure for SAEs.

Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below:

- ″Spontaneous abortion″ includes miscarriage, abortion and missed abortion
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the Investigator
- In the case of a delivery of a living newborn, the ″normality″ of the infant is evaluated at the birth
- Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination.

If during the conduct of a clinical trial, a male subject makes his partner pregnant, the subject should report the pregnancy to the Investigator. The Investigator will report the pregnancy to the Sponsor as an SAE.

5.5.9 Emergency Procedures and Management of Overdose

In the event of suspected bleselumab overdose, the subject should receive supportive care and monitoring. The Astellas Medical Monitor/Expert should be contacted as applicable.

5.5.10 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the Sponsor will inform all Investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

5.6 Test Drug Concentration

5.6.1 Blood Sampling and Processing for Bleselumab

Whole blood samples (4 mL/sample) for pharmacokinetics will be collected via venipuncture or cannulation of a forearm vein(s) into a serum separating tube (SST).

Blood collection for analysis will be performed according to Table 1. Schedule of Assessments.

Refer to the laboratory manual for detailed instructions on sample collection, processing, labeling, storage and shipment procedures.

Measurement of the pharmacokinetics, anti-bleselumab antibodies, bleselumab bi-specific antibodies, auto-anti-CD40 antibodies, and potentially for podocyte injury, in serum, will be performed using a validated method at a bioanalytical laboratory specified by the Sponsor.

5.7 Other Measurements, Assessments or Methods

5.7.1 Patient-reported Outcomes

All patient-reported outcome (PRO) measures will be completed by the subject via computerized administration on a sponsor-sourced, vendor-provided electronic device.

If a subject is not able to provide an answer to the question(s), it is not a requirement to complete the rest of the ePRO assessment(s) at the respective visit.

5.7.1.1 Short Form 36-Item Health Survey Score

The Short Form 36-Item Health Survey Score (SF-36s, version 2.0, Appendix 12.9) is a measure of health status. The SF-36 provides scores for each of the 8 health domains and psychometrically-based physical component summary (PCS) and mental component summary (MCS) scores.

The 8 domains are the weighted sums of the questions in their section. Each domain is directly transformed into a 0 - 100 scale on the assumption that each question carries equal weight. Lower scores indicate greater disability. 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).

The SF-36s is a multipurpose health survey that measures overall health status, functional status, and health-related quality of life. It is a generic measure and its use is not restricted to a single disease state. Using an 8-scale profile of physical and mental health summary measures, the SF-36s is a valid and reliable tool that allows comparisons between and within clinical and general populations.

Subjects will complete this self-assessment at screening, days 14 and 90/month 3, and months 6 and 12/EOS visits.

5.7.1.2 European Quality of Life – 5 - Dimensions - 5 Levels

The European Quality of Life – 5-Dimensions – 5 Levels (EQ-5D-5L, Appendix 12.10) is an international standardized non-disease specific (i.e., generic) instrument for describing and valuing health status. It is a measure of health-related QoL, capable of being expressed as a single index value and specifically designed to complement other health status measures. The questionnaire will be provided in the local language of the subject. The EQ-5D-5L has 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. In the newest version, each dimension has 5 response levels (e.g., no problems, slight problems, moderate problems, severe problems and unable to perform the activity). In addition, it has a visual analogue scale (VAS) that elicits a self-rating by the respondent of his/her health status.

The EQ-5D-5L is to be completed by the subject at screening, and at the day 90/month 3 and month 12/EOS visits.

5.7.1.3 Kidney Transplant Questionnaire

The Kidney Transplant Questionnaire (KTQ, Appendix 12.11) is a 25-item questionnaire that includes 5 domains or subscales (i.e., physical symptoms [based on 6 items], fatigue [based on 5 items], uncertainty/fear [based on four items], appearance [based on four items], and emotional [based on six items].

A mean score ranging from 1 to 7 is reported for each of the 5 subscales, with higher scores representing better functioning, well-being, or fewer problems [Laupacis et al, 1993].

Subjects are to complete this self-assessment at screening, days 14 and 90/month 3, and months 6 and 12/EOS visits.

5.7.2 Blood Sample for Future Pharmacogenetic Analysis (Retrospective PGx Analysis)

Pharmacogenetic (PGx) research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics, and toxicity/safety issues. After randomization (see schedule of assessments), a 4 mL sample of whole blood for possible retrospective PGx analysis will be collected using a vacutainer tube containing EDTA. After collection, gently invert the blood sample 8 to 10 times. The blood collection tube may either

be stored upright at 4°C for up to 5 days prior to shipment or stored frozen at -20°C or below at the site for extended storage. Samples will be shipped to a Sponsor designated banking CRO.

Labels should uniquely identify each sample and contain at least:

- Protocol number (7163-CL-3201)
- Subject number
- Purpose and biological matrix (i.e., "biobanking," "whole blood")

Details on sample collection, labeling, storage and shipment procedures will be provided in the laboratory manual.

See Appendix 12.4. Retrospective Pharmacogenetic Sub-study for further details on the banking procedures.

5.8 Total Amount of Blood

The total volume of whole blood (including for clinical laboratory, pharmacokinetic and pharmacogenetic sampling) that is to be collected during the entire study is approximately 415 mL per subject for subjects in Arm 2 and approximately
360 mL for subjects in Arm 1.

A volume of approximately 300 mL will be collected from screening through month 12/EOS for scheduled clinical "safety" laboratory evaluations including serum pregnancy (for females).

A total of approximately 118 and 64 mL will be collected during the study for pharmacogenetic and pharmacokinetic sampling over the course of the study for subjects in Arms 2 and 1, respectively.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who enrolled in the study and for whom study drug is permanently discontinued for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

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 (Table 1. Schedule of Assessments – Screening through 12 months Post-Transplant), for the collection of safety and clinical assessment information.

If a subject declines to be followed upon permanently discontinuing bleselumab, tacrolimus or MMF, the EOS visit (visit 21/month 12) procedures are to be completed within 30 days post-last dose.

Subjects must discontinue bleselumab per below, but are allowed to continue on the protocol-defined visit schedule for the collection of safety and clinical assessment information:

- Subjects whose liver function tests meet one of the following criteria, verified by two (2) consecutive measurements, and in the absence of other etiologies (e.g., biliary stenosis or obstruction, viral hepatitis other than CMV, etc.):
  - ALT or AST > 8 x upper limit of normal (ULN)
  - ALT or AST > 5 x ULN for more than 2 weeks
  - ALT or AST > 3 x ULN and (total bilirubin [TBL] > 2 x ULN or international normalized ratio [INR] > 1.5 x ULN)
  - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- BK nephropathy confirmed by renal biopsy (Section 5.5.1.1.5)
- CMV End Organ Disease (Appendix 12.6)
- Subjects who develop severe bone marrow suppression as defined by the following in the absence of other etiologies (e.g., bleeding, other established causes of neutropenia) and have been verified by two (2) consecutive results within 14 days of the first detection that occur after Day 28 post-transplant:
  - Anemia: Hemoglobin < 6.5 g/dL graded National Cancer Institute Common Terminology Criteria for Adverse Events criteria (NCI-CTCAE) Grade 4 and/or
  - Agranulocytosis: Absolute Neutrophil Count (ANC) < 100 cells/mm^3 graded NCI-CTCAE Grade 4
- Subjects who require plasmapheresis for any reason post-initial bleselumab treatment
- In the subjects' best interest per Investigator discretion

6.2 Discontinuation of the Site

If an Investigator intends to discontinue participation in the study, the Investigator must immediately inform the Sponsor.

6.3 Discontinuation of the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of APGD. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures (TLFs) to be produced. The SAP will be finalized prior to the interim data analysis of the 3-month primary endpoint, rFSGS. Any changes from the analyses planned in the SAP will be justified in the clinical study report (CSR).

Prior to database lock, a final meeting will be held to review data and tables, listings and figures (TLFs) 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 lock.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints. There will be no adjustment for multiplicity in this proof-of-concept study.

7.1 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.

It has been estimated from the literature that the expected FSGS recurrence rate for the SOC group is between 30 and 50% with most occurring by 3 months post-transplant. In the previous study with these same treatments in kidney transplant patients, there were 3 of approximately 50 patients, who experienced death, graft loss or lost to follow-up, in each of the two planned treatment arms. Thus, imputing death, graft loss or lost to follow-up as rFSGS is not expected to have a sizeable and differential impact on the rFSGS estimates. 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 2-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 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)
Difference 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 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 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 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

SOC = standard of care

7.2 Analysis Set

Detailed criteria for analysis sets will be specified in Classification Specifications and allocation of subjects to analysis sets will be determined prior to database hard-lock.

7.2.1 Full Analysis Set

The full analysis set (FAS) will consist of all subjects who are randomized, receive at least one dose of study drug and receive a transplanted kidney. This will be the primary analysis set for efficacy analyses.

7.2.2 Per Protocol Set

No per protocol set (PPS) is planned for this study; however, exploratory analyses including certain subjects may be performed if clinically meaningful.

7.2.3 Safety Analysis Set

The Safety Analysis Set (SAF) consists of all subjects who took at least one dose of study medication, and will be used for safety analyses.

7.2.4 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PKAS) will consist of subjects from the SAF who have at least one measureable pharmacokinetic concentration. The PKAS will be used for summaries and exploratory analysis of the pharmacokinetic data.

7.3 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized overall and by treatment group for age, sex, race, ethnicity, height, weight, donor type (living [related/nonrelated] or deceased donor), donor and recipient serology, donor demographics, panel reactive antibody and total ischemia time.

Continuous variables will be summarized by descriptive statistics (n, mean, standard deviation, and minimum, median, maximum). The means will be compared among treatment groups using an analysis of variance (ANOVA) or analysis of covariance (ANCOVA) with treatment group as a factor.

Discrete variables will be summarized by number/percentage of subjects in each category. A 2-sided 95% confidence interval will be constructed for the treatment differences.

7.4 Analysis of Efficacy

General Considerations

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 is a sufficient number of patients with more than one kidney transplant. Endpoints analyzed with Fisher's Exact test may be analyzed with a CMH test stratifying by previous kidney transplant status (no or yes) if there is a sufficient number of patients with multiple kidney transplants. For time-to-event endpoints, Cox regression will be used comparing the

2 treatment groups and will include previous kidney transplantation (no or yes) in the model provided there are sufficient multi-transplant patients.

There are two treatment arms for comparison in this study:

- Bleselumab with Tacrolimus (Arm 2) vs. SOC (Arm 1)

Fisher's Exact test will be used to analyze all count data, unless otherwise specified. An ANOVA or ANCOVA will be used to analyze continuous data.

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

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.

The percentage of subjects who have rFSGS will be computed, along with a 2-sided 95% confidence interval (CI) for each of the treatment groups. The difference between the two groups will be given and a 2-sided 95% CI will be constructed for the treatment differences using the normal approximation. As a secondary analysis, Fishers' exact will be used to test for treatment differences.

7.4.1.2 Subgroup Analysis

For each treatment group, incidence of rFSGS at three months will be calculated for the following subgroups: age (<65, ≥ 65), gender, race (African-American vs Others), donor types (deceased donors vs others), and donor relationship (related vs non-related).

7.4.2 Analysis of Secondary Endpoints

7.4.2.1 Recurrence of Focal Segmental Glomerulosclerosis through 6 and 12 Months

The percentage of subjects with rFSGS through 6 and 12 months post-transplant will be computed along with a 2-sided 95% CI for each of the treatment groups and for the treatment difference (Arm 2 - Arm 1). As a secondary analysis, Fishers' exact will be used to test for treatment difference. Death, graft loss or lost to follow-up will be imputed as rFSGS.

7.4.2.2 Biopsy-Proven Acute Rejection determined by Local Review

By-treatment group summaries will be provided for the incidence of BPAR (Banff Grade ≥ 1, local read) through 3, 6 and 12 months post-transplant. A 2-sided 95% CI will be constructed for each of the treatment groups and for the treatment difference. Subjects with an unknown outcome prior to each of the defined time points (3, 6 or 12 months post transplant), if any, will be counted as a BPAR in a secondary analysis. A 2-sided 95% CI will be constructed for the treatment differences using the normal approximation.

7.4.2.3 Efficacy Failure

The incidence of efficacy failure defined as death, graft loss, BPAR (Banff Grade >1; local read) and lost to follow-up through 12 months post-transplant will be summarized by treatment group. A 2-sided 95% CI for each of the treatment groups and for the difference using the normal approximation will be constructed. As a secondary analysis, Fisher's exact will be used to test for treatment differences.

For each treatment group, Kaplan-Meier estimates will be provided for efficacy failure at one year. The treatment difference will be computed as Arm 2 - Arm 1. A 2-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 Recurrence of Focal Segmental Glomerulosclerosis through 3, 6 and 12 Months determined by Central Blinded Review of the Biopsy Slides

Biopsy-proven rFSGS will include only those for whom slides are reviewed by the independent pathologist who will be the blinded, central reader. All subjects are required to provide a biopsy either 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 "for-cause" biopsies after 3 months post-transplant will be reviewed by the blinded, central reader for rFSGS.

Summaries of biopsy-proven rFSGS will be provided by treatment group and the results for the comparison of the two treatment groups using all provided biopsies will be provided for 3, 6 and 12 months post-transplant.

The percentage of subjects who have rFSGS will be computed along with a 2-sided 95% CI for each of the treatment groups and for the treatment difference (Arm 2 - Arm 1).

7.4.3 Analysis of Exploratory Endpoints

7.4.3.1 Graft and Patient Status (Graft and Patient Survival)

Summaries by treatment group (and a 2-sided 95% CI for each) for graft and patient status through 12 months' post-transplant will be given. Subject 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. The treatment difference and a 2-sided 95% CI for the difference will be provided.

For each treatment group, Kaplan-Meier estimates will be used to estimate graft and subject 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 2-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 3, 6 and 12 months and analyzed at each time point using an ANCOVA with treatment as a 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.

Between-group comparisons at each visit of the mean eGFR based on the MDRD criterion will be made with an ANCOVA with treatment as the factor and the week 4 eGFR as the covariate.

7.4.3.3 Time to rFSGS; Time to rFSGS or Initiation of Plasmapheresis; Time to Death, Graft Loss or Lost to Follow-up Imputed as rFSGS; Time to Biopsy-Proven rFSGS

For each of the listed variables, Kaplan-Meier will be used to provide estimates for each treatment group at one year. The treatment difference will be computed as Arm 2 - Arm 1. A 2-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. Those who drop out of the study prematurely without sufficient information to determine recurrence will be censored at the time of withdrawal.

7.4.3.4 Time to First BPAR

Kaplan-Meier will be used to provide estimates for each treatment group and their difference at one year. The treatment difference will be computed as Arm 2 - Arm 1. A 2-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. Those who drop out of the study prematurely without sufficient information to determine recurrence will be censored at the time of withdrawal.

7.4.3.5 Urine Protein-Creatinine Ratio

The urine protein-creatinine ratio, the change from week 1 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 a factor 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.

7.4.3.6 Urine Albumin-Creatinine Ratio

The urine albumin-creatinine ratio, the change from week 1 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 albumin-creatinine ratio collected up to week 4 will be analyzed with an ANCOVA with treatment group as a factor and the post-transplant value as the covariate. The urine albumin-creatinine ratio after week 4 will be analyzed with an ANCOVA with treatment as a factor and the week 4 value as a covariate.

7.4.3.7 Auto-anti-CD40 antibodies

Auto-anti-CD40 antibodies (present or absent), antibody level and change from baseline will be summarized by treatment group.

7.4.3.8 Patient-Reported Outcomes

7.4.3.8.1 Short Form 36-Item Health Survey Score

The SF-36 (SF-36, v2) provides scores for each of 8 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 8t subscales are summarized into two scores, the PCS and MCS scores. SF-36 scale scores, and the PCS and MCS will be calculated by QualityMetric. Descriptive statistics (n, mean, median, sd, min and max) will be provided for each of the 8 domains and the PCS and MCS at each visit by treatment group. Between-group comparisons of the scores will be provided.

7.4.3.8.2 European Quality of Life – 5 – Dimensions - 5 Levels

The EQ-5D-5L is an international and standardized non-disease specific instrument for describing and valuing health status. The percentage of patients in each treatment arm who report problems (dichotomized to no, yes) for each of the each of the 5 dimensions will be tabulated and graphically displayed. The distribution of responses ranging from none, slight, moderate, severe, and unable to function will be given for each treatment group. The percentage of patients who report ‘Yes’ for each of the EQ-5D-5L dimensions will be compared between the treatment groups at each visit using Fisher’s Exact test. For the EQ-5D-5L VAS records, summaries by treatment group and visit will be given for the EQ-5D-5L VAS score and the change from baseline. The change from baseline for the VAS score will be analyzed by using an ANCOVA model with treatment group as a fixed factor and the baseline VAS score as a covariate.

7.4.3.8.3 Kidney Transplant Questionnaire

The change from baseline at 3 and 12 months in the score for each of the 5domains of the KTQ (i.e., physical symptoms, fatigue, uncertainty/fear, appearance, and emotional) will be analyzed using ANCOVA with treatment as a factor and baseline as a covariate.

7.5 Analysis of Safety

For each treatment arm, the frequencies and percentages will be displayed for the following TEAEs (coded using MedDRA by system organ class and preferred term:

- Overall
- Serious
- Related (considered by the Investigator to be possible or probable related) to study drug
- Leading to the permanent discontinuation of study drug

Descriptive statistics for each laboratory test (e.g., hematology, biochemistry, urinalysis) and its change from baseline (month 1 for renal tests) and vital signs will be tabulated by treatment group and scheduled time point.

The viral load data (CMV, BKV and EBV) will be summarized by scheduled visit and treatment group.

The number and percent of subjects with positive anti-bleselumab antibodies will be displayed by visit. The maximum titer, time to first positive titer and time to last positive titer will also be provided. Efficacy and safety data may be examined for those with and without anti-bleselumab antibodies.

Bi-specific bleselumab antibody concentrations will be listed and summarized (n, mean, sd, %CV, min, median, max and GM) by treatment group for each collection time point.

7.6 Analysis of Pharmacokinetics

The serum concentration data of bleselumab will be listed and summarized using descriptive statistics for the concentrations obtained for peak and trough concentrations at each visit for Arm 2.

7.7 Protocol Deviations and Other Analyses

Protocol deviations as defined in Section 8.1.6, Protocol Deviations**,** will be summarized for all randomized subjects by treatment group and total as well as by site. A data listing 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

Study drug exposure will be summarized by treatment group and visit using descriptive statistics. Tacrolimus trough levels will also be summarized.

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

An interim analysis is planned once all subjects have completed the 3 months post-transplant follow-up to assess treatment differences for rFSGS. The purpose of this analysis is to support strategic decision making for future project development and study design. The result will aid in determining if this compound will continue development for rFSGS.

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

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to allocate the concomitant medication and AEs to a treatment group, in addition to determining whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

See the SAP for details of the definitions for windows to be used for analyses by visit.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The Investigator (or site designee) will enter data collected using an electronic data capture system. In the interest of collecting data in the most efficient manner, the Investigator should record data (including laboratory values, if applicable) in the eCRF within 5 days after the subject visit.

The Investigator is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

When laboratory tests are performed at a central laboratory, data will be transferred electronically to the Sponsor or designee at predefined intervals during the study. The laboratory will provide the Sponsor or designee with a complete and clean copy of the data.

ECGs are to be performed locally. A 12-lead ECG will be performed as part of screening, day 90/month 3 and month 12/EOS visits. The results (normal, abnormal not clinically significant, abnormal clinically significant) will be recorded in the eCRF. Subjects who have a clinically significant abnormal ECG during Screening will not be eligible for the study.

Chest x-rays are to be performed locally. An x-ray will be performed as part of screening, day 90/month 3 and month 12/EOS visits. The results (normal, abnormal not clinically significant, abnormal clinically significant) will be recorded in the eCRF

For screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and AEs will be collected in the eCRF.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated ICFs
- Visit dates
- Medical history and physical examination details including the pathology report to confirm the subject's pFSGS
- Key efficacy and safety data, if applicable (as specified in the protocol)
- AEs and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts (if applicable)
- Dispensing and return of study drug details
- Reason for premature discontinuation (if applicable)
- Randomization number (if applicable)

All patient-reported outcome measures will be completed by the subject via computerized administration on a sponsor-sourced, vendor-provided device. The SF-36, EQ-5D-5L and the KTQ surveys will be completed directly on a device and may then be considered as source.

Electronic case report form (eCRF) data of biopsy image(s) and slide assessment(s) via EM and LM, respectively, for the rFSGS will be directly entered by the blinded, central reader.

8.1.3 Clinical Study Monitoring

The Sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents

(Section 8.1.2, Specification of Source Documents) when they are requested by the Sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by the Data Science department of the Sponsor in accordance with the SOPs for data management. All study specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and WHO Drug Dictionary respectively.

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The Investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an Investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria
- Developed withdrawal criteria during the study and not withdrawn
- Received wrong treatment or incorrect dose
- Received excluded concomitant treatment

When a deviation from the protocol is identified for an individual subject, the Investigator or designee must ensure the Sponsor is notified. The Sponsor will follow-up with the Investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the Investigator must contact the Sponsor immediately.

The Investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File (TMF).

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

8.1.7 End of Trial in All Participating Countries

The end of trial in all participating countries is defined as the last subject's last visit.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to Sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding one year. The investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit for APGD-sponsored studies, or for APEB/APEL-sponsored studies within one year after last subject out (LSO) or termination of the study.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the ICF and any other signatories according to local requirements. A copy of the signed ICF will be given to the subject and the original

will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

The Investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.

The Investigator must update their ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The Investigator or his/her designee must re-consent subjects with the updated ICF even if relevant information was provided orally. The Investigator or his/her representative who obtained the written informed consent and the subject should sign and date the informed consent form. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The Sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

The Sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the Sponsor. However, the Sponsor requires the Investigator to permit the Sponsor, Sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The Sponsor will ensure that the use and disclosure of protected health information obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., HIPAA).

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The Investigator may use this information for the purpose of the study only. It is understood by the Investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical Investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study.

Publication of the study results is discussed in the Clinical Study Agreement.

8.3.2 Documents and Records Related to the Clinical Study

The Investigator will archive all study data (e.g., Subject Identification Code List, source data, eCRFs, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, two years after approval of the NDA or discontinuation of the IND). The Investigator agrees to obtain the Sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The Sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered on the eCRFs supplied for each subject.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or non-substantial amendments. Amendments to this protocol must be signed by the Sponsor and the Investigator. Depending on the nature of the amendment, either IRB/IEC, Competent Authority approval or notification may be required. The changes will become effective only after the approval of the Sponsor, the Investigator, the regulatory authority and the IRB/IEC (if applicable).

Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the Informed Consent, written verification of IRB/IEC approval must be forwarded to the Sponsor. An approved copy of the new Informed Consent must also be forwarded to the Sponsor.

8.3.4 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator (s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

The Sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be organized to assess the progress of the study, the safety data and the critical efficacy endpoints, and to recommend to the Sponsor whether to continue, modify or stop the study. A separate DMC Charter will be maintained detailing the complete roles and responsibilities of the DMC and will be provided to sites upon request. Stopping rules for safety events will be described in the DMC Charter.

10.2 Other Study Organization

Not applicable.

11 REFERENCES

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Company Reports:

Bleselumab (ASKP1240) Investigator Brochure

12 APPENDICES

12.1 List of Excluded Concomitant Medications

The following medications are prohibited:

- Another investigational drug intervention treatment up to 30 days or 5 half-lives (depending on medication) prior to transplant and throughout participation in the study.
- Prior treatment with bleselumab (ASKP1240).
- Currently receiving or have received up to 8 weeks prior to transplant any immunologic biologic compound.
- Induction agent other than study-assigned basiliximab (Simulect®).

Subjects who require plasmapheresis for any reason post-initial bleselumab dosing cannot continue receiving bleselumab.

If bleselumab is discontinued subjects in Arm 2 can continue to receive study-supplied Prograf through 12 months post-transplant as previously assigned.

12.1.1 List of known Drug-Induced Hepatotoxicity

Causality assessment of suspected drug-induced liver injury (DILI) related to antibiotics can be difficult, particularly because some cases occur long after the drug has been stopped. Antibiotic-induced DILI appears, in most instances, to be idiosyncratic. Genetic-association studies have recently identified genotypes (flucloxacillin, amoxicillin-clavulanate)

- *Antibiotics*: Penicillins, amoxicillin-clavulanate Amoxicillin, oxacillin, (di-) cloxacillin, flucloxacillin. Cephalosporins, ceftriaxone Ciprofloxacin, Sulfamethoxazole/trimethoprim,nitrofurantoin. Macrolides, Erythromycin, telithromycin.Tetracyclines, Minocycline and Quinolones (rare)
- *Antifungals*: Fluconazole and itraconazole
- *Anti-Hyperlipidemic Drugs*: Lovastatin, Simvastatin, Atorvastatin, Pravastatin, Niacin, Ezetimibe, Clofibrate and Gemfibrozil
- *TNF inhibitors:* adalimumab, etanercept and infliximab
- *Anti-Hypertensive Drugs*: Methyl dopa
- *Anti-Retroviral Drugs:* Protease inhibitors: Ritonavir, Indinavir, Saquinavir, Nelfinavir.
- *Nucleoside analogues reverse transcriptase inhibitors (NRTI):* Lamivudine, Tenofovir, Zidovudine, Didanosine, Stavudine, Abacavir and Tenofovir
- *Non-nucleoside analogues reverse transcriptase inhibitors (NNRTI):* Nevirapine, Emtricitabine and Efavirenz
- *Oral contraceptives*
- *Anti-Rheumatic Drugs:* Sulfasalazine, Gold-salt-induced cholestasis, Azathioprine and Methotrexate
- *Anti-TB:* Rifampicin, Isoniazid and Pyrazinamide
- *Non-Steroidal Anti-Inflammatory Drugs:* Acetaminophen, Nimesulide, Diclofenac, Ibuprofen and Sulindac

- *Selective COX-2 inhibitors*: celecoxib, rofecoxib, nimesulide
- *Anthranilic acid derivatives:* Cinchophen and Glafanine
- *Acetic acid derivatives:* Amphenac, Fenclozic acid, Isoxepac and Bromofenac
- *Propionic acid derivatives:* Benoxaprofen, Ibufenac, Pirprofenac, Suprofenac and Fenbufen
- *Pyrazolone derivatives:* Phenylbutazone and Oxyphenbutazone
- *Oxicams:* Isoxicam and Sudoxicam
- *Quinazonlone derivatives:* Fluproquazone
- *Anaesthetic Agents:* Halothane, Chloroform, Isoflurane, Enflurane, Desflurane and Nitrous oxide
- *Anti-Epileptic Drugs (AED):* Carbamazepine (CBZ), Chlorpromazine (CPZ), Haloperidol,(rare), Risperidone and Quetiapine (cholestasis), Olanzapine and Clozapine (neuroleptic)
- *Anti-Depressants*: Most tricyclic antidepressants(less extent amitriptyline, desipramine), Amineptine and Amineptine
- *MAO inhibitors*: Hydrazines and phenelzine
- *Acetylcholinesterase Inhibitors:* Tacrine
- *Drugs of Abuse:* Cocaine

12.2 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases to > 3 × ULN, or bilirubin > 2 × ULN, should undergo detailed testing for liver function analyses (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 48 - 72 hours of notification of the test results.

Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Complete physical examination searching for sign or symptoms of hepatitis such as:

- fever, scleral icterus (Jaundice), darkening of the urine, pale or clay-colored stools
- fainting, weakness, fatigue
- altered mental status
- hepatomegaly

Definition of Liver Abnormalities

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

	ALT or AST		**Total Bilirubin**
Moderate	> 3 × ULN	Or	> 2 × ULN
Severe*	> 3 × ULN	and	> 2 × ULN

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

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT or AST > 3 x ULN and (TBL > 2 x ULN or INR > 1.5 x ULN)
- ALT or AST > 3 x 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 severe abnormalities and require additional monitoring and follow-up.

*Hy's Law or rule is based on the combined evidence of hepatic injury, decreased hepatic function and the absence of disease related damage.

Subjects with all 4 of the below criteria are considered Hy's Law cases:

1. Increased rate (compared to control) of aminotransferase elevation to ≥ 3 x ULN indicating hepatocellular injury, greater elevation cause greater concern, but alone do not predict severe toxicity
2. Total BIL > 2 x ULN (or INR > 1.5 × ULN), if the change is clinically significant in the absence of obstruction
3. Alkaline phosphatase (ALP) close to normal
4. No other good explanation for the liver injury (viral excluded, alcohol ingestion, congestive heart failure)

Exclusion of alcoholic hepatitis:

Heavy alcohol use is a prerequisite for the development of alcoholic hepatitis. The history is usually apparent; however, in some subjects, alcohol use may be covert.

Follow-up Procedures

Confirmed moderate and severe 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.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The Sponsor should be contacted immediately and informed of all Investigators and subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

In order to distinguish if bleselumab is likely to cause DILI or have a low potential for causing severe liver injury, subjects will be evaluated and closely monitored.

For further detection, assessment, mitigation and reporting of 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 the eCRF. 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 hyper-lipoproteinemic, and/or diabetic subjects and may be associated with fluctuating aminotransferase levels. Gilbert’s syndrome which characterized by fluctuating elevation of serum bilirubin. 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, specific toxic insults such as *Amanita sp.* (mushroom), and special diets. Medications should be entered on the concomitant medication page of the eCRF. 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, total and 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

Subjects must discontinue bleselumab per below, but are allowed to continue on the protocol-defined visit schedule for the collection of safety and clinical assessment information:

- Subjects whose liver function tests meet one of the following criteria, verified by two (2) consecutive measurements, and in the absence of other etiologies (e.g., biliary stenosis or obstruction, viral hepatitis other than CMV, etc.):
  - ALT or AST > 8 x upper limit of normal (ULN)
  - ALT or AST > 5 x ULN for more than 2 weeks
  - ALT or AST > 3 x ULN and (total bilirubin [TBL] > 2 x ULN or international normalized ratio [INR] > 1.5 x ULN)
  - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- BK nephropathy confirmed by renal biopsy (Section 5.5.1.1.5)
- CMV End Organ Disease (Appendix 12.6)
- Subjects who develop severe bone marrow suppression as defined by the following in the absence of other etiologies (e.g., bleeding, other established causes of neutropenia) and have been verified by two (2) consecutive results within 14 days of the first detection that occur after Day 28 post-transplant:
  - Anemia: Hemoglobin < 6.5 g/dL graded National Cancer Institute Common Terminology Criteria for Adverse Events criteria (NCI-CTCAE) Grade 4 and/or
  - Agranulocytosis: Absolute Neutrophil Count (ANC) < 100 cells/mm^3 graded NCI-CTCAE Grade 4
- Subjects who require plasmapheresis for any reason post-initial bleselumab treatment
- In the subjects' best interest per Investigator discretion

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

Reference

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

12.3 Common Serious Adverse Events

The following is a list of SAEs that the Sponsor considers to be associated with the disease state being studied. **The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed in Section 5.4.2, Definition of Serious Adverse Event (SAE)**. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs". You are required to follow the requirements detailed in Section 5.5.5, Reporting of Serious Adverse Events (SAE).

For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting to the FDA. If aggregate analysis of these events indicates they occur more frequently with study drug, an expedited IND safety report may be submitted to the FDA.

1. Kidney Transplant Rejection
2. Kidney allograft loss
3. Blood creatinine increased
4. Diabetes mellitus
5. Hyperglycemia
6. Increase blood glucose

12.4 Retrospective Pharmacogenetic Sub-Study

INTRODUCTION

Pharmacogenetic research aims to provide information regarding how naturally occurring changes in a subject's gene and/or expression based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of pharmacogenetic by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies (GWAS), the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by one or more genetic variations, pharmacogenetic research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

OBJECTIVES

The pharmacogenetic research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics, and toxicity/safety issues.

By analyzing genetic variations, it may be possible to predict an individual subject's response to treatment in terms of efficacy and/or toxicity.

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study may participate in this pharmacogenetic sub-study. As part of this sub-study, subjects must provide separate written consent prior to providing any blood samples that may be used at a later time for genetic analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this sub-study will provide one 4 mL tube of whole blood per Astellas' instructions. Each sample will be identified by the unique subject number (first code). Samples will be shipped frozen to a designated banking CRO either directly from site or via a central laboratory as directed by Astellas.

PHARMACOGENETIC ANALYSIS

Details on the potential pharmacogenetic analysis cannot be established yet. Astellas may initiate the pharmacogenetic analysis in case evidence suggests that genetic variants may be influencing the drug's kinetics, efficacy and/or safety.

DISPOSAL OF PHARMACOGENETIC SAMPLES/DATA

All pharmacogenetic samples collected will be stored for a period of up to 15 years following study database hard lock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the pharmacogenetic sample

will be destroyed. The results of any pharmacogenetic analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely.

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory pharmacogenetic analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the genetic analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the pharmacogenetic analysis will be the property of Astellas.

12.5 List of Secondary Causes of Focal Segmental Glomerulosclerosis

1. **Familial**
   a. Mutations in a-actinin 4
   b. Mutations in NPHS1 (nephrin)
   c. Mutations in NPHS2 (podocin)
   d. Mutations in WT-1
   e. Mutations in TRPC6
   f. Mutations in SCARB2 (LIMP2)
   g. Mutations in INF2 (formin)
   h. Mutations in CD2-associated protein
   i. Mitochondrial cytopathies
2. **Virus associated**
   a. HIV-associated nephropathy
   b. Parvovirus B19
3. **Medication**
   a. Heroin-nephropathy
   b. Interferon-a
   c. Lithium
   d. Pamidronate/alendronate
   e. Anabolic steroids
4. **Adaptive structural-functional responses likely mediated by glomerular hypertrophy or hyperfiltration**

4.1 Reduced kidney mass
   a. Oligomeganephronia
   b. Unilateral kidney agenesis
   c. Kidney dysplasia
   d. Cortical necrosis
   e. Reflux nephropathy
   f. Surgical kidney ablation
   g. Chronic allograft nephropathy
   h. Any advanced kidney disease with reduction in functioning nephrons

4.2 Initially normal kidney mass
   a. Diabetes mellitus
   b. Hypertension
   c. Obesity
   d. Cyanotic congenital heart disease
   e. Sickle cell anemia

5. **Malignancy (lymphoma)**
6. **Nonspecific pattern of FSGS caused by kidney scarring in glomerular disease**
   a. Focal proliferative glomerulonephritis (IgAN, LN, pauci-immune focal necrotizing and crescentic GN)
   b. Hereditary nephritis (Alport syndrome)
   c. Membranous glomerulopathy
   d. Thrombotic microangiopathy

Reference

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. Kidney Int Suppl. 2012;2:182.

12.6 Definition of Cytomegalovirus Disease in Solid Organ Transplant Recipients

Disease type	Probable	Definite
CMV syndrome	One or more of the following: 1. Fever > 38°C for at least 2 days 2. New or increased malaise 3. Leukopenia 4. ≥ 5% atypical lymphocytes 5. Thrombocytopenia 6. Elevation of hepatic transaminases (ALT or AST) to 2 × upper limit of normal (applicable to nonliver transplant recipients) plus evidence of CMV in blood by viral culture, antigenemia or a DNA/RNA-based assay	Clinical and laboratory findings as in 'probable' case and no other cause of symptoms/signs identified
Pneumonia[1]	Signs and/or symptoms of pulmonary disease in the absence of other documented cause plus evidence of CMV in blood and/or[3] bronchoalveolar lavage (BAL) fluid by viral culture, antigenemia or a DNA/RNA-based assay	Signs and/or symptoms of pulmonary disease plus detection of CMV in lung tissue by culture, immunohistochemical analysis or *in situ* hybridization[4] with or without evidence of CMV in blood or BAL fluid by viral culture, antigenemia (BAL) or a DNA/RNA-based assay
Gastrointestinal disease	Symptoms of upper or lower gastrointestinal disease plus macroscopic mucosal lesions on endoscopy plus evidence of CMV in blood or biopsy tissue by viral culture, antigenemia or an RNA/DNA-based assay	Symptoms or signs of upper or lower gastrointestinal disease plus detection of CMV in gastrointestinal tissue by culture, immunohistochemical analysis or *in situ* hybridization[4]
Hepatitis	Elevation of bilirubin and/or hepatic enzymes in the absence of other documented cause of hepatitis[2] plus evidence of CMV in blood by anti-genemia or a DNR/RNA-based assay	Elevation of bilirubin and/or hepatic enzymes plus detection of CMV in liver tissue by culture, immunohistochemical analysis or *in situ* hybridization[4]
CNS disease	CNS symptoms in the absence of other documented cause plus evidence for CMV in CSF samples by viral culture or DNA-based assay	CNS symptoms plus detection of CMV in CNS tissue by culture, immuno-histochemical analysis or *in situ* hybridization[4]
Retinitis	Not applicable	Lesions typical of CMV retinitis must be confirmed by an ophthalmologist
Other tissue invasive disease (nephritis, cystitis, myocarditis, pancreatitis, etc.)	Evidence of organ dysfunction in the absence of other documented cause[2] plus evidence of CMV in blood by viral culture, antigenemia or DNA/RNA-based assay	Symptoms/signs of organ dysfunction plus detection of CMV in affected tissue by culture, immunohistochemical analysis or *in situ* hybridization[4]

BAL= bronchoalveolar lavage; CMV=cytomegalovirus ; CNS=central nervous system; DNA=deoxyribonucleic acid ; RNA=ribonucleic acid

Table footnotes appear on next page

[1] Superinfection or coinfection with other pathogens may occur and should be noted when present.

[2] If affected organ is the allograft; acute rejection must be excluded as a cause for the clinical symptoms.

[3] The detection of CMV in both BAL and peripheral blood strengthens the evidence for probable CMV pneumonitis.

[4] Although, immunohistochemistry and *in situ* hybridization techniques are more sensitive for the detection of CMV-infected cells than morphologic examination, the presence of typical cytomegalovirus inclusions should be considered evidence of definite disease.

Reference:

Humar A. American society of Transplantation Recommendations for Screening, Monitoring and Reporting of Infectious Complications in Immunosuppression Trials in Recipients of Organ Transplantation. Am J Transplantation. 2006;6:262-74.

12.7 Categories of Post-transplant Lymphoproliferative Disorders

Categories of Post-transplant Lymphoproliferative Disorders (PTLD) are the following:

- Early Lesions
  - Reactive plasmacytic hyperplasia
  - Infectious mononucleosis-like
- Polymorphic PTLD
- Monomorphic PTLD (classify according to lymphoma classifications)
  - B-cell neoplasms
    - Diffuse large B cell lymphoma (immunoblastic, centroblastic, anaplastic)
    - Burkitt/Burkitt-like lymphoma
    - Plasma cell myeloma
    - Plasmacytoma-like lesions
    - Maltoma
  - T-cell neoplasm
    - Peripheral T cell lymphoma, unspecified type
    - Anaplastic large cell lymphoma (T or null cell)
    - Hepatosplenic gamma-delta T cell lymphoma
    - Other (i.e., T-NK type)
- Hodgkin lymphoma and Hodgkin lymphoma-like PTLD

Reference:

AST Infectious Disease Community. Epstein-Barr virus and lymphoproliferative disorders after transplantation. Am J Transplantation. 2004;4(Suppl 10):59-65.

12.8 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 antidonor antibody, and C4d or allograft pathology C4d depletion without morphologic evidence of active rejection Cd4+, presence of circulating antidonor 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 antidonor 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 antidonor antibodies, morphologic evidence of chronic tissue injury, such as glomerular double contours and/or peritubular capillary basement membrane multilayering 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) tubulitus
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)
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)

12.9 Short-Form 36 Item Health Survey Score Version 2.0

Refer to your Study Binder for copies of the ePRO device subject-facing screenshots.

12.10 European Quality of Life 5 Dimensions - 5 Levels Questionnaire

Refer to your Study Binder for copies of the ePRO device subject-facing screenshots.

12.11 Kidney Transplant Questionnaire

Refer to your Study Binder for copies of the ePRO device subject-facing screenshots.

13 ATTACHMENT 1: NONSUBSTANTIAL AMENDMENT 2

I. The purpose of this amendment is:

Nonsubstantial Changes
1. Inclusion/Exclusion Criteria clarification
DESCRIPTION OF CHANGE:
The revised language is to clarify the enrollment of subjects who have had a previous kidney transplant and indicate that the current graft failure must be due to the rFSGS.
RATIONALE:
A subject's current graft failure must be due to rFSGS. This was incorrectly documented in substantial amendment 2.

II. Amendment Summary of Changes:

IV. Synopsis, Section 3.2 Inclusion Criteria and 3.3 Exclusion Criteria
WAS:
Inclusion: 3. Subject is a recipient of a de novo kidney from a living or deceased donor and has biopsy-proven, pFSGS as a cause of ESRD in their native kidneys (initial diagnosing biopsy report is required). A subject who has biopsy-proven pFSGS as a cause of ESRD, and their prior graft failure(s) is due to the recurrence of FSGS, is eligible. *Exclusion:* 3. Subject has previously received any organ transplant including a kidney and the prior graft failure(s) is not due to the recurrence of FSGS.
IS AMENDED TO:
Inclusion: 3. Subject is a recipient of a de novo kidney from a living or deceased donor and has biopsy-proven, pFSGS as a cause of ESRD in their native kidneys (initial diagnosing biopsy report is required). A subject who has biopsy-proven pFSGS as a cause of ESRD, and their ~~prior~~ **most current** graft failure(s) is due to the recurrence of FSGS, is eligible. *Exclusion:* 3. Subject has previously received any organ transplant including a kidney and the ~~prior~~ **most current** graft failure(s) is not due to the recurrence of FSGS

III. Nonsubstantial Amendment Rationale:

Rationale for Nonsubstantial Designation
All revisions made to the protocol are administrative in nature and do not impact the safety or scientific value of the clinical study.

14 SPONSOR'S SIGNATURES