CLINICAL STUDY PROTOCOL

A Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Pharmacokinetics and Efficacy of MAU868 for the Treatment of BK Viremia in Kidney Transplant Recipients

Investigational Product: MAU868
Protocol Number: MAU868-201

Sponsor:
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SIGNATURE PAGE

STUDY TITLE: A Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Pharmacokinetics and Efficacy of MAU868 for the Treatment of BK Viremia in Kidney Transplant Recipients

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature Date 16th April 2020

Michael R. Hodges, MD
Chief Medical Officer
Amplyx Pharmaceutical, Inc.

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Amplyx Pharmaceuticals, Inc. (Amplyx) to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Amplyx and that it may not be further disclosed to third parties. I understand that the study may be terminated, or enrollment suspended at any time by Amplyx, with or without cause.

I agree to conduct this study in full accordance with United States Food and Drug Administration (FDA) Regulations, Institutional Review Board/Ethic Committee Regulations and International Council for Harmonization Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A randomized, double-blind, placebo-controlled study to assess the safety, pharmacokinetics and efficacy of MAU868 for the treatment of BK viremia in kidney transplant recipients

PROTOCOL NUMBER: MAU868-201

INVESTIGATIONAL PRODUCT: MAU868

PHASE: 2

INDICATION: Treatment of BK viremia

OBJECTIVES:

The primary objective of this study is:

- To assess the safety and tolerability of MAU868

Secondary objectives of this study are:

- To assess the impact of MAU868 on BK virus related outcomes including viruria, viremia, BK virus nephropathy, graft function and rejection among renal transplant recipients with BK viremia
- To assess the pharmacokinetics of MAU868

BACKGROUND:

Infection with BK virus (BKV) is essentially ubiquitous, with estimates ranging between 80 and 90% of the population globally. Primary infection occurs in childhood (usually by 10 years of age) and is either a mild, non-specific, self-limited illness or asymptomatic. Persistent infection is established in the epithelial cells of the renal tubules, ureters, and bladder, and is effectively controlled, though never eliminated by the immune system. Compromised immune function can lead to uncontrolled viral replication and development of disease. The two best-characterized BKV-associated diseases are a nephropathy that affects kidney transplant recipients (i.e., a disease of the allograft) and hemorrhagic cystitis, with or without renal involvement, that affects hematopoietic stem cell transplant (HSCT) recipients. BKV nephropathy (BKVN) is a leading cause of premature allograft loss, second only to allograft rejection. Patients who develop BK viremia irrespective of whether biopsy confirms BKVN have been reported to have significantly lower allograft survival at 10 years (24.8% vs 85.6%, P <0.001; Moura et al 2017). BKV-associated hemorrhagic cystitis prolongs hospitalizations, often requires administration of blood products and urologic intervention, can involve the native kidneys and can lead to death in the most severe cases. BKV has four major genotypes, but genotype is not linked with the risk or severity of disease.

MAU868 is a human monoclonal antibody (IgG1) that binds the viral capsid protein, VP1, that is responsible for binding to the surface of host cells (i.e., the first step in the infection of new cells; Tsai and Qian 2010). MAU868 neutralizes all four BKV genotypes at sub-nanomolar

concentrations *in vitro*. It binds to an epitope on VP1 that is highly conserved. Resistance-associated BKV variants were not identified in two independent long-term *in vitro* selection studies, demonstrating that MAU868 has a high *in vitro* barrier-to-resistance. It is being developed for the treatment of clinically significant BKV infection in immunosuppressed populations, notably solid organ and hemopoietic stem cell transplant (HSCT) recipients.

The results of the non-clinical studies identify no specific risk for investigation of MAU868 in human subjects, as expected for a human monoclonal antibody that recognizes a foreign (i.e., non-human) antigen. No MAU868-related effects were observed in rats after once weekly dosing (5 doses total) of MAU868 up to 750 mg/kg IV and 150 mg/kg SC. In addition, MAU868 did not bind human tissues (42 normal tissues) or blood smears as assessed by immunohistochemistry.

To date, a total of 27 subjects (26 healthy volunteers and 1 subject with BKV nephropathy) have received MAU868. A first-in-human, randomized, blinded, placebo-controlled, single ascending dose study to assess the safety, tolerability and pharmacokinetics of MAU868 following IV or SC administration to healthy adult subjects was performed. Twenty-six subjects received doses of MAU868 up to 100 mg/kg IV or 3 mg/kg SC; all doses were safe and well tolerated. No deaths or SAEs were reported, and there were no AEs that led to the discontinuation of dosing or the study. After single doses, serum concentrations of MAU868 declined in a biphasic manner with a terminal half-life of 23 to 30 days. The estimated relative bioavailability of MAU868 following SC administration was 57.6%. Administration of MAU868 increased anti-BKV antibody titers and the neutralizing potency of the serum, while administration of placebo had no effect.

One adult female kidney transplant recipient was treated with MAU868 1350 mg IV for refractory BKV nephropathy (i.e., preceding persistent BK viremia for ~7 months with biopsy confirmation) as part of an individual patient managed access program requested and initiated by the treating physician. She received a total of 11 doses over 6 months, most of which were administered every two weeks. The treating physician elected to pre-treat the patient with steroids, antihistamines, and acetaminophen for each infusion. MAU868 was considered safe and well tolerated by the patient with no adverse events related to MAU868 or the infusion.

Further details of non-clinical and clinical studies conducted to date with MAU868 can be found in the Investigator's Brochure (IB).

To date, there are no effective antiviral therapies directed at BKV. MAU868 has the potential to be a safe and well-tolerated therapy that can eliminate a threat to the survival of the renal allograft and greatly simplify the post-transplantation care of kidney transplant recipients.

POPULATION:

Inclusion Criteria:

Subjects must meet all of the following criteria to be eligible for study entry:

1. Be a male or female 18 years of age or older.
2. Recipient of a kidney (or kidney-pancreas) transplant within the year prior to enrollment.
3. Documented BKV viremia based on local or central laboratory testing within 10 days prior to randomization of either
    a) $\geq 10^4$ copies/mL OR
    b) a detectable viral load in 2 consecutive plasma samples (collected between 1 and 3 weeks apart) where the most recent sample demonstrates a BK viral load of $\geq 10^3$ copies/mL. (Note: only the second, most recent sample must be collected within 10 days prior to randomization)
4. Have a functioning graft that is producing urine.
5. Females of childbearing potential (i.e., not postmenopausal or surgically sterilized) with male partners, and males with female partner(s) of childbearing potential, must agree to use two forms of highly effective contraception, 1 of which must be a barrier method, throughout the duration of the study and for 90 days following the last study drug administration. Acceptable barrier forms of contraception are condom and diaphragm. Acceptable non-barrier forms of contraception for this study are oral birth control pill, depot, patch, implants or injectable, abstinence, intrauterine device, and/or spermicide.
6. Females of childbearing potential must have a negative urine or serum pregnancy test result within 96 hours prior to Baseline (i.e., pre-dose on Study Day 1).
7. Be willing to participate in the study, to give written informed consent and to comply with the study restrictions.

Exclusion Criteria:

Subjects who meet any of the following criteria will not be eligible for study entry:

1. A BKV plasma viral load which has exceeded 10^3 copies/mL for >4 months.
2. A BKV plasma viral load of $\geq 10^7$ copies/mL.
3. Are receiving, at the time of informed consent, systemic mTOR inhibitors.
4. Kidney transplant recipients who are anticipated to require Intravenous Immune Globulin (IVIG) treatment during the study period or who have received IVIG in the previous 9 months.
5. Kidney transplant recipients who, in the opinion of the Investigator, are likely to require antibody-depletion. Antibody-depleting therapies include but are not necessarily limited to hemodialysis, plasmapheresis and immunoadsorption.
6. Treatment within the previous month with the following medications: cidofovir, leflunomide.

7. History of hypersensitivity or intolerance to intravenous or subcutaneous administration of biologic medications or to any of the excipients included in the formulation of MAU868.
8. Platelet count <50,000/mm^3 at the time of informed consent, as determined by local laboratory.
9. History of splenectomy or asplenia.
10. Are lactating and/or pregnant.
11. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or longer than 5 half-lives if required by local regulations.
12. Prior exposure to MAU868.
13. Any other condition or laboratory abnormality that, in the opinion of the Investigator or the Sponsor, would put the patient at unacceptable risk for participation in the study or would interfere with the assessments included in the study.

STUDY DESIGN AND DURATION:

This is a randomized, placebo-controlled, double-blinded, proof-of-concept study in kidney transplant recipients. Up to 36 subjects with BK viremia will participate in 1 of 3 sequential cohorts. Each cohort will randomize approximately 12 subjects (8 MAU868 and 4 placebo).

The study will consist of a screening period, a 12-week treatment period and a 24-week follow-up period.

Protocol-specific procedures should not be performed until the patient has consented to participation in the study. However, assessments and procedures performed as part of standard of care prior to informed consent, including determination of BK viral load in plasma may be used to qualify a patient for the study. Once qualifying BK viremia has been confirmed, subjects should be randomized as soon as possible and no more than 10 days after the sample documenting the viremia was collected.

During the treatment period, subjects will receive MAU868 or placebo approximately every 28 days (every 4 weeks) for 12 weeks (4 doses total). Urine and blood will be monitored for BKV DNA by PCR weekly for the first 6 weeks after initiation of treatment. For the remainder of the treatment period, urine and blood must be collected for BKV DNA by PCR at least every other week. However, the Investigator may also request testing more frequently (i.e., weekly) than mandated by the protocol after the first 6 weeks of treatment and when clinically indicated. During the study, BKV DNA by PCR will be tested at the central laboratory. Pharmacokinetics (PK), viral resistance, and anti-drug antibodies (ADA) will also be monitored. Subjects should continue study drug until the last scheduled dose, regardless of changes in plasma BK viral load, use of rescue therapy, and/or need for change in immunosuppressive regimen for any reason.

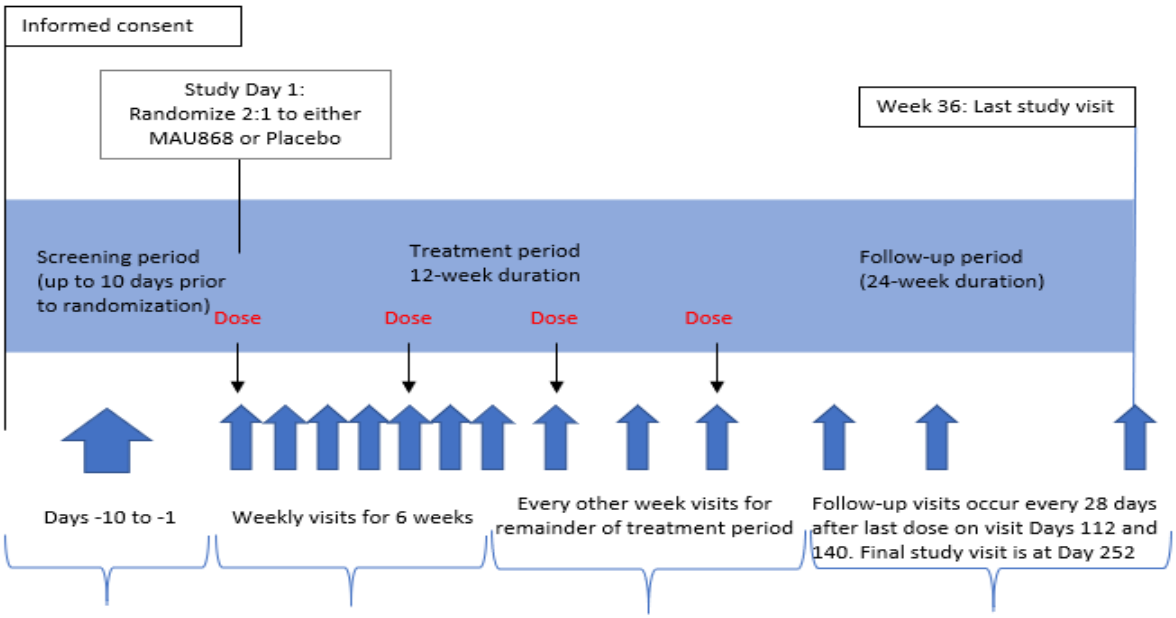
During the 24-week follow-up period, 3 follow-up visits will be scheduled. At each visit, urine and blood samples for BKV DNA and samples for PK will be collected. Investigators may collect samples for BKV DNA more often as clinically indicated. During the follow-up period, BKV DNA by PCR will be tested at the central laboratory.

Routine post-transplantation care is to be guided by the Investigator's discretion and site standard of care. This includes decisions to change the immunosuppressive regimen for a subject for any reason except for changes in immunosuppression in response to BK viremia. In order to treat BK viremia, prior to randomization, (i.e., prior to screening, during the screening period and at the Baseline Visit) Investigators are permitted to decrease or alter immunosuppressive therapy at their discretion and/or per standard of care at their site. However, in the first 4 weeks after randomization, Investigators should refrain from additional changes in immunosuppressive regimen in response to BKV unless the viral load has increased by ≥1 log and the Investigator determines that a change is in the best interest of the subject. Use of other antiviral agents including cidofovir and leflunomide as well as IVIG are not permitted during the first 4 weeks of therapy and are strongly discouraged thereafter.

Use of fluoroquinolones for reasons other than treatment of BKV is permitted.

Between screening and the last visit, subjects will attend a total of 14 planned visits. Unscheduled visits are permitted at the Investigator's discretion.

A schematic representing the study's design is included below:



Progression from Cohort 1 to Cohort 2

Approximately 12 weeks after the 9th subject in Cohort 1 has been randomized, blinded safety data will be reviewed by the Sponsor Study Review Committee (SSRC). Members of this committee will include a Sponsor medical representative, the Medical Monitor and the study's Principal Investigator. Cohort 2 will be opened for screening once the following criteria have been met:

1. All 12 subjects from Cohort 1 have been randomized,

2. No significant safety issues related to the administration of MAU868 have been identified by the SSRC based on the blinded safety review described above as well as an assessment of any new SAEs reported after the SSRC review and before randomization of the 12th subject in Cohort 1.
3. No significant safety issues related to the administration of MAU868 have been identified by the independent Data Safety Monitoring Board (DSMB) (see below).

   The Chair of the DSMB will be notified of the SSRC's decision to open Cohort 2.

   Accordingly, some subjects enrolled in Cohort 1 will continue participation in the study through the 24-week follow-up period while new subjects are screened and enrolled into Cohort 2.

Progression from Cohort 2 to Cohort 3

Cohort 3 will not be opened for screening and enrollment until an evaluation of unblinded safety, efficacy and pharmacokinetics findings from both Cohorts 1 and 2 through the 12-week treatment period has been completed by the SSRC.

DOSAGE FORMS AND DOSE REGIMEN:

The following treatment arms and dosing regimens are planned.

Treatment Arms:

- Cohort 1: MAU868 1350 mg IV approximately every 28 days for a total of 4 doses
- Cohort 2: MAU868 6750 mg IV on Study Day 1 and then 1350 mg IV approximately every 28 days for a total of 4 doses
- Cohort 3: MAU868 6750 mg IV approximately every 28 days for a total of 4 doses

Cohorts 1, 2, and 3 Placebo Arms:

- 5% dextrose in water [D5W] IV delivered every 28 days for a total of 4 doses

MAU868

MAU868 450 mg/3 mL (150 mg/mL) solution for infusion and injection is a slightly opalescent and colorless to slightly colored aqueous solution packaged in a 6 mL clear glass vial with a grey rubber stopper, which is sealed with an aluminum cap with plastic flip-off disk. The vial is overfilled by 10% (containing a total volume of 3.3 mL) to allow for the complete removal of the dose (450 mg).

MAU868 450 mg/3 mL solution for infusion and injection contains, in addition to MAU868 drug substance, L-histidine, L-histidine-hydrochloride monohydrate, sucrose and polysorbate 20. The excipients utilized are standard pharmacopeial grade excipients that are commonly used in antibody parenteral products. The formulation does not contain any preservative; it is to be used for single-dose administration only.

Placebo

Placebo solution D5W will be supplied by the clinical site.

RATIONALE FOR DOSE AND SCHEDULE SELECTION:

In Cohort 1, MAU868 will be administered as an IV infusion of 1350 mg in 250 mL D5W over a period of at least 60 minutes. In Cohort 2, MAU868 will be administered as an IV infusion of 6750 mg in 250 mL D5W over a period of at least 180 minutes on Study Day 1 and at 1350 mg in 250 mL D5W over a period of at least 60 minutes for subsequent doses. In Cohort 3, MAU868 will be administered as an IV infusion of 6750 mg in 250 mL D5W over a period of at least 180 minutes. All infusions will be followed by at least a 25 mL D5W flush to run at the same infusion rate as the dose of IP.

There are no rigorous clinical studies that identify target exposures required for BKV antiviral efficacy and no robust animal model of BKV infection or disease; therefore, the most robust estimate of the clinical dose considers the following parameters 1) MAU868 BKV neutralizing activity *in vitro,* 2) simulation of serum concentrations based on a model created from Phase 1 data in healthy volunteers, and 3) published literature on the extravascular distribution of immunoglobulin (renal 13.7%). For clinical efficacy, our therapeutic approach is to maintain the C_{trough} in target tissues ≥10-fold the 50% effective concentration (EC_{50}) of the least susceptible BKV genotype (genotype III). A review of the information is as follows:

A high-content imaging-based *in vitro* neutralization assay in RPTE cells was used to characterize the antiviral activity of MAU868 determined against representative isolates from the four major genotypes of BKV (genotypes I, II, III, and IV, respectively); genotypes I and IV account for approximately 95% of the global seroprevalence, while genotypes II and III account for the remaining 5% (Zheng et al 2007; Zhong et al 2009).

Table 1. MAU868 *In Vitro* Neutralization Activity

Genotype	EC_{50} (µg/mL)	EC_{90} (µg/mL)
BKV Genotype I	0.009 ± 0.010	0.102 ± 0.028
BKV Genotype II	0.040 ± 0.025	4.160 ± 6.076
BKV Genotype III	0.093 ± 0.057	2.662 ± 2.805
BKV Genotype IV	0.020 ± 0.020	0.465 ± 0.318

A first-in-human study explored single ascending doses of MAU868 (1, 3, 10, 30, and 100 mg/kg IV) and the serum concentration data was used to develop a PK model. The model was then used to estimate C_{trough} concentrations for a series of 3 treatment regimens. To have a treatment effect on BK viremia, MAU868 would need to curtail BKV replication in the target tissue (i.e., kidney). Based on an *in vivo* radiolabeled study in animals and physiologically based pharmacokinetic (PBPK) modeling estimates, the antibody biodistribution coefficient in kidney is 13.7% (Shah and Betts 2013). The estimated trough levels for each treatment arm were compared directly to *in vitro*-determined antiviral activity (EC_{50} and EC_{90}) for each BKV genotype and corrected for the assumed antibody distributions in kidney.

These data show that the planned dose regimens of MAU868 for each treatment arm provides high virus neutralizing tissue levels with kidney exposures at C_{trough} ≥10-fold the EC_{50} of the least susceptible BKV genotype (III). Specifically, kidney exposures at C_{trough} range from 253 to 2618-fold (Cohort 1), 365 to 3775-fold (Cohort 2), and 1264 to 13,061-fold (Cohort 3) above the EC_{50} at the end of treatment (12 weeks, range = least to most susceptible BKV genotype). Using EC_{90} determinations, kidney exposures at C_{trough} range from 6 to 231-fold (Cohort 1), 8 to 33-fold (Cohort 2), and 28 to 1152-fold (Cohort 3) above the EC_{90} at the end of treatment.

A 12-week treatment period was selected to ensure sustained levels of MAU868 to inhibit virus replication and promote virus clearance. The subsequent 24-week follow-up period will allow evaluation of the durability of effect and additional safety and PK observations.

From a safety perspective, the highest administered dose of MAU868 expected in this study (6750 mg = 100 mg/kg for a 67.5 kg patient) was also the highest administered dose (MAU868 100 mg/kg) investigated in the first-in-human study and below the no observed adverse effect level (NOAEL) exposure (750 mg/kg) in the 4-week repeat-dose toxicity study in rats. Specifically, human steady-state AUC exposure at the proposed dose of MAU868 1350 mg (20 mg/kg for a 67.5 kg patient) once monthly (206231 µg·hr/mL) provides safety margins of 6.9X and 5.0X, respectively, compared to the NOAEL (750 mg/kg; 1420000 µg·hr/mL) in the 4-week rat study and to the AUC at the highest human dose (100 mg/kg; 1031155 µg·hr/mL) tested to date. Likewise, human steady-state AUC exposure at the proposed dose of MAU868 6750 mg once monthly (1031155 µg·hr/mL) provides a safety margin of 1.4X compared to the NOAEL (750 mg/kg; 1420000 µg·hr/mL) in the 4-week rat study.

EFFICACY OBJECTIVES:

Efficacy objectives of this study are secondary and include:

- To assess the impact of MAU868 on BKV related outcomes including viremia, BKV nephropathy, graft function and rejection among renal transplant patients with BK viremia
- To assess the pharmacokinetics of MAU868

Exploratory:

- To investigate the potential immunogenicity of MAU868
- To investigate genotypic resistance
- To investigate viral kinetics

EFFICACY ENDPOINTS:

- Time (weeks) to decrease of BKV plasma viral load by 1 log
- Time (weeks) to first decrease of BKV plasma viral load to <lower limit of quantification
- Proportion of subjects with ≥1 log decrease of BKV plasma viral load by 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks, and 36 weeks
- Proportion of subjects with decrease of BKV plasma viral load to <lower limit of quantification by 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks, and 36 weeks

- Rate of decrease in BKV plasma viral load by 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks and 36 weeks
- Change in eGFR from baseline to week 12 and from Baseline to week 36
- Proportion of subjects with BKV nephropathy during the study
- Proportion of subjects with graft failure during the study
- Proportion of subjects with acute rejection during the study
- Mortality rate during the study

Exploratory:

- Proportion of subjects with presence of anti-drug antibodies (ADA) at any time during the study
- Presence of genotypic resistance
- Viral kinetics of BKV in plasma and urine

SAFETY ENDPOINTS:

- Physical examinations, vital signs, clinical safety laboratory parameters, 12-lead ECGs, and adverse events.

PHARMACOKINETIC ENDPOINTS:

- MAU868 serum concentrations

DISCONTINUATION OF STUDY DRUG OR STUDY PARTICIPATION:

Study drug for an individual subject must be discontinued for any of the following reasons:

- The subject withdraws consent or requests discontinuation for any reason.
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
- Any SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator or Sponsor that continued participation is not in the best interest of the subject. Specifically, study drug must be discontinued in subjects with development of a treatment-related SAE, a treatment-related AE Grade 3 or higher, or a clinically significant treatment-related laboratory abnormality Grade 3 or higher.
- Pregnancy during treatment period.
- Subject failure to comply with protocol requirements or study-related procedures.

- Subject experiences study drug related symptoms that the Investigator determines are consistent with any of the following:
    - Anaphylaxis or severe allergic reaction.
    - An infusion reaction determined to be Grade 3 or higher based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.
    - Cytokine release syndrome determined to be Grade 2 or higher based on CTCAE version 5.
    - Serum sickness determined to be Grade 2 or higher based on CTCAE version 5.

Changes in BKV plasma viral load, use of rescue therapy, and/or need for change in immunosuppressive regimen for any reason should not prompt early discontinuation of therapy.

If a subject is discontinued from study drug treatment administration the subject will still be encouraged to complete follow-up visits and assessments necessary for appropriate safety follow-up.

Study participation by an individual subject must be prematurely discontinued for any of the following reasons:

- The subject withdraws consent or requests discontinuation for any reason.
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
- Any SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator or Sponsor that continued participation is not in the best interest of the subject.
- Subject failure to comply with protocol requirements or study-related procedures.

If a subject withdraws prematurely from the study, study staff should make every effort to contact the Sponsor prior to discontinuation, if possible, and to complete the full panel of assessments scheduled for the Early Termination Visit. The reason for subject withdrawal must be documented in the electronic Case Report Form.

In the case of subjects lost to follow-up, attempts to contact the subject must be made and documented in the subject's medical records.

STUDY STOPPING RULES:

The study may be discontinued, or paused, for reasons that may include (but are not limited to): reasons of safety, lack of study drug availability, inability to enroll the study, or decision by a regulatory authority or the Sponsor (see Appendix D).

In the event that a dosing cohort shows efficacy and it is not anticipated that additional dosing would show added efficacy, the sponsor may choose to stop and not complete the study.

Further, in the instance of 2 or more treatment-related SAEs, 2 or more treatment related AEs Grade 3 or higher or 2 or more clinically significant treatment-related Grade 3 or higher laboratory abnormalities, the study will be paused pending an SSRC review of the safety events. The Sponsor will inform the applicable regulatory authority(ies) of any safety-related pause in the study.

In the case that the study is discontinued, the Sponsor will promptly inform the Investigators and applicable regulatory authority(ies) of the termination of the study and the reason(s) for the termination. The Investigators are responsible for promptly informing subjects that they must discontinue study drug. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will also be informed promptly and provided the reason(s) for the termination, as specified by the applicable regulatory requirement(s).

DATA SAFETY MONITORING BOARD:

An independent data safety monitoring board (DSMB) will review cumulative unblinded safety data as outlined in the DSMB charter.

STATISTICAL CONSIDERATIONS:

Analysis Populations**:**

The primary efficacy analysis will be performed in the modified ITT (MITT) analysis population. The MITT includes subjects who meet all of the following criteria:

- Received at least 1 dose of study drug
- Has at least 1 post-baseline plasma BK viral load result available

Additional analyses will be performed in the Intent-To-Treat (ITT) analysis population (all subjects randomized).

The safety population will include all subjects who received at least 1 dose of study drug.

The PK population will include all subjects with at least 1 post-baseline PK sample available.

Efficacy Analyses

In all efficacy analyses, the placebo subjects from the cohorts will be combined. Thus, the analysis models will include treatment group (four levels: placebo, low dose, medium dose, high dose) as a factor. Time-to-event endpoints will be analyzed using Cox proportional hazards regression models. Proportion endpoints will be analyzed using logistic regression models. Quantitative endpoints will be analyzed using one-way analysis of variance (ANOVA) models. In all analyses, pairwise contrasts comparing each of the three active groups to the combined placebo group will be tested. All efficacy and exploratory analyses will be conducted using two-sided tests at the alpha=0.05 level of significance, with no adjustment for multiplicity.

Additional efficacy analyses will be conducted using the data from each cohort. Quantitative endpoints will be analysed using the two-sample t test and proportion endpoints will be analysed using Fisher's exact test. Due to the small sample sizes, time-to-event variables will be summarized descriptively.

Safety Analyses

All safety analyses will be performed on data from the Safety Analysis Population. Adverse events (AEs), vital signs, ECGs and clinical laboratory evaluations will be summarized by appropriate descriptive statistics.

Pharmacokinetic Analysis

MAU868 levels in serum will be determined by a validated ELISA-based method. A detailed description of the method used will be included in the PK bioanalytical data report. The anticipated Lower Limit of Quantification (LLOQ) is 50.0 ng/mL. Concentrations will be expressed in mass per volume units (e.g., ng/mL). Missing values or those concentrations below the LLOQ will be labeled as such in the data listings and reported as "zero" in data presentations and calculations.

MAU868 serum concentration data will be listed by subject and visit/sampling time point. Descriptive summary statistics of trough levels will be provided by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics.

Summary statistics (e.g., mean, standard deviation) and individual subject listing of serum concentration measurements of MAU868 at the assigned time points will be provided as surrogates of systemic exposure.

Interim Analyses

Separate from the blinded safety review by the SSRC which will enable enrollment of subjects into Cohort 2, unblinded safety and tolerability data (adverse events, clinical laboratories, vitals/physical exams and ECGs), efficacy data (BK viral load in the plasma) and PK (MAU868 plasma levels) will be reviewed by the SSRC once all 12 subjects in Cohort 1 have completed the treatment period. The treatment assignment in Cohort 1 will be unblinded; however, these data will not include associated subject or site identifiers. The objectives of this interim analysis

are to evaluate whether four doses MAU868 1350 mg IV administered every 28 days for a total of 4 doses demonstrate:

- safety and tolerability signals compared to placebo
- a decrease in BK viral load in plasma compared to placebo
- predicted MAU868 plasma levels

The conclusions from this first analysis will be used by the Sponsor to evaluate the safety and efficacy of MAU868 early-on in this first-in-patient study. Unless a significant safety issue related to administration of MAU868 has been identified, the conclusions will have no impact on Cohort 2 or the study's design.

Following completion of the 12-week treatment periods for Cohorts 1 and 2, cumulative unblinded data from both cohorts will be reviewed for safety and tolerability (adverse events, clinical laboratories, vitals/physical exams and ECGs), efficacy (BK viral load in the plasma) and PK (MAU868 plasma levels). The treatment assignments will be unblinded; however, these data will not include associated subject or site identifiers. The objectives of this second interim analysis are to evaluate whether four doses MAU868 1350 mg IV administered every 28 days or MAU868 6750 mg IV administered as a first dose followed by 3 more doses of MAU868 1350 mg IV administered every 28 days demonstrate:

- safety and tolerability signals compared to placebo
- a decrease in BK viral load compared to placebo
- predicted MAU868 plasma levels

Based on the SSRC's safety, efficacy and PK conclusions for Cohorts 1 and 2, the dosing regimen for Cohort 3 may be *adjusted* in dosage and/or duration; however, the dosage and duration for Cohort 3 will not exceed the dose already specified in the protocol. Cohort 3 will not be opened for screening and enrollment until this evaluation has been completed.

Sample Size Determinations**:**

This study will randomize approximately 36 subjects (12 per cohort) to MAU868 and placebo in a 2:1 ratio (24 MAU868 and 12 placebo; 8 MAU868 and 4 placebo per cohort). This study is not powered to an efficacy endpoint. The number of subjects chosen will provide data useful in determining proof of concept.

SITES: Approximately 20 sites

SPONSOR:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
ADA	antidrug antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analyzed using one-way analysis of variance
AST	aspartate aminotransferase
BKV	BK virus
BUN	blood urea nitrogen
CFR	U.S. Code of Federal Regulation
CK	creatinine kinase
CO_2	carbon dioxide
CRF	case report/record form (paper or electronic)
CRO	contract research organization
CTA	clinical trial authorization
CTC	common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
D5W	5% dextrose in water
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EC_{50}	effective concentration
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
H2 Blocker	histamine receptor antagonist
HBsAg	hepatitis B surface antigen
HCT	hematopoietic cell transplant
Hr	Hour
IV	Intravenous

Abbreviation	Definition
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
I/E	Inclusion and Exclusion
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IVIG	intravenous immunoglobulin
IWRS	Interactive Web Response System
KDPI	Kidney Donor Profile Index
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
MedDRA	medical dictionary for regulatory activities
Mg	milligram(s)
mITT	modified intent-to-treat
mL	milliliter(s)
mTOR	mammalian target of rapamycin
NOAEL	No observed adverse effect level
PBPK	physiologically based pharmacokinetics
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	prothrombin time
RAV	resistance-associated variance
RBC	red blood cell(s)
SC	Subcutaneous
SAE	serious adverse event
SAP	statistical analysis plan
sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SSRC	Sponsor Study Review Committee

Abbreviation	Definition
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
ULN	upper limit of normal
ULQ	upper limit of quantification
VP	viral protein
WBC	white blood cell(s)
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 BKV Infection and Nephropathy

The human polyomavirus BK (BK virus or BKV) is a DNA virus that infects 80-90% of the world's population (Kean 2009; Boothpur and Brennan 2010; Egli et al 2009). It is generally acquired during childhood and, subsequently, establishes a lifelong infection in renal tubular and uroepithelial cells (Antonsson 2010). Although the primary and persistent infections are generally clinically silent, BKV reactivation may occur in the setting of organ transplantation when innate immune T cell immunity is compromised by immunosuppressive drugs (Ambalathingal 2017). In particular, recipients of kidney transplant may develop nephropathy and recipients of hematopoietic stem cell transplants may develop hemorrhagic cystitis.

BKV replication in immunosuppressed kidney transplant recipients follows a well-established clinical course from viruria (~35% of all kidney transplant recipients) to viremia (~11%) to nephropathy (3-5%; Sawinski and Goral 2015; Hirsch et al 2013; Dharnidharka et al 2011). The median onset of detectable viruria is 5 weeks post-transplantation (range 2 to 41 weeks), and the median onset of viremia is 10 weeks (range 5 to 51 weeks; Babel et al 2009). The median onset of BKV nephropathy is 42 weeks post-transplantation (range 7 to 113 weeks; Hirsch and Steiger 2003).

Patients who develop BK viremia irrespective of whether biopsy confirms BKV nephropathy have been reported to have significantly lower allograft survival at 10 years (24.8% vs 85.6%, P <0.001; Moura et al 2017). By contrast, patients without viruria do not develop viremia; likewise, patients without viremia do not develop nephropathy (Babel et al 2009).

The main risk factor for BKV replication and the development of disease is the level of immunosuppression, including the type of induction therapy used prior to transplantation. A number of other risk factors including recipient age, male sex, allograft rejection, degree of human leukocyte antigen mismatching, length of cold ischemia time, and recipient and donor BKV serostatus (e.g., donor positive-recipient negative) have also been implicated (Sawinski and Goral 2015). No single risk factor is reliably predictive.

Current treatment guidelines recommend reduction of immunosuppression to control the infection, typically when BK viremia is >10^4 copies/mL (KDIGO Clinical Practice Guideline 2009). Clearance of the viremia takes months and often requires multiple stepwise reductions in the immunosuppression. Subjects for whom immunosuppression is reduced have an increased risk of acute allograft rejection (Bohl and Brennan 2007; Sood et al 2012).

There are no specific or effective anti-BKV therapies. These data underscore the need for more effective means to control or prevent BKV reactivation. MAU868 has the potential to be a safe and well-tolerated therapy that can eliminate a threat to the survival of the renal allograft and greatly simplify the post-transplantation care of kidney transplant recipients.

1.2 MAU868

BKV encodes only seven proteins and lacks the traditional targets for antiviral drugs (e.g., protease, polymerase). The non-enveloped icosahedral virion of BKV is composed of three different viral proteins (VP1, VP2, VP3), but only VP1 (the major viral capsid protein) is exposed on the virion surface.

MAU868 is a human monoclonal antibody (IgG1) that binds the viral capsid protein, VP1, that is responsible for binding to the surface of host cells (i.e., the first step in the infection of new cells; Tsai and Qian 2010). MAU868 neutralizes all four BKV genotypes at sub-nanomolar concentrations *in vitro*. It recognizes a conformational epitope on VP1 that is highly conserved, resulting in a high barrier to resistance *in vitro*. It is being developed for the prevention of clinically significant BKV infection in immunosuppressed populations, notably solid organ and HCT recipients.

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the MAU868 Investigator's Brochure.

1.3 Non-clinical Data

The non-clinical evaluation of MAU868, a human monoclonal antibody recognizing a non-human antigen, was performed according to the ICH S6(R1) guidelines. Details regarding all non-clinical studies conducted to date with MAU868 are provided in the Investigator's Brochure.

No genotoxicity or reproductive toxicology studies were conducted because MAU868 1) is a fully human monoclonal IgG1 antibody comprising native non-modified amino acids, 2) does not contain any chemical linkers or chelators, 3) is highly specific for an epitope unique to human polyomaviruses BK and JC, and 4) there are no pharmacologically relevant animal models.

Because MAU868 is a protein comprised of native amino acids and because if its pharmacological mechanism of action it is considered to be non-genotoxic.

BKV VP1 is the major viral capsid protein and the only protein exposed on the virion surface. Binding of VP1 to ganglioside receptors on the host cell surface initiates internalization of the virus (Tsai and Qian 2010). Binding of MAU868 to VP1 blocks these interactions and prevents infection of new cells.

MAU868 has picomolar affinity for BKV VP1 and sub-nanomolar neutralization potency against all four BKV genotypes.

Table 2. MAU868 Binding Affinity and Neutralizing Activity

GENOTYPE	Kd (pM)	EC_{50} (nM)	EC_{50} (µg/mL)
Genotype I	5.8 ± 1.8	0.062 ± 0.068	0.009 ± 0.010
Genotype II	2.8 ± 0.6	0.278 ± 0.175	0.040 ± 0.025
Genotype III	8.4 ± 3.7	0.645 ± 0.397	0.093 ± 0.057
Genotype IV	4.1 ± 1.3	0.143 ± 0.135	0.021 ± 0.020

MAU868 binds to a conformation-dependent epitope on VP1. The key contact residues (Y169, R170, and K172), all located within the VP1 EF loop, are 100% conserved among reference isolates and 156 (genotype I) and 66 (genotype IV) GenBank sequences analyzed. Mutations at these locations confer either a loss of viral fitness (i.e., inability to replicate) or no change in susceptibility to MAU868.

Resistance selection experiments in renal proximal tubule epithelial cells infected with BKV genotype I and genotype IV, which comprise 95% of global seroprevalence, failed to generate virus with genotypic resistance to MAU868 after six serial passages (>84 days in cell culture). Mutant BK viruses harboring a series of VP1 polymorphisms at other locations in VP1 that were identified through analyses of available sequences in GenBank also confer no reduced susceptibility to MAU868 *in vitro*. The available non-clinical data demonstrate a high barrier to the development of resistance to MAU868 *in vitro*.

Repeated dose-toxicity studies were conducted in rats. Once weekly IV or SC administration for 4-weeks (5 doses total) of MAU868 up to 750 mg/kg IV and 150 mg/kg SC to rats was well tolerated. The NOAEL for IV administration was 750 mg/kg/week; the NOAEL for SC administration was 150 mg/kg/week.

1.4 Clinical Data

To date, a total of 27 subjects (26 healthy volunteers and 1 subject with BKV nephropathy) have received MAU868.

A first-in-human, randomized, blinded, placebo-controlled, single ascending dose study to assess the safety, tolerability and pharmacokinetics of MAU868 following IV or SC administration to healthy adult subjects was performed. A total of 33 subjects participated in the study; 26 subjects received MAU868 and 7 received placebo. MAU868 doses of 1, 3, 10, 30 and 100 mg/kg (4 subjects received each dose) were administered IV as 1-hr infusions. Six subjects received MAU868 3 mg/kg as a bolus SC injection. Administration of study drug was followed by assessments for safety, pharmacokinetics, and testing for anti-drug antibodies up to 105 days post-dose. Ex vivo assessments of neutralizing serostatus were also performed prior to and 28 days after administration of MAU868 or placebo. No deaths or SAEs were reported, and there were no AEs that led to the discontinuation of the infusion or the study.

One adult female kidney transplant recipient was treated with MAU868 1350 mg IV for refractory BKV nephropathy (i.e., preceding persistent BK viremia for ~6 months with biopsy confirmation) as part of an individual patient managed access program requested and initiated by the treating physician. She received a total of 11 doses over 7 months, most of which were administered every two weeks. The treating physician elected to pretreat the patient with steroids, antihistamines, and acetaminophen for each infusion. MAU868 was safe and well tolerated by the patient with no adverse events considered related to MAU868 or the infusion.

1.4.1 Human Safety and Tolerability Data

Single doses up to 100 mg/kg MAU868 were safe and well tolerated. Eleven (11) of 26 subjects exposed to MAU868 (42%) and one of seven subjects exposed to placebo (14%) reported adverse events. Events occurring in more than one subject included nasal congestion (3), oropharyngeal pain (3), and injection site hemorrhage (2) - all in subjects who received MAU868.

1.4.2 Human Pharmacokinetic Data

The time course of exposure to MAU868 following IV administration was consistent with that of a typical monoclonal IgG1 and therefore dose-proportional and predictable. The observed C28d ("trough") concentrations of MAU868 (mean ± SD) were 4.9 ± 1.4, 19.4 ± 5.0, 59.9 ± 11.0, 171.3 ± 12.7 and 509.8 ± 145.9 ug/mL following administration of 1, 3, 10, 30 and 100 mg/kg doses, respectively. Consistent with predictions of population PK, these observed systemic exposures on Day 28 for all doses of MAU868 were 50- to 5000-fold higher than the highest EC50 of 0.093 ug/mL *in vitro* (versus BKV).

1.4.3 Human Pharmacodynamic Data

Administration of MAU868 increased the BKV neutralizing potency of the serum from participating subjects in a manner that was proportional to the dose. No increase was observed for the subjects who received placebo.

1.5 Study Rationale

The purpose of this study is to determine whether MAU868 warrants further clinical development for the treatment of renal allograft threatening BKV infection in kidney transplant recipients.

1.6 Rationale for Dose and Schedule Selection

In Cohort 1, MAU868 will be administered as an IV infusion of 1350 mg in 250 mL D5W over a period at least 60 minutes. In Cohort 2, MAU868 will be administered as an IV infusion of 6750 mg in 250 D5W over a period of at least 180 minutes on Study Day 1 and at 1350 mg in 250 mL D5W over a period of at least 60 minutes for subsequent doses. In Cohort 3, MAU868 will be administered as an IV infusion of 6750 mg in 250 mL D5W over a period of at least 180 minutes.

There are no rigorous clinical studies that identify target exposures required for BKV antiviral efficacy and no robust animal model of BKV infection or disease; therefore, the most robust estimate of the clinical dose considers the following parameters 1) MAU868 BKV neutralizing activity *in vitro,* 2) simulation of serum concentrations based on a model created from Phase 1 data in healthy volunteers, and 3) published literature on the extravascular distribution of immunoglobulin (renal 13.7%). For clinical efficacy, our therapeutic approach is to maintain the C_{trough} in target tissues ≥10-fold the EC_{50} of the least susceptible BKV genotype (genotype III). A review of the information is as follows:

A high-content imaging-based *in vitro* neutralization assay in RPTE cells was used to characterize the antiviral activity of MAU868 was determined against representative isolates from the four major genotypes of BKV (genotypes I, II, III, and IV, respectively); genotypes I and IV account for approximately 95% of the global seroprevalence, while genotypes II and III account for the remaining 5% (Zheng et al 2007; Zhong et al 2009).

Table 3. MAU868 *In Vitro* Neutralization Activity

Genotype	EC_{50} (µg/mL)	EC_{90} (µg/mL)
BKV Genotype I	0.009 ± 0.010	0.102 ± 0.028
BKV Genotype II	0.040 ± 0.025	4.160 ± 6.076
BKV Genotype III	0.093 ± 0.057	2.662 ± 2.805
BKV Genotype IV	0.020 ± 0.020	0.465 ± 0.318

A first-in-human study explored single ascending doses of MAU868 (1, 3, 10, 30, and 100 mg/kg IV) and the serum concentration data was used to develop a PK model. The model was then used to estimate C_{trough} concentrations for a series of 3 treatment regimens. To have a treatment effect on BK viremia, MAU868 would need to curtail BKV replication in the target tissue (i.e., kidney). Based on an *in vivo* radiolabeled study in animals and PBPK modeling estimates, the antibody biodistribution coefficient in kidney is 13.7% (Shah and Betts 2013). The estimated trough levels for each treatment arm were compared directly to *in vitro*-determined antiviral activity (EC_{50} and EC_{90}) for each BKV genotype and corrected for the assumed antibody distributions in kidney.

These data show that the planned dose regimens of MAU868 for each treatment arm provides high virus neutralizing tissue levels with kidney exposures at C_{trough} ≥10-fold the EC_{50} of the least susceptible BKV genotype (genotype III). Specifically, kidney exposures at C_{trough} range from 253 to 2618-fold (Cohort 1), 365 to 3775-fold (Cohort 2), and 1264 to 13,061-fold (Cohort 3) above the EC_{50} at the end of treatment (12 weeks, range = least to most susceptible BKV genotype). Using EC_{90} determinations, kidney exposures at C_{trough} range from 6 to 231-fold (Cohort 1), 8 to 333-fold (Cohort 2), and 28 to 1152-fold (Cohort 3) above the EC_{90} at the end of treatment.

A 12-week treatment period was selected to ensure sustained levels of MAU868 to inhibit virus replication and promote virus clearance. The subsequent 24-week follow-up period will allow evaluation of the durability of effect and additional safety and PK observations.

From a safety perspective, the highest administered dose of MAU868 expected in this study (6750 mg = 100 mg/kg for a 67.5 kg patient) was also the highest administered dose (MAU868 100 mg/kg) investigated in the first-in-human study and below the no observed adverse effect level (NOAEL) exposure (750 mg/kg) in the 4-week repeat-dose toxicity study in rats. Specifically, human steady-state AUC exposure at the proposed dose of MAU868 1350 mg (20 mg/kg for a 67.5 kg patient) once monthly (206231 µg·hr/mL) provides safety margins of 6.9X and 5.0X, respectively, compared to the NOAEL (750 mg/kg; 1420000 µg·hr/mL) in the 4-week rat study and to the AUC at the highest human dose (100 mg/kg; 1031155 µg·hr/mL) tested to date. Likewise, human steady-state AUC exposure at the proposed dose of MAU868 6750 mg once monthly (1031155 µg·hr/mL) provides a safety margin of 1.4X compared to the NOAEL (750 mg/kg; 1420000 µg·hr/mL) in the 4-week rat study.

1.7 Rationale for Choice of Comparator and Background Therapy

Placebo is the comparator because there are no therapies available for treating BKV reactivation following kidney transplantation.

Induction and maintenance immunosuppression is to be determined at the discretion of the attending physician(s).

1.8 Assessment of Potential Risks and Benefits

MAU868 may prevent progression of BKV infection to irreversible renal allograft injury. Since current management of BKV reactivation involves reduction of immunosuppressive regimens (with accompanying increased risk for rejection), if MAU868 is effective in preventing BKV nephropathy in the post-kidney transplant setting, post-transplant care could be simplified with improved clinical outcomes.

To date, no MAU868-specific risks have been identified. The overall adverse event profile from the first-in human study was quite satisfactory. Based on clinical data from pooled immunoglobulin preparations and a monoclonal antibody active against respiratory syncytial virus, potential risks of MAU868 include infusion-related reactions, including allergic (e.g., hypersensitivity, anaphylaxis) and non-allergic (e.g., cytokine release syndrome) reactions, renal dysfunction, and thromboembolic events.

The excipients and their respective concentrations in the formulation of MAU868 have been safely used in humans. However, since this is the first study in which renal transplant recipients specifically will be exposed, there may be unknown risks associated with either the excipients or the dosing of MAU868 that may be unanticipated and serious.

Risks associated with participation in a clinical trial include risks associated with venipuncture and placement of intravenous cannulas, including infection, erythema, and pain or tenderness at the site. The safety of MAU868 during pregnancy has not been investigated and the potential risks of MAU868 during pregnancy are unknown. Women of child-bearing potential who may participate will be required to follow contraceptive measures to avoid becoming pregnant during the study.

Potential risks to the study participants will be minimized by adherence to the eligibility criteria and protocol provisions, diligent clinical monitoring, and appropriate management of participating subjects. In addition, the doses MAU868 used in this study are well below doses of immunoglobulin typically associated with renal or thromboembolic risk.

There are no specific or effective anti-BKV therapies. The risks of BKV reactivation and associated nephropathy in the post-renal transplant setting are potentially catastrophic. Thus, there is a critical unmet need for effective means to treat the consequences of BKV reactivation in the post-transplant setting. MAU868, a BKV-specific therapy, may be successful in treating clinically significant BKV infection in those at risk and, thus, has the potential to greatly simplify post-transplantation care and eliminate a threat to the survival of the renal allograft.

1.9 Blood Sample Volumes

The timing of blood sample collections during the study is outlined in Appendix A (Schedule of Events).

A summary blood log is provided in the Laboratory Manual. Instructions for all sample collection, processing, storage and shipment information are made available in the central laboratory manual. All lab samples will be shipped to a Central Laboratory for dispatch, and as appropriate, to specialty laboratories.

See Section 8.6.1 regarding the potential use of residual samples.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

The primary objective of this study is:

- To assess the safety and tolerability of MAU868

Secondary objectives of this study are:

- To assess the impact of MAU868 on BKV related outcomes including viremia, BKV nephropathy, graft function and rejection among renal transplant recipients with BK viremia
- To assess the pharmacokinetics of MAU868

2.2 Safety Endpoints

Safety endpoints include physical examinations, vital signs, clinical safety laboratory parameters, 12-lead ECGs, and adverse events.

2.3 Efficacy Endpoints

- Time (weeks) to decrease of BKV plasma viral load by 1 log
- Time (weeks) to first decrease of BKV plasma viral load to <LLOQ
- Proportion of subjects with >1 log decrease of BKV plasma viral load by 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks, and 36 weeks.
- Proportion of subjects with decrease BKV plasma viral load to <LLOQ by 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks, and 36 weeks
- Rate of decrease in BKV plasma viral load over time by 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks, and 36 weeks
- Change in eGFR from baseline to week 12 and from baseline to week 36

- Proportion of subjects with BKV nephropathy
- Proportion of subjects with graft failure during the study
- Proportion of subjects with acute rejection during the study
- Mortality rate during the study

2.4 Exploratory

- Presence of anti-drug antibodies (ADA)
- Presence of genotypic resistance
- Viral kinetics of BKV in plasma and urine

2.5 Pharmacokinetic Endpoints

- MAU868 serum concentrations

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a randomized, placebo-controlled, blinded, proof-of-concept study in kidney transplant recipients. Up to 36 subjects with BK viremia will participate in 1 of 3 sequential cohorts. Each cohort will randomize approximately 12 subjects (8 MAU868 and 4 placebo). The study will consist of a Screening period (pre-treatment) of up to 10 days, a treatment period of 12 weeks and a follow-up period of 24 weeks.

Protocol specific procedures should not be performed until the subject has consented to participation in the study. However, assessments and procedures performed as part of standard of care prior to informed consent, including determination of BK viral load in plasma may be used to qualify a subject for the study. Once qualifying BK viremia has been confirmed, subjects should be randomized as soon as possible and no more than 10 days after the sample documenting the viremia was collected.

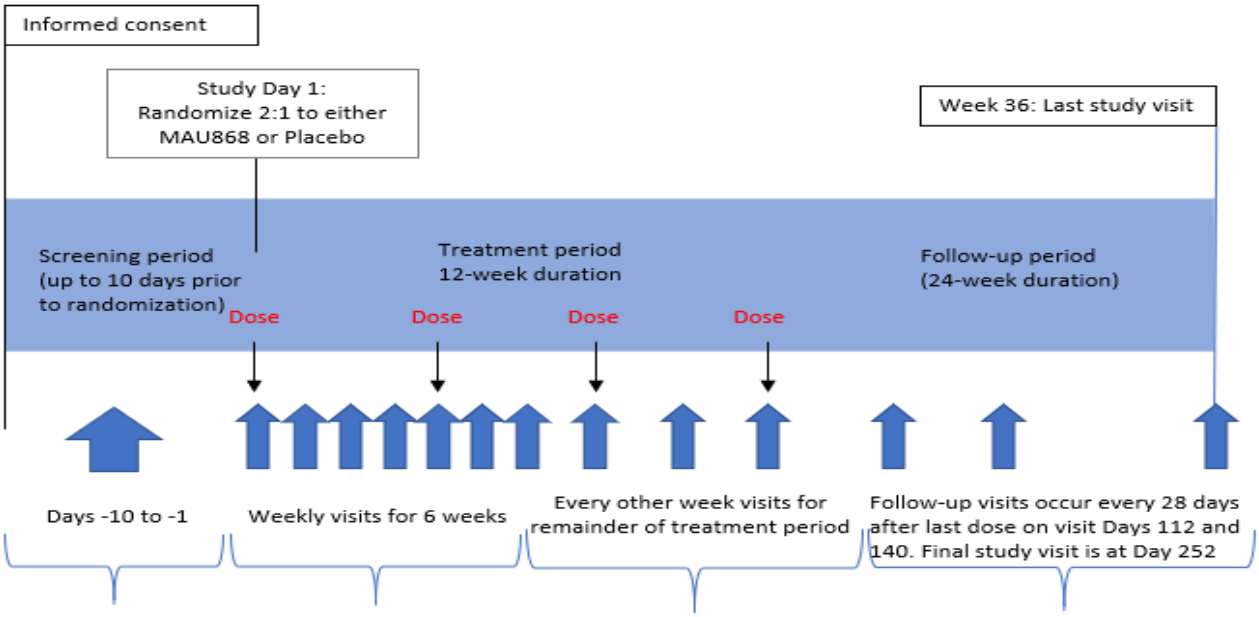
MAU868 or placebo will be administered approximately every 28 days (every 4 weeks) for 12 weeks (4 doses total). Urine and blood will be monitored for BKV DNA by PCR weekly for the first 6 weeks after initiation of treatment. For the remainder of the treatment period, urine and blood must be collected for BKV DNA by PCR at least every other week. PK, viral resistance and anti-drug antibodies will also be monitored. However, the Investigator may also request testing more frequently (i.e., weekly) than mandated by the protocol after the first 4 weeks of treatment when clinically indicated. During the study, BKV DNA by PCR will be tested at the central laboratory. Subjects should continue study drug until the last scheduled dose, regardless of changes in plasma BK viral load, use of rescue therapy and/or need for change in immunosuppressive regimen for any reason.

During the 24-week follow up period, 3 follow up visits will be scheduled at 4, 8 and 24-weeks post-treatment. At each visit, urine and blood samples for BKV DNA and samples for PK will be collected. Investigators may collect samples for BKV DNA more often as clinically indicated. During the follow-up period, BKV DNA by PCR will be tested at the central laboratory.

Routine post-transplantation care is to be guided by the Investigator discretion and site standard of care. This includes decisions to change the immunosuppressive regimen for a subject for any reason except for changes in immunosuppression in response to BK viremia. In order to treat BK viremia, prior to randomization, (ie, prior to screening, during the screening period and at the Baseline Visit) Investigators are permitted to decrease or alter immunosuppressive therapy per their discretion and/or per standard of care at their site. However, in the first 4 weeks after randomization, Investigators should refrain from additional changes in immunosuppressive regimen in response to BKV unless the viral load has increased by ≥1 log and the Investigator determines that a change is in the best interest of the subject. Use of other antiviral agents including cidofovir and leflunomide as well as IVIG are not permitted during the first 4 weeks of therapy and are strongly discouraged thereafter. Use of fluoroquinolones for reasons other than treatment of BKV is permitted.

Between screening and the last visit, subjects will attend a total of 14 visits.

A schematic representing the study's design is included below:



Progression from Cohort 1 to Cohort 2

Approximately 12 weeks after the 9th subject in Cohort 1 has been randomized, blinded safety data will be reviewed by the SSRC. Members of this committee will include a Sponsor medical representative, the Medical Monitor and the study's Principal Investigator. Cohort 2 will be opened for screening once the following criteria have been met:

1. All 12 subjects from Cohort 1 have been randomized,
2. No significant safety issues related to the administration of MAU868 have been identified by the SSRC based the blinded safety review described above as well as an assessment of any new SAEs reported after the SSRC review and before randomization of the 12th subject in Cohort 1.
3. No significant safety issues related to the administration of MAU868 have been identified by the independent DSMB.

The Chair of the DSMB will be notified of the SSRC's decision to open Cohort 2.

Accordingly, some subjects enrolled in Cohort 1 will continue participation in the study through the 24-week follow-up period while new subjects are screened and enrolled into Cohort 2.

Progression from Cohort 2 to Cohort 3

Cohort 3 will not be opened for screening and enrollment until an evaluation of unblinded safety, efficacy and pharmacokinetics findings from both Cohorts 1 and 2 through the 12-week treatment period has been completed by the Sponsor Study Review Committee SSRC.

3.2 Selection and Withdrawal of Subjects

This study will enroll male and female subjects, aged 18 years and above, who meet study entry criteria for BK viremia AND have received a kidney transplant within the prior year.

Subjects with BK viremia will be randomized to receive either MAU868 or placebo administered approximately every 28 days (every 4 weeks) for 12 weeks (4 doses total).

3.2.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study entry:

1. Be a male or female 18 years of age or older.
2. Recipient of a kidney (or kidney-pancreas) transplant within the year prior to enrollment.
3. Documented BK viremia based on local or central laboratory testing within 10 days prior to randomization of either
   a) $\geqq 10^4$ copies/mL OR

b) a detectable BK viral load in 2 consecutive plasma samples (collected between 1 and 3 weeks apart) where the most recent sample demonstrates a BK viral load of $\geq 10^3$ / mL. (Note: only the second, most recent sample must be collected within 10 days prior to randomization)

4. Have a functioning graft that is producing urine.
5. Females of childbearing potential (i.e., not postmenopausal or surgically sterilized) with male partners, and males with female partner(s) of childbearing potential, must agree to use 2 forms of highly effective contraception, 1 of which must be a barrier method, throughout the duration of the study and for 90 days following the last study drug administration. Acceptable barrier forms of contraception are condom and diaphragm. Acceptable non-barrier forms of contraception for this study are oral birth control pill, depot, patch, implants or injectable, abstinence, intrauterine device, and/or spermicide.
6. Females of childbearing potential must have a negative urine or serum pregnancy test result within 96 hours prior to Baseline (i.e. predose on Study Day 1).
7. Be willing to participate in the study, to give written informed consent and to comply with the study restrictions.

3.2.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible for entry into the study:

1. A BK plasma viral load which has exceeded 10^3 copies/mL for >4 months.
2. A BK plasma viral load of $\geq 10^7$ copies/mL.
3. Are receiving, at the time of informed consent, mTOR inhibitors.
4. Kidney transplant recipients who are anticipated to require Intravenous Immune Globulin (IVIG) treatment during the study period or who have received IVIG in the previous 9 months.
5. Kidney transplant recipients who, in the opinion of the Investigator, are likely to require antibody-depletion. Antibody-depleting therapies include but are not necessarily limited to hemodialysis, plasmapheresis and immunoadsorption.
6. Treatment within the previous month with the following medications: cidofovir, leflunomide.
7. History of hypersensitivity or intolerance to intravenous or subcutaneous administration of biologic medications or to any of the excipients included in the formulation of MAU868.
8. Platelet count <50,000/mm^3 at the time of informed consent, as determined by local laboratory.
9. History of splenectomy or asplenia.
10. Are lactating and/or pregnant.
11. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or longer than 5 half-lives if required by local regulations.
12. Prior exposure to MAU868.

13. Any other condition or laboratory abnormality that, in the opinion of the Investigator or the Sponsor, would put the patient at unacceptable risk for participation in the study or would interfere with the assessments included in the study.

3.3 Discontinuation Rules

3.3.1 Study Stopping Rules

The study may be discontinued or paused for reasons that may include (but are not limited to): reasons of safety, lack of study drug availability, inability to enroll the study, or decision by a regulatory authority or the Sponsor (see Appendix D).

In the event that a dosing cohort shows efficacy and it is not anticipated that additional dosing would show added efficacy, the Sponsor may choose to stop and not complete the study.

Further, in the instance of 2 or more treatment-related SAEs, 2 or more treatment-related AEs Grade 3 or higher or 2 or more clinically significant treatment-related Grade 3 or higher laboratory abnormalities, the study will be paused pending an SSRC review of the safety events. The Sponsor will inform the applicable regulatory authorities of any safety-related pause in the study.

In the case that the study is discontinued, the Sponsor will promptly inform the Investigators and applicable regulatory authority(ies) of the termination of the study and the reason(s) for the termination. The Investigators are responsible for promptly informing subjects that they must discontinue study drug. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will also be informed promptly and provided the reason(s) for the termination, as specified by the applicable regulatory requirement(s).

3.3.2 Discontinuation from Study Drug

Study drug dosing for an individual subject must be discontinued for any of the following reasons:

- The subject withdraws consent or requests discontinuation for any reason.
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
- Any SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator or Sponsor that continued participation is not in the best interest of the subject. Specifically, study drug must be discontinued in subjects with development of a treatment-related SAE, a treatment-related AE Grade 3 or higher, or a clinically significant treatment-related laboratory abnormality Grade 3 or higher.
- Pregnancy during the study.
- Subject failure to comply with protocol requirements or study-related procedures.

- Subject experiences study drug related symptoms that the Investigator determines are consistent with any of the following:
    - Anaphylaxis or severe allergic reaction.
    - An infusion reaction determined to be Grade 3 or higher based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.
    - Cytokine release syndrome determined to be CTCAE version 5 Grade 2 or higher.
    - Serum sickness determined to be CTCAE version 5 Grade 2 or higher.

Changes in plasma BK viral load, use of rescue therapy, and/or need for change in immune-suppressive regimen for any reason should not prompt early discontinuation of therapy. As long as the subject is tolerating, study drug should be continued regardless of viremia (i.e., even if not responding).

If a subject must be discontinued from study drug administration, the subject will still be encouraged to complete all follow-up visits and assessments necessary for appropriate safety follow-up. Subjects who are found to be pregnant should continue to be monitored for safety following study treatment discontinuation and the outcome of the pregnancy should be reported.

In the case of discontinuation from study drug, subjects should be considered to have completed the treatment period and should complete the assessments required in the follow-up period (see Appendix A). Although the actual study days will vary between subjects and will not align with protocol-defined visit study days, time from last study dose remains the same (i.e., subjects will be seen approximately every 28 days for 2 follow up visits and then once again approximately 24 weeks after the last study dose). If the subject cannot be seen on the precise protocol-defined study day, the acceptable visit window is ±10 days.

3.3.3 Discontinuation from Study Participation

Study participation by an individual subject must be prematurely discontinued for any of the following reasons:

- The subject withdraws consent or requests discontinuation for any reason.
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
- Any SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator or Sponsor that continued participation is not in the best interest of the subject.
- Subject failure to comply with protocol requirements or study-related procedures.

If a subject withdraws prematurely from the study, study staff should make every effort to contact the Sponsor prior to discontinuation, if possible, and to complete the full panel of assessments scheduled for the Early Termination Visit. The reason for subject withdrawal must be documented in the electronic Case Report Form (CRF).

In the case of subjects lost to follow-up, attempts to contact the subject must be made and documented in the subject's medical records.

The SSRC may recommend enrolling more than 12 subjects into a cohort (Cohort 1, 2, and/or 3) to allow adequate data collection for assessment of cohort progression and/or study objectives. Expansion of a given cohort, if needed, will not affect the size of subsequent cohort(s).

3.4 Early Termination Visit and Withdrawal Procedures

For subjects who are withdrawn from the study prior to completion of the study, the subject should return for an Early Termination Visit. The reason for subject withdrawal from the study must be documented in the eCRF.

4 TREATMENTS ARMS

The following treatment arms and dosing regimens are planned.

4.1 Treatment Groups

Subjects entering Cohort 1will be randomized to 1 of 2 treatment arms in a ratio of 2:1 (MAU868:placebo):

- MAU868 1350 mg every 28 days for a total of 4 doses
- Placebo every 28 days for a total of 4 doses.

Subjects entering Cohort 2 will be randomized to 1 of 2 treatment arms in a ratio of 2:1 (MAU868:placebo):

- MAU868 6750 once and 1350 mg every 28 days for a total of 4 doses
- Placebo every 28 days for a total of 4 doses.

Subjects entering Cohort 3 will be randomized to 1 of 2 treatment arms in a ratio of 2:1 (MAU868:placebo):

- MAU868 6750 mg every 28 days for a total of 4 doses
- Placebo every 28 days for a total of 4 doses.

Minimum duration of the infusion for 6750 mg is at least 180 minutes and for 1350 mg is at least 60 minutes. All infusions will be followed by at least a 25 mL D5W flush to run at the same infusion rate as the dose of study drug.

A Pharmacy Manual will provide instructions for preparation of the infusion. The study drug is prepared as a dilution of the 450 mg/3mL stock solution in a total volume of 250 mL D5W. The investigational product is to be stored at 2° to 8° Celsius, protected from light and not shaken.

4.2 Randomization

Study participants will be randomly assigned to their treatments. Two participants will be assigned to receive treatment with MAU868 for each participant assigned to receive treatment with placebo (2:1 randomization). Randomization will occur via an Interactive Web Response System (IWRS). The Investigator or delegate will contact the IWRS after confirming that a potential study participant is eligible. The IWRS will assign a randomization number that will be used to link the subject to a treatment arm.

The randomization number is only used to identify which treatment study participants have been assigned to receive. The number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see "Subject numbering" section in the IWRS manual. The randomization numbers will be generated using procedures that ensure that treatment assignment is unbiased and concealed from the Sponsor, subjects, and Investigator staff. A subject randomization list will be produced by a CRO.

The randomization scheme for subjects will be reviewed and approved by the Sponsor.

Follow the details outlined in the IWRS Manual regarding the process and timing of treatment assignment and randomization of subjects.

4.3 Treatment Arm Blinding

This is a subject, Investigator, and Sponsor-blinded study. Subjects and Investigators will remain blinded to study treatment arm (MAU868 or placebo) throughout the study.

Drug product will be supplied in bulk, so an unblinded pharmacist, or appropriately designated study site staff who is independent of the study team, will be required in order to maintain the blind. This unblinded associate at the site will be notified by the IWRS that a subject is randomized and to which treatment arm, which will then enable and instruct them to prepare the study drug.

4.3.1 Breaking the Treatment Blind

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the Investigator should contact the Medical Monitor to review the situation prior to breaking the blind.

Before breaking the blind of an individual subject's treatment, the Investigator should have determined that the information is necessary (i.e., that it will alter the subject's immediate management). In many cases, particularly when the emergency is clearly not investigational product related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding.

When the Investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The Investigator will then receive details of the investigational drug treatment for the specified subject via the IWRS. The system will automatically inform the study monitor for the site and the Study Team that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IWRS /code break at any time in case of emergency.

An assessment will be done by the appropriate site personnel and Sponsor after an emergency unblinding to assess whether or not study drug should be discontinued for a given subject.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt to preserve the blind is made.

5 DRUG SUPPLIES

5.1 Formulation and Packaging

There is no administration kit. A disposable syringe will be used to withdraw the contents of the vial.

MAU868

MAU868 450 mg/3 mL (150 mg/mL) solution for infusion and injection is a slightly opalescent and colorless to slightly colored aqueous solution packaged in a 6 mL clear glass vial with a grey rubber stopper, which is sealed with an aluminum cap with plastic flip-off disk. The vial is overfilled by 10% (containing a total volume of 3.3 mL) to allow for the complete removal of the dose (450 mg).

MAU868 450 mg/3 mL solution for infusion and injection contains, in addition to MAU868 drug substance, L-histidine, L-histidine-hydrochloride monohydrate, sucrose and polysorbate 20. The excipients utilized are standard pharmacopeial grade excipients that are commonly used in antibody parenteral products. The formulation does not contain any preservative; it is to be used for single-dose administration only.

Placebo

Placebo solution D5W will be supplied by the clinical site.

5.2 Study Drug Preparation and Dispensing

MAU868 will be administered via IV infusion. Refer to the Pharmacy Manual for dose preparation and administration instructions.

5.3 Study Drug Administration

Study drug should be administered only at clinical sites. All clinical sites must have the appropriate equipment and trained personnel needed to effectively manage hypersensitivity reactions including anaphylaxis and infusion reactions.

Cohort 1 MAU868 Arm:

- MAU868 1350 mg IV over at least 60 minutes approximately every 28 days for a total of 4 doses.

Cohort 2 MAU868 Arm:

- MAU868 6750 mg IV over at least 180 minutes on Study Day 1, then 1350 mg IV over at least 60 minutes for subsequent doses approximately every 28 days for a total of 4 doses.

Cohort 3 MAU868 Arm:

- MAU868 6750 mg IV over at least 180 minutes approximately every 28 days for a total of 4 doses.

Placebo

- Cohort 1: Placebo (D5W) will be administered as an IV infusion over at least 60 minutes approximately every 28 days for a total of 4 doses.
- Cohort 2: Placebo (D5W) will be administered as an IV infusion over at least 180 minutes on Day 1 and then over 60 minutes approximately every 28 days for a total of 4 infusions.
- Cohort 3: Placebo (D5W) will be administered as an IV infusion over at least 180 minutes approximately every 28 days for a total of 4 infusions.
- Placebo is prepared as a standard 250 mL volume of intravenous fluid.

All infusions will be followed by at least a 25 mL D5W flush to run at the same infusion rate as the dose of study drug.

Refer to the Pharmacy Manual for additional dose preparation and administration instructions.

5.3.1 Dose Adjustments and Interruption of Study Drug

Dose adjustments and interruptions of study drug are not permitted. Interruptions of individual infusions, however, are permitted in the event venous access becomes compromised or a subject is not tolerating the infusion (Section 7.3.1). The details of any interruption of an infusion, including the reason(s), the timing, and the resumption and completion of the infusion if applicable, must be recorded in the source documents and the eCRF.

For subjects who may require a hemodialysis, plasmapheresis, or immunoadsorption treatment, it shall be assumed that the study drug has been removed. A blood sample for PK analysis should be collected prior to and following these treatments. In the event that a subject requires hemodialysis, plasmapheresis, or immunoadsorption treatments; if <15 days since last MAU868/placebo treatment another dose will be given as soon as possible, and the next scheduled monthly dose skipped. Regular dosing will occur the following month. If the last dose was 15 days or greater no interim dose will be administered, and the regular monthly schedule will be followed. No subject will receive more than 4 doses. Subjects anticipated to require hemodialysis, plasmapheresis or immunoadsorption treatment at the time of randomization should not be randomized (Exclusion Criterion 5).

5.3.2 Study Drug Compliance

All study drug will be administered at the clinical center, by qualified site staff, under the supervision of the Investigator or qualified designee. Any interruption to the IV infusion or changes to the infusion rate and duration must be recorded in the source documents and in the eCRF.

All study drug must be recorded in the Drug Accountability Log.

5.4 Storage and Accountability

The recommended storage condition of the drug product is 2-8°C, protected from light. The drug product should not be shaken or frozen. Details on the requirements for storage and management of study drug, and instructions to be followed for subject numbering, prescribing/dispensing and administering the study drug are outlined in the Pharmacy Manual.

6 PRIOR AND CONCOMITANT MEDICATIONS AND/OR PROCEDURES

6.1 Excluded Medications and/or Procedures

The following medications are excluded from use during this study and patients anticipated to require these interventions should not be included:

- Systemic mTOR inhibitors (e.g., rapamycin, sirolimus, everolimus, temsirolimus, etc.)
- IVIG
- antibody-depleting therapies (e.g., hemodialysis, plasmapheresis, immunoadsorption, etc.)
- any other investigational drug

If, after randomization, it is determined that these therapies are essential for the subject's health and well-being and cannot be delayed until study completion, the subject should not be discontinued from study medication or the study due to receipt of these medications. See Section 5.3.1 and the Schedule of Events (Appendix A) for more information regarding dosing and PK collection in the event a subject requires hemodialysis, plasmapheresis, or immunoadsorption treatments.

6.2 Rescue Medication

In order to treat BK viremia, prior to randomization, (ie, prior to screening, during the screening period and at the Baseline Visit), Investigators are permitted to decrease or alter immunosuppressive therapy per their discretion and/or per standard of care at their site. However, in the first 4 weeks after randomization, Investigators should refrain from additional changes in immunosuppressive regimen in response to BKV unless the viral load has increased by $\geq$1 log and the Investigator determines that a change is in the best interest of the patient.

Additional rescue medication including cidofovir, leflunomide and IVIG is strongly discouraged. However, if 4 weeks after randomization, the Investigator feels the subject is failing study drug and the subject is at significant risk of graft damage, and that additional medications are required for the subject's care, the Investigator may add additional therapies at their discretion.

Regardless of the use of rescue medication (changes in immunosuppressive regiment or addition of anti-viral medication), all subjects should complete study infusion(s) as long as they are tolerating the study drug.

6.3 Documentation of Prior and Concomitant Medication Use

The Investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study.

All prescription medications; including over-the-counter drugs and significant non-drug therapies (including blood transfusions) received by the subject within 10 days prior to the initial dose of study drug administration and any concomitant medications used through the Follow-Up Visit will be recorded in the source documents and on the appropriate eCRF. In addition, all immunosuppressive therapy received since kidney transplantation (including the induction regimen) will be recorded.

6.4 Infusion Reactions

Although not previously reported following administration of MAU868, infusion reactions and infusion associated symptoms may occur following infusion of a monoclonal antibody due to sensitization due to the antibody or to the excipients in the infusion materials.

Symptoms indicative of anaphylaxis, or (based on CTCAE version 5 classification) Grade 3 or higher infusion reaction, Grade 2 or higher cytokine release syndrome, or Grade 2 or higher serum sickness should result in immediate halting of the infusion and prompt initiation of appropriate therapy. Subjects should not be re-challenged with study drug. Study drug should be permanently discontinued, but the patient should remain in the study for continued follow-up. Milder symptoms that do not meet criteria for immediate discontinuation from study drug may be managed by drug interruption and symptom management. The infusion should be temporarily stopped and the subject assessed. Diphenhydramine 50 mg and acetaminophen 650 mg should be administered. Ifsymptoms improve after 30-60 minutes, the subject may be re-challenged with a reduced infusion rate of approximately 50% the initial rate. Medication(s) to treat gastrointestinal symptoms may also be given if needed. If the subject tolerates a re-challenge, they should receive pre-medication

with diphenhydramine 50 mg and acetaminophen 650 mg administered approximately 30-60 minutes prior to start of the next scheduled infusion. Subsequent infusions should be administered at a slower rate. For subsequent infusions of 1350 mg, study drug should be administered over approximately 120 minutes (2 hours). For subsequent infusions of 6750 mg, study drug should be administered over approximately 240 minutes (4 hours).

It is expected that the clinical site will have adequate facilities at the location of the study drug infusions to effectively manage and treat infusion reactions promptly.

7 STUDY PROCEDURES

7.1 Informed Consent

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). However, assessments or procedures performed as standard of care may be used for the purposes of screening. The process of obtaining informed consent must be documented in the subject source documents.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate. New information might require an update to the informed consent and then must be discussed with the subject.

Once the subject has signed the informed consent, the subject may enter the Screening Period of the study.

7.2 Screening Period

Subjects who have had their renal transplant within the previous year may be considered for participation and entrance into the Screening Period following signing of the consent. Subjects may, enter the Screening Period (pre-treatment period) of up to 10 days following signing of the consent. If a subject does not meet all criteria within the 10-day window they will be considered a screen failure.

No study-specific procedures or activities may be performed until the informed consent process has been completed and the subject has signed the Informed Consent Form. However, assessments or procedures performed as standard of care may be used for the purposes of screening. Once a subject has signed the Informed Consent Form for study participation, the subject enters the Screening Period.

See Section 8, Study Procedures and Assessments.

During the Screening Period, the following activities will be performed:

- Review of Inclusion Criteria (Section 3.2.1) and Exclusion Criteria (Section 3.2.2).
- Review and record medical and surgical history and current medical conditions.
- Review and record concomitant medications (see Section 6.1 Excluded Medications and/or Procedures, for a list of prohibited medications).
- Review and record subject demography.
- Review and record Kidney Donor Profile Index (KDPI).
- Perform urine or serum pregnancy test on women of childbearing potential only. Note: either serum or urine must be documented as negative within 96 hours prior to Baseline.
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation and height and weight.
- Perform physical examination.
- Review of local and/or central plasma BKV PCR results
- Review of Adverse Events after informed consent is signed.

If the subject meets all inclusion and has no exclusion criteria during the Screening Period, the subject may enter the randomization portion of the study.

7.3 Treatment Period (Day 1 to Day 84)

If the subject meets all inclusion and exclusion criteria, the subject may then be randomized to receive either MAU868 or placebo. Randomization should occur as soon as possible, but not longer than 10 calendar days, after the local qualifying sample was collected.

Subjects will be randomized to study drug in the ratio of 2:1 (MAU868: placebo).

During the treatment period, subjects will receive MAU868 or placebo approximately every 28 days (every 4 weeks) for 12 weeks (4 doses total). Urine and blood will be monitored for BKV DNA weekly by PCR for the first 6 weeks of treatment and then every other week until completion of treatment and at each follow up visit. During this time, BKV DNA by PCR will be tested at the central laboratory.

During the treatment period, subjects should be seen approximately every 7 days (+/- 3 days) during the first 6 weeks and approximately every 14 days (+/-5 days) for the duration of treatment. Subjects may be seen more often at the Investigator's discretion. Visit dates are determined from the Baseline Visit.

NOTE:

- After the first 4 weeks of treatment, the Investigator may request BK viral load (urine and blood) testing more frequently (e.g., weekly) than mandated by the protocol, if clinically indicated.

- Subjects should continue with the study drug (i.e., MAU868 or placebo) until the last scheduled dose, regardless of documented viremia, need for rescue therapy and/or changes in the subject's immunosuppressive regimen.

7.3.1 Day 1 (Baseline; Study Drug Infusion 1)

The day on which the subject receives their first study drug infusion will be designated Day 1 (Baseline).

The following procedures will be performed **prior to initiation of the study drug infusion**; see Schedule of Events (Appendix A):

- Review and record medical conditions.
- Review and record concomitant medications.
- Obtain subject weight
- Collect blood (serum and plasma) and urine samples for BKV testing, pharmacokinetics, immunogenicity, hematology, clinical chemistry, and urinalysis for analysis at central laboratories.
- Females of childbearing potential must have a negative urine or serum pregnancy test result within 96 hours prior to Baseline. If applicable, perform urine or serum pregnancy test.
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation within 30 minutes prior to the initiation of the infusion.
- Perform electrocardiogram (12-lead).

The following procedures will be performed **after the initiation of the study drug infusion**; see Schedule of Events (Appendix A):

- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation approximately every 30 minutes (+/- 10 minutes) after the start of the infusion until at least 2 hours after completing the infusion. Vital signs may also be collected at any time during or after the infusion at the Investigator's discretion.
- Collect blood (serum) for pharmacokinetics within 30 minutes following the completion of the infusion and again within 3 to 6 hours after the end of the infusion.
- Review and record adverse events.
- Review and record any new concomitant medications.

It is expected that the clinical site will have adequate facilities at the location of the study drug infusions to effectively manage and treat infusion reactions.

If a subject has experienced an infusion reaction following an infusion of study drug, the Investigator should discontinue the infusion. If symptoms resolve promptly the infusion may be resumed at a slower rate. In this case, the Investigator is encouraged to continue the subject's participation in the study. If the subject continues in the study, future infusions should be administered at a slower rate and preceded by use of premedication.

Cohort 1: Study Drug Administration Day 1

The subject will receive their study drug infusion (MAU868 1350 mg or Placebo). The respective infusions will be delivered over at least 60 minutes. Following completion of the infusion (infusion bag completely emptied into the drip chamber) a 25 mL D5W flush is to infuse at the same infusion rate as the dose of IP. Start and stop times will be recorded on the eCRF.

Cohort 2: Study Drug Administration Day 1

The subject will receive their study drug infusion (MAU868 6750 mg or Placebo). The respective infusions will be delivered over at least 180 minutes. Start and stop times will be recorded on the eCRF. For subsequent doses the subject will receive their study drug infusion (MAU868 1350 mg or Placebo). The respective infusions will be delivered over at least 60 minutes. Following completion of the infusion (infusion bag completely emptied into the drip chamber) a 25 mL D5W flush is to infuse at the same infusion rate as the dose of IP. Start and stop times will be recorded on the eCRF.

Cohort 3: Study Drug Administration Day 1

The subject will receive their study drug infusion (MAU868 6750 mg or Placebo). The respective infusions will be delivered over at least 180 minutes. Following completion of the infusion (infusion bag completely emptied into the drip chamber) a 25 mL D5W flush is to infuse at the same infusion rate as the dose of IP. Start and stop times will be recorded on the eCRF.

7.3.2 Day 7

The following procedures will be performed at this visit; see Schedule of Events (Appendix A):

- Record vital signs (if visit performed in person), including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.
- Review and record adverse events.
- Review and record concomitant medications.
- Collect blood (serum and plasma) and urine samples for BK viral load testing, viral resistance, and pharmacokinetics for analysis at central laboratories.

7.3.3 Day 14

The following procedures will be performed at this visit; see Schedule of Events (Appendix A):

- Record vital signs (if visit performed in person), including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.
- Review and record adverse events.
- Review and record concomitant medications.
- Collect blood (serum and plasma) and urine samples for BK viral load testing, viral resistance, pharmacokinetics, hematology, clinical chemistry, and urinalysis for analysis at central laboratories

7.3.4 Day 21

The following procedures will be performed at this visit; see Schedule of Events (Appendix A):

- Record vital signs (if visit performed in person), including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.
- Review and record adverse events.
- Review and record concomitant medications.
- Collect blood (serum and plasma) and urine samples for BKV testing, viral resistance, and pharmacokinetics for analysis at central laboratories.

7.3.5 Day 28 (Study Drug Infusion 2)

The following procedures will be performed **prior to initiation of the study drug infusion**; see Schedule of Events (Appendix A):

- Review and record adverse events.
- Review and record concomitant medications.
- Obtain subject weight
- Collect blood (serum and plasma) and urine samples for BK viral load testing, viral resistance, immunogenicity, pharmacokinetics, hematology, clinical chemistry, and urinalysis for analysis at central laboratories.
- Perform urine or serum pregnancy test for women of childbearing potential.
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation within approximately 30 minutes prior to the initiation of the infusion.

If the subject experienced an infusion reaction during their prior administration of study drug, future infusions should be preceded by use of premedication and decreasing the infusion rate (see Section 6.4).

The following procedures will be performed **after the initiation of the study drug infusion**; see Schedule of Events (Appendix A):

- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation approximately every 30 minutes (+/- 10 minutes) after the start of the infusion until at least 2 hours after completing the infusion**.** Vital signs may also be collected at any time during or after the infusion at the Investigator's discretion.
- Collect blood (serum) for pharmacokinetics within approximately 30 minutes following the completion of the infusion.
- Review and record adverse events.
- Review and record any new concomitant medications.

Study Drug Administration

Cohort 1: Study Drug Administration Day 28

The subject will receive their study drug infusion (MAU868 1350 mg or Placebo). The respective infusions will be delivered over at least 60 minutes. Following completion of the infusion (infusion bag completely emptied into the drip chamber) a 25 mL D5W flush is to infuse at the same infusion rate as the dose of IP. Start and stop times will be recorded on the eCRF.

Cohort 2: Study Drug Administration Day 28

The subject will receive their study drug infusion (MAU868 1350 mg or Placebo). The respective infusions will be delivered over at least 60 minutes. Following completion of the infusion (infusion bag completely emptied into the drip chamber) a 25 mL D5W flush is to infuse at the same infusion rate as the dose of IP. Start and stop times will be recorded on the eCRF.

Cohort 3: Study Drug Administration Day 28

The subject will receive their study drug infusion (MAU868 6750 mg or Placebo). The respective infusions will be delivered over at least 180 minutes. Following completion of the infusion (infusion bag completely emptied into the drip chamber) a 25 mL D5W flush is to infuse at the same infusion rate as the dose of IP. Start and stop times will be recorded on the eCRF.

7.3.6 Day 35

The following procedures will be performed at this visit; see Schedule of Events (Appendix A):

- Record vital signs (if visit performed in person), including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation
- Review and record adverse events
- Review and record concomitant medications
- Collect blood (serum and plasma) and urine samples for BKV testing and viral resistance for analysis at central laboratories

7.3.7 Day 42

The following procedures will be performed at this visit; see Schedule of Events (Appendix A):

- Record vital signs (if visit performed in person), including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation
- Review and record adverse events
- Review and record concomitant medications
- Collect blood (serum and plasma) and urine samples for BK viral load testing and viral resistance for analysis at central laboratories

7.3.8 Day 56 (Study Drug Infusion 3)

The following procedures will be performed prior to initiation of the study drug infusion; see Schedule of Events (Appendix A):

- Review and record adverse events
- Review and record concomitant medications
- Obtain subject weight
- Collect blood (serum and plasma) and urine samples for BK viral load testing, viral resistance, immunogenicity, pharmacokinetics, hematology, clinical chemistry, and urinalysis for analysis at central laboratories
- Perform urine or serum pregnancy test for women of childbearing potential
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation within approximately 30 minutes prior to the initiation of the infusion

If the subject experienced an infusion reaction during their prior administration of study drug, future infusions should be preceded by use of premedication and decreasing the infusion rate (refer to Section 6.4).

The following procedures will be performed **after the initiation of the study drug infusion**; see Schedule of Events (Appendix A).

- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation approximately every 30 minutes (+/- 10 minutes) after the start of the infusion until at least 2 hours after completing the infusion. Vital signs may also be collected at any time during or after the infusion at the Investigator's discretion.
- Collect blood (serum) for pharmacokinetics within approximately 30 minutes following the completion of the infusion
- Review and record adverse events
- Review and record any new concomitant medications

Study Drug Administration

Cohort 1: Study Drug Administration Day 56

The subject will receive their study drug infusion (MAU868 1350 mg or Placebo). The respective infusions will be delivered over at least 60 minutes. Following completion of the infusion (infusion bag completely emptied into the drip chamber) a 25 mL D5W flush is to infuse at the same infusion rate as the dose of IP. Start and stop times will be recorded on the eCRF.

Cohort 2: Study Drug Administration Day 56

The subject will receive their study drug infusion (MAU868 1350 mg or Placebo). The respective infusions will be delivered over at least 60 minutes. Following completion of the infusion (infusion bag completely emptied into the drip chamber) a 25 mL D5W flush is to infuse at the same infusion rate as the dose of IP. Start and stop times will be recorded on the eCRF.

Cohort 3: Study Drug Administration Day 56

The subject will receive their study drug infusion (MAU868 6750 mg or Placebo). The respective infusions will be delivered over at least 180 minutes. Following completion of the infusion (infusion bag completely emptied into the drip chamber) a 25 mL D5W flush is to infuse at the same infusion rate as the dose of IP. Start and stop times will be recorded on the eCRF.

7.3.9 Day 70

The following procedures will be performed at this visit; see Schedule of Events (Appendix A):

- Record vital signs (if visit performed in person), including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation
- Review and record adverse events
- Review and record concomitant medications
- Collect blood (serum and plasma) and urine samples for BK viral load testing and viral resistance for analysis at central laboratories

7.3.10 Day 84 (Study Drug Infusion 4)

The following procedures will be performed prior to initiation of the study drug infusion; see Schedule of Events (Appendix A):

- Review and record adverse events
- Review and record concomitant medications
- Obtain subject weight
- Collect blood (serum and plasma) and urine samples for BK viral load testing, viral resistance, immunogenicity, pharmacokinetics, hematology, clinical chemistry, and urinalysis for analysis at central laboratories

- Perform urine or serum pregnancy test for women of childbearing potential
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation within approximately 30 minutes prior to the initiation of the infusion
- Perform physical examination

If the subject experienced an infusion reaction during their prior administration of study drug, future infusions should be preceded by use of premedication and decreasing the infusion rate.

The following procedures will be performed **after the initiation of the study drug infusion**; see Schedule of Events (Appendix A):

- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation approximately every 30 minutes (+/- 10 minutes) after the start of the infusion until at least 2 hours after completing the infusion. Vital signs may also be collected at any time during or after the infusion at the Investigator's discretion.
- Collect blood (serum) for pharmacokinetics within approximately 30 minutes following the completion of the infusion and again within approximately 3 to 6 hours after the end of the infusion
- Perform electrocardiogram (12-lead)
- Review and record adverse events
- Review and record any new concomitant medications

Study Drug Administration

Cohort 1: Study Drug Administration Day 84

The subject will receive their study drug infusion (MAU868 1350 mg or Placebo). The respective infusions will be delivered over at least 60 minutes. Following completion of the infusion (infusion bag completely emptied into the drip chamber) a 25 mL D5W flush is to infuse at the same infusion rate as the dose of IP. Start and stop times will be recorded on the eCRF.

Cohort 2: Study Drug Administration Day 84

The subject will receive their study drug infusion (MAU868 1350 mg or Placebo). The respective infusions will be delivered over at least 60 minutes. Following completion of the infusion (infusion bag completely emptied into the drip chamber) a 25 mL D5W flush is to infuse at the same infusion rate as the dose of IP. Start and stop times will be recorded on the eCRF.

Cohort 3: Study Drug Administration Day 84

The subject will receive their study drug infusion (MAU868 6750 mg or Placebo). The respective infusions will be delivered over at least 180 minutes. Following completion of the infusion (infusion bag completely emptied into the drip chamber) a 25 mL D5W flush is to infuse at the same infusion rate as the dose of IP. Start and stop times will be recorded on the eCRF.

7.4 Follow-up Period (Day 112 to Day 252)

Subjects will be seen approximately every 28 days for 2 follow up visits and then once again approximately 24 weeks after the last study dose. If the subject cannot be seen on the precise protocol-defined study day, the acceptable visit window is ±10 days.

7.4.1 Day 112 (Follow Up 1)

The following procedures will be performed; see Schedule of Events (Appendix A):

- Review and record adverse events
- Review and record concomitant medications
- Collect blood (serum and plasma) and urine samples for BK viral load testing, viral resistance, immunogenicity, pharmacokinetics, hematology, clinical chemistry, and urinalysis for analysis at central laboratories
- Record vital signs (if visit performed in person), including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation

7.4.2 Day 140 (Follow Up 2)

The following procedures will be performed; see Schedule of Events (Appendix A):

- Review and record adverse events
- Review and record concomitant medications
- Collect blood (serum and plasma) and urine samples for BK viral load testing, viral resistance, immunogenicity, pharmacokinetics, hematology, clinical chemistry, and urinalysis for analysis at central laboratories
- Record vital signs (if visit performed in person), including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation

7.4.3 Day 252 (Last Follow Up)

The following procedures will be performed at this visit; see Schedule of Events (Appendix A):

- Review and record adverse events
- Review and record concomitant medications
- Obtain subject weight
- Collect blood (serum and plasma) and urine samples for BK viral load testing, viral resistance, immunogenicity, pharmacokinetics, hematology, clinical chemistry, and urinalysis for analysis at central laboratories
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation

- Perform physical examination
- Perform electrocardiogram (12-lead)

7.4.4 Early Termination Visits

For subjects who are withdrawn from the study prior to completion, the following procedures will be performed at the Early Termination Visit:

- Review and record adverse events
- Review and record concomitant medications
- Obtain subject weight
- Collect blood (serum and plasma) and urine samples for BKV testing, viral resistance, immunogenicity, pharmacokinetics, hematology, clinical chemistry, and urinalysis for analysis at central laboratories
- Record vital signs, including temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation
- Perform physical examination
- Perform electrocardiogram (12-lead)

8 STUDY PROCEDURES AND ASSESSMENTS

8.1 Schedule of Events

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible.

Missed, late, or rescheduled visits should not lead to automatic discontinuation from the study.

Subjects who prematurely discontinue study drug should remain in the study. In the case of premature discontinuation from study drug, subjects should be considered to have completed the treatment period and should complete the assessments required in the follow-up period (see Appendix A). Although the actual study days will vary between subjects and will not align with protocol-defined visit study days, time from last study dose remains the same (i.e., subjects will be seen approximately every 28 days for 2 follow up visits and then once again approximately 24 weeks after the last of study dose received). If the subject cannot be seen on the precise protocol-defined study day, the acceptable visit window is ±10 days.

Subjects who prematurely discontinue the study for any reason should be scheduled for a final study visit as soon as possible, at which time all of the assessments listed for the Early Termination Visit will be performed. At this final visit, all investigational product should be reconciled, and the adverse event and concomitant medications recorded on the eCRF and the reason for discontinuation of study documented. (See Appendix A, Schedule of Events).

8.2 Subject Demographics/Other Baseline Characteristics

Demographic and other baseline characteristics will be collected for all subjects. Relevant medical and surgical history, including the primary cause of end-stage renal disease and other past or ongoing conditions, shall be recorded. Investigators have the discretion to determine the relevance of the medical and surgical history for individual subjects.

The Kidney Donor Profile Index (KDPI) will be recorded for all subjects who receive a kidney from a deceased donor. The information necessary for determining the KDPI includes donor age, height, weight, ethnicity, history of hypertension, history of diabetes mellitus, cause of death, serum creatinine, hepatitis C serostatus, and whether donation occurred after circulatory death.

More specific instructions and details regarding the baseline characteristics of subjects are outlined in the eCRF completion guidelines.

8.3 Efficacy / Pharmacodynamics

The efficacy of MAU868 in treating BK viremia will be measured primarily by measuring the viral load in the plasma over time.

Samples (plasma or urine) will be collected for viral load assessment at the time points defined in the Assessment schedule. (See Appendix A, Schedule of Events.)

Follow instructions outlined in the Laboratory Manual regarding sample collection, numbering, processing and shipment. A centralized, validated quantitative PCR (qPCR) assay, targeting multiple conserved regions of the viral genome, will be utilized for quantification of BKV viral load. These results of each subject's testing will be reported to the Investigator. It is recommended that these results be used by the Investigator in the management of the subject during their participation in the study. The presence of MAU868 is not expected to affect the results of the qPCR BKV viral load assay because viral nucleic acid will first be isolated from the sample for quantitation, removing all antibodies and virus/host proteins. A detailed Virology Analysis Plan will be prepared separately.

8.4 Clinical Outcome Assessments (COAs)

Several clinical outcome assessments will be evaluated. These include:

- Graft function as measured by eGFR using the CK-EPI equation,
- Graft survival as determined by presence of a functioning graft that has not required a re-transplant or permanent renal replacement therapy,
- Subject survival,
- Graft rejection based on kidney biopsy results and 2017 Banff Kidney Meeting Report,

- BKV nephropathy: based on kidney biopsy results and the Banff Working Group on Polyomavirus Nephropathy classification system

  NOTE: Renal biopsies are not mandated, but if they are performed during the study period, results will be recorded in the eCRF. The assessments are incorporated into endpoints analyzed for efficacy. See Section 10.5, Efficacy Analysis.

8.5 Safety

Safety assessments are specified below.

8.5.1 Pregnancy

Pregnancy tests (urine or serum) of β-hCG are required of all female study participants of childbearing potential within 96 hours prior to Study Day 1. In addition, urine or serum pregnancy testing for all females of childbearing potential will be performed before infusions #2 on Day 28, #3 on Day 56 and #4 on Day 84.

8.5.2 Physical Examination

Information from physical examinations will be kept at the clinical site as source data and will not be transferred to the Sponsor as part of the study analysis (i.e., recorded in the eCRF) unless findings are related to an adverse event or are otherwise significant (and so are reported as an adverse event or medical history).

The eCRF manual provides more details.

8.5.3 Vital Signs

Vital signs will include temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation.

8.5.4 Laboratory Evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. See Section 9, Safety Assessments.

Screening laboratory assessments to determine eligibility should be performed at the local laboratory and may be collected as standard of care within 10 days prior to Study Day 1 (Baseline). Laboratory assessments collected after Screening will be sent to the central laboratory for analysis.

Clinical laboratory assessments (serum chemistry, hematology [including CBC with differential], and urinalysis) will occur at Screening, and on Days 1 (Baseline), 14, 28, 56, 84, 112, 140 and 252. These assessments will also occur at the Early Termination Visit (if applicable).

A urine or serum pregnancy test will be performed locally at Screening.

If clinically indicated and at the discretion of the Investigator, or if a suspected adverse event is identified, clinical laboratory assessments may be conducted at any time during the study and compared to Baseline. See Appendix B for a complete list of clinical laboratory analytes.

8.5.5 Electrocardiogram

Standard 12-lead electrocardiograms (ECGs) will be performed in a supine position. Interpretation of the tracing must be made by a qualified physician and documented on the ECG / in the ECG section of the eCRF. Original ECG tracings, appropriately signed, will be archived at the study site.

8.5.6 Pharmacokinetics

PK samples will be collected at the timepoints defined in the Schedule of Events (Appendix A). Follow instructions outlined in the Laboratory Manual. regarding sample collection, numbering, processing and shipment. See Section 8.3, Use of Residual Biological Samples.

MAU868 levels in serum will be determined by a validated ELISA-based method. A detailed description of the method used will be included in the PK bioanalytical data report.

Actual time of dosing and actual times of blood collection will be recorded on the PK blood collection eCRF page. For a detailed description of blood sampling, handling, labeling and shipment instructions please refer to the Laboratory Manual.

PK samples obtained after study drug infusion should be collected from a vein opposite the arm into which the study drug was infused.

Results of PK samples will not be reported to the site. These samples will be analyzed, and the results reported by centralized third-party specialty labs.

8.5.7 BKV by PCR Sample Collection

Plasma and urine for BKV by PCR samples will be collected at the timepoints defined in the Schedule of Events (Appendix A). Follow the instructions outlined in the Laboratory Manual, regarding sample collection, numbering, processing and shipment.

8.5.8 Other Assessments: Viral Resistance and Immunogenicity

To monitor for the possible development of resistance-associated variants (RAVs) to MAU868, the BKV VP1 coding region will be sequenced and translated to the corresponding amino acid sequence. The VP1 amino acid sequences from subjects will be aligned to their corresponding baseline sequences (derived from BKV detected in the urine at Baseline) and reference isolate sequences to determine if any change from-baseline or change-from-reference RAVs are present. The susceptibility of RAVs to MAU868 will be determined by cloning the subject derived VP1 gene into a BKV reference isolate vector, generating a chimeric virus for MAU868 phenotypic assessment. The EC50 and EC90 values and fold change from baseline and reference values will be reported. If the resulting chimeric virus does not replicate, the individual RAV(s) may be engineered directly into the BKV reference isolate vector through site-directed mutagenesis and

assessed for susceptibility to neutralization by MAU868. The emergence of RAV(s) conferring reduced susceptibility will be correlated to the MAU868 exposure. For subjects with confirmed RAV(s) displaying reduced MAU868 susceptibility, the persistence of the RAV(s) will be monitored for at least 6 months following the end of MAU868 therapy by periodic BKV sequencing provided the virus remains detectable in either the blood or the urine. To date, no epitope-mutant BK viruses with both a significant loss of susceptibility to MAU868 and a preservation of replicative fitness have been identified.

Details of viral resistance monitoring and detection will be described in the Virology Analysis Plan.

Immunogenicity will be evaluated using a validated ligand binding assay (ELISA or MSD) for the detection of potential anti-MAU868 antibodies.

The detailed methods for immunogenicity assessment will be described in the Bioanalytical Data Report.

Results of the viral resistance and immunogenicity samples will not be reported to the site. These samples will be analyzed, and the results reported by centralized third-party specialty labs.

8.6 Other Samples

8.6.1 Use of Residual Biological Samples

Any residual blood or urine samples remaining at the central laboratories after the protocol-defined analyses have been performed may be used for additional exploratory analyses and will be completed within 5 years after the protocol defined analyses are reported. These exploratory analyses may include, but are not necessarily limited to, investigations of other biomarkers related to kidney disease or kidney function, other immunologic markers, other viral RNA or DNA, protein binding, metabolite profiling, biomarkers of transporters or metabolic enzyme activity (such as 4-beta-hydroxycholesterol levels) or other bioanalytical purposes (e.g., investigations related to individual infusion reactions or other adverse events). Given the exploratory nature of the work, the analytical methods used for these investigations may not be validated. The results from these exploratory analyses, if pursued, will not be included in the clinical study report.

9 SAFETY ASSESSMENTS

9.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to the study drug. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time the subject signs consent through the Follow Up Visit. Subjects should be instructed to report any adverse event that they experience to the Investigator, whether or not they think the event is due to study drug. Beginning at Screening (following completion of an Informed Consent Form by the subject), Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure itself.

Any medical condition already present at consent should be recorded as medical history and not be reported as an adverse event unless the medical condition or signs or symptoms present at Baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Subjects who develop treatment-related SAEs, treatment-related Grade 3 or higher AEs, or clinically significant treatment-related Grade 3 or higher laboratory abnormalities should be followed until resolution of the AE or laboratory abnormality, or, if the AE or laboratory abnormality was present at baseline, until the value returns to baseline level.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study or are present at initial dosing and significantly worsen during the study should be reported as adverse events, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an adverse event. Laboratory abnormalities or other abnormal clinical findings (e.g., ECG abnormalities) should be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action taken with the study drug is required as a result of the abnormality
- Based on the clinical judgment of the Investigator

9.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a study drug related to any dose should be considered an adverse drug reaction. “Responses” to a study drug means that a causal relationship between a study drug and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

9.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For MAU868 the reference safety information is included in the IB currently in force. The reference safety information will be reviewed yearly, and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

9.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event and will also categorize each adverse event as to its potential relationship to study drug using the categories of "yes" or "no."

Assessment of Severity

The severity of all adverse events should be graded according to the CTCAE v5.0. For those adverse event terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- CTCAE Grade 4: Life threatening consequences; urgent intervention indicated

  CTCAE Grade 5: Death related to the adverse event

Causality Assessment

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

No (not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant drug

  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug.

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug.

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

9.1.4 AEs of Special Interest

For subjects experiencing infusion-associated AEs, the Investigator, or designee, is responsible for determining if immediate discontinuation of study therapy is required (see Section 3.3.2). In addition, for all cases of AEs associated with study infusion that occur during or within 2 hours after the completion of infusion require enhanced reporting using the specified Infusion-associated AE Report eCRF, regardless of whether drug discontinuation criteria are met.

> Note: All treatment-related AEs of grade 3 or higher and treatment-related AEs of cytokine release syndrome and serum sickness of grate 2 or higher require discontinuation from study drug (see Section 3.3.2).

9.2 Serious Adverse Events

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

- Death.

- A life-threatening adverse event.

  Note: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations.

  Note: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from Baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

  Note: All treatment related SAEs require discontinuation from study drug (see Section 3.3.2)

9.3 Serious Adverse Event Reporting − Procedures for Investigators

9.3.1 Initial Reports

All SAEs occurring from the time of initial dosing until the Follow Up Visit must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (After the Follow Up Visit, any SAE that the Investigator considers related to study drug must be reported to the Medpace Clinical Safety or the Sponsor/designee).

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at Medpace safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed in

Section 13.2 Address List) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information:

Medpace Clinical Safety
Medpace SAE reporting line – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
Email: Medpace-safetynotification@medpace.com

9.3.2 Follow-up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

9.4 Pregnancy Reporting

If a subject becomes pregnant during the treatment period, the Investigator is to stop dosing with study drug immediately.

A pregnancy is not considered to be an adverse event or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male subject becomes pregnant while the subject is receiving study drug or within the safety follow-up period defined in the protocol, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

9.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSAR) that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), Health Canada, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA, applicable competent authorities concerned, and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to Study MAU868-201.

9.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- Overdose: Refers to the administration of a quantity of a study drug given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the subject has taken additional dose(s) or the Investigator has reason to suspect that the subject has taken additional dose(s).
- Misuse: Refers to situations where the study drug is intentionally and inappropriately used not in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- Abuse: Is defined as persistent or sporadic, intentional excessive use of a study drug, which is accompanied by harmful physical or psychological effects.
- Medication error: Is any unintentional error in the prescribing, dispensing, or administration of a study drug by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of subjects missing doses of study drug are not considered reportable as medication error.
- Product complaint: Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to Medpace Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All adverse events associated with these Special Situation reports should be reported as adverse events or SAEs as well as recorded on the adverse event eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information:

Medpace Clinical Safety
Medpace SAE reporting line – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
Email: Medpace-safetynotification@medpace.com

9.7 Data Safety Monitoring Board

An independent data safety monitoring board (DSMB) will review cumulative unblinded safety data as outlined in the DSMB charter.

9.8 Evaluations for Safety

See Section 7, Study Procedures for a description of various tests performed during this study. See Appendix A for a complete list of clinical laboratory analytes and Appendix A, Schedule of Events, for timing of various determinations.

10 STATISTICS

A detailed analysis plan will be described in a separate Statistical Analysis Plan (SAP). The SAP will supersede the protocol in the event of any differences between the 2 documents in the plans for data analysis, and the protocol will be amended if appropriate. The SAP will be included as an appendix in the clinical study report for this protocol.

10.1 General Design and Analysis

This is a randomized, double-blind, placebo-controlled Phase 2 study to assess the safety, tolerability, and efficacy of MAU868 for the treatment of BK viremia in kidney transplant recipients. The study will be conducted at approximately 20 clinical trial sites in the United States and Canada.

The Study includes a Screening Period (up to 10 days), a double-blind, placebo-controlled, randomized Treatment Period (12 weeks) and a Follow-up Period of 24 weeks.

Approximately 36 subjects will be randomized. Cohorts 1, 2 and 3 will randomize subjects to 1 of 2 treatment arms in a ratio of 2:1 (MAU868: placebo). Treatment groups within each cohort are:

Cohort 1

- MAU868 1350 mg IV q28 days for 4 doses
- Placebo (D5W) q28 days for 4 doses

Cohort 2

- MAU868 6750 mg Study Day 1 then 1350 mg IV q28 days for 3 doses (4 doses total)
- Placebo (D5W) q28 days for 4 doses

Cohort 3

- MAU868 6750 mg IV q28 days for 4 doses
- Placebo (D5W) q28 days for 4 doses

10.2 Determination of Sample Size

This study will randomize approximately 36 subjects (12 per cohort) to MAU868 and placebo in a 2:1 ratio (24 MAU868 and 12 placebo; 8 MAU868 and 4 placebo per cohort). This study is not powered to an efficacy endpoint. The number of subjects chosen will provide data useful in determining proof of concept.

10.3 Analysis Populations

The primary efficacy analysis will be performed in the modified ITT (MITT) analysis population. The MITT includes subjects who meet all of the following criteria:

- Received at least 1 dose of study drug.
- Has at least 1 post baseline plasma BKV PCR result available.

Additional analyses will be performed in the intent-to-treat (ITT) analysis population (all subjects randomized). The safety population will include all subjects who received at least 1 dose of study drug. The PK population will include all subjects with at least 1 post baseline PK sample available.

10.4 Safety Analysis

The primary objective of this study is to assess the safety and tolerability of MAU868 as measured by adverse events, vital signs (blood pressure, pulse rate, body temperature, oxygen saturation), ECG, and laboratory measurements.

10.5 Efficacy Analysis

Efficacy objectives of this study are secondary and include:

- To assess the impact of MAU868 on BKV related outcomes including viremia, BKV nephropathy, graft function and rejection among renal transplant patients with BK viremia

- To assess the pharmacokinetics of MAU868

Exploratory:

- To investigate the potential immunogenicity of MAU868
- To investigate genotypic resistance

10.5.1 Efficacy Endpoints

The efficacy endpoints for this study are:

- Time (weeks) to decrease of BKV plasma viral load by 1 log
- Time (weeks) to decrease of BKV plasma viral load to < lower limit of detection
- Proportion of subjects with > 1 log decrease of BKV plasma viral load at 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks, and 36 weeks
- Proportion of subjects with BKV plasma viral load to < lower limit of detection at 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks, and 36 weeks
- Rate of decrease in BKV plasma viral load over time.
- Change in eGFR from baseline to Week 12 and from baseline to Week 36 calculated using CK-EPI
- Proportion of subjects with BKV nephropathy
- Proportion of subjects with graft failure
- Proportion of subjects with acute rejection
- Survival

Exploratory:

- Presence of anti-drug antibodies (ADA)
- Presence of genotypic resistance

Statistical Methods

Efficacy Analyses

In all efficacy analyses, the placebo subjects from the cohorts will be combined. Thus, the analysis models will include treatment group (four levels: placebo, low dose, medium dose, high dose) as a factor. Time-to-event endpoints will be analyzed using Cox proportional hazards regression models. Proportion endpoints will be analyzed using logistic regression models. Quantitative endpoints will be analyzed using one-way analysis of variance (ANOVA) models. In all analyses, pairwise contrasts comparing each of the three active groups to the combined placebo group will be tested. All efficacy analyses will be conducted using two-sided tests at the alpha=0.05 level of significance, with no adjustment for multiplicity.

Additional efficacy analyses will be conducted using the data from each cohort. Quantitative endpoints will be analysed using the two-sample t test and proportion endpoints will be analysed using Fisher's exact test. Due to the small sample sizes, time-to-event variables will be summarized descriptively. Details of the data and process for the interim analyses will be described in the Statistical Analysis Plan and SSRC Charter.

Safety Analyses

All safety analyses will be performed on data from the Safety Analysis Population. Adverse events (AEs), vital signs, ECGs and clinical laboratory evaluations will be summarized by appropriate descriptive statistics.

Pharmacokinetic Analysis

MAU868 levels in serum will be determined by a validated ELISA-based method. A detailed description of the method used will be included in the PK bioanalytical data report. The anticipated LLOQ is 50.0 ng/mL. Concentrations will be expressed in mass per volume units (e.g., ng/mL). Missing values or those concentrations below the LLOQ will be labeled as such in the data listings and reported as "zero" in data presentations and calculations.

MAU868 serum concentration data will be listed by subject and visit/sampling time point. Descriptive summary statistics of trough levels will be provided by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics.

10.6 Disposition, Demographics and Baseline Characteristics

Enrollment and randomization, protocol deviations, disposition and demographic data will be summarized and listed by treatment group Continuous variables will be summarized by treatment group and combined using traditional statistics such as number of subjects, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized using frequency counts and percentages.

No inferential testing will be performed.

10.7 Concomitant Medications

Prior and concomitant medications will be identified using the most current version of the WHO Drug dictionary. The incidence of prior and concomitant medications will be summarized.

10.8 Safety

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory results, and ADA results will be summarized and listed by treatment group.

10.8.1 Vital Signs

All vital signs data will be listed by treatment, subject, and visit/time and if normal ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

10.8.2 ECG Evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

10.8.3 Clinical Laboratory Evaluations

All laboratory data will be listed by treatment, subject, and visit/time and abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

10.8.4 Adverse Events

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with adverse events overall, treatment emergent AEs (TEAEs), related TEAEs, TEAEs leading to discontinuation of study drug or study and serious TEAEs will be tabulated by System Organ Class and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

10.8.5 Pharmacokinetics

Population PK will be performed on all subjects. The PK analysis of MAU868 plasma concentration data will be performed using validated software in order to derive the population mean (and variance) values of specific PK parameters. Plasma concentrations will be summarized descriptively by time point of collection.

The PK endpoints for MAU868 are: area under the concentration-time curve to the end of the dosing period ($AUC_{0\text{-}24}$), area under the concentration-time curve up to the last measurable concentration ($AUC_{0\text{-}last}$), concentration at the end of infusion (C_{eoi}) and minimum concentration observed (C_{trough}). Plasma samples for pharmacokinetic (PK) evaluations will be collected at the time points described in the Schedule of Events (Appendix A).

Results of the PK analysis will be reported separately.

10.8.6 Interim Analysis

Interim Analyses

Following completion of the 12-week treatment period of Cohort 1, unblinded safety and tolerability data (adverse events, clinical laboratories, vitals/physical exams and ECGs), efficacy data (BKV viral load in the plasma) and PK (MAU868 plasma levels) will be reviewed by the Sponsor Study Review Committee (SSRC). The treatment assignment in Cohort 1 will be unblinded; however, these data will not include associated subject or site identifiers. The objectives of this interim analysis are to evaluate whether four doses MAU868 1350 mg IV administered every 28 days for a total of 4 doses demonstrate:

- safety and tolerability signals compared to placebo
- a decrease in BK plasma viral load compared to placebo
- predicted MAU868 plasma levels

The conclusions from this first analysis will be used by the Sponsor to evaluate the safety and efficacy of MAU868 early-on in this first-in-patient study. Unless a significant safety issue related to administration of MAU868 has been identified, the conclusions will have no impact on Cohort 2 or the study's design.

Following completion of the 12-week treatment periods for Cohorts 1 and 2, cumulative unblinded data from both cohorts will be reviewed for safety and tolerability (adverse events, clinical laboratories, vitals/physical exams and ECGs), efficacy (BKV viral load in the plasma) and PK (MAU868 plasma levels). The treatment assignments will be unblinded; however, these data will not include associated subject or site identifiers. The objectives of this second interim analysis are to evaluate whether four doses MAU868 1350 mg IV administered every 28 days for a total of 4 doses or MAU868 6750 mg IV administered as a first dose followed by 3 more doses of MAU868 1350 mg IV administered every 28 days demonstrate:

- safety and tolerability signals compared to placebo
- a decrease in viral load compared to placebo
- predicted MAU868 plasma levels

Based on the SSRC's safety, efficacy and PK conclusions for Cohorts 1 and 2, the dosing regimen for Cohort 3 may be *adjusted* in dosage and/or duration; however, the dosage and duration for Cohort 3 will not exceed the dose already specified in the protocol. Cohort 3 will not be opened for screening and enrollment this evaluation has been completed

11 DATA MANAGEMENT AND RECORD KEEPING

11.1 Data Management

11.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

11.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

11.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

11.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and adverse events
- World Health Organization Drug Dictionary for prior and concomitant medications

11.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries. The eCRFs must be reviewed and electronically signed by the Investigator.

11.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study drug, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or

destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

12.1 Ethical Conduct of the Study

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

12.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, informed consent form (ICF), advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and International Council for Harmonization (ICH) Guidelines require that approval be obtained from an IRB/IEC prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject must be approved by the IRB/IEC.

No drug will be released to the site for dosing until written IRB/IEC authorization has been received by the Sponsor.

12.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

12.4 Subject Card

On enrollment in the study, the subject will receive a subject card to be carried at all times. The subject card will state that the subject is participating in a clinical research study, type of treatment, and contact details in case of an SAE.

12.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, Directive 2001/20/EC, applicable regulatory requirements, and the Declaration of Helsinki and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, IB, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

12.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Subjects may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

12.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations,

or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

12.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

12.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out subject liability insurance for all subjects who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

12.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (i.e., initiation of study centers) when the CTA and favorable Ethics opinion have been received.

13 STUDY ADMINISTRATIVE INFORMATION

13.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

13.2 Address List

13.2.1 Sponsor

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13.2.2 Contract Research Organization

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Appendix A: Schedule of Events

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible.

	Pre-treatment[1,7]	Treatment Period[2] (12 weeks)										Follow-up Period[3] (24 weeks)		
Visit Name	**Screening**	**Baseline**	**Tx1**	**Tx2**	**Tx3**	**Tx4**	**Tx5**	**Tx6**	**Tx7**	**Tx8**	**Tx9**	**FU1**	**FU2**	**FU3/ET**
Study Weeks		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**16**	**20**	**36**
Study Days	**-10 to -1**	**1[4]**	**7**	**14**	**21**	**28**	**35**	**42**	**56**	**70**	**84**	**112**	**140**	**252**
Informed consent	X													
I/E criteria	X	X												
Medical history	X													
KDPI[5]	X													
Prior and concomitant medications[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography	X													
Randomization[7]		X												
Dose administration[4,8]		X				X			X		X			
Urine for BKV PCR and resistance testing[9]		X[10]	X	X	X	X	X	X	X	X	X	X	X	X
Plasma for BKV PCR and resistance testing[11]	X	X[10]	X	X	X	X	X	X	X	X	X	X	X	X
PK sample[12,]		X[13]	X	X	X	X[14]			X[14]		X[13]	X	X	X
Anti-drug antibodies[10]		X[10]				X			X		X	X	X	X
Anti-donor antibodies[15]														
Pregnancy test[16]	X					X			X		X			X
Vital signs[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body height	X													
Body weight	X	X				X			X		X			X
Physical examination	X										X			X
ECG (12-lead)[18]		X									X			X

	Pre-treatment[1,7]	Treatment Period[2] (12 weeks)										Follow-up Period[3] (24 weeks)		
Visit Name	**Screening**	**Baseline**	**Tx1**	**Tx2**	**Tx3**	**Tx4**	**Tx5**	**Tx6**	**Tx7**	**Tx8**	**Tx9**	**FU1**	**FU2**	**FU3/ET**
Study Weeks		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**16**	**20**	**36**
Study Days	**-10 to -1**	**1[4]**	**7**	**14**	**21**	**28**	**35**	**42**	**56**	**70**	**84**	**112**	**140**	**252**
Blood and urine for safety[19]		X[10]		X		X			X		X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BKV BK virus; PCR polymerase chain reaction; PK pharmacokinetic; ECG electrocardiogram

1. Protocol specific procedures should not be performed until the subject has consented to participation in the study. However, assessments and procedures performed as part of standard of care prior to informed consent, including determination of BK viral load in plasma may be used to qualify a subject for the study.
2. During the treatment period, subjects should be seen approximately every 7 days (+/-3 days) during the first 6 weeks and approximately every 14 days (+/-5 days) for the duration of treatment. Subjects may be seen more often at the Investigator's discretion. Visit dates are determined from the Baseline Visit.
3. During the follow-up period, if the subject cannot be seen on the precise protocol-defined study day, the acceptable visit window is +/10 days.
4. Study Day 1 is the calendar day on which the first dose of study drug is administered. Subsequent study days are based on calendar days.
5. The information necessary for determining the KDPI includes *donor* age, height, weight, ethnicity, history of hypertension, history of diabetes mellitus, cause of death, serum creatinine, hepatitis C serostatus, and whether donation occurred after circulatory death.
6. Record any and all immunosuppressive medication from induction to randomization as well as any other medications taken during the 10 days prior to randomization.
7. Randomization should occur as soon as possible after confirmation of qualifying viremia but not more than 10 days after the qualifying sample was collected. Dosing of study drug should occur as soon as possible after randomization.
8. In the event that a subject requires hemodialysis, plasmapheresis, or immunoadsorption treatments; if <15 days since last MAU868/placebo treatment another dose will be given as soon as possible, and the next scheduled monthly dose skipped. Regular dosing will occur the following month. If the last dose was 15 days or greater no interim dose will be administered and the regular monthly scheduled will be followed. No subject will receive more than 4 doses.
9. A sufficient amount of urine should be collected at each assessment to accommodate three tests; one for BKV DNA PCR, one for possible genotypic resistance testing and a back up sample. Refer to the study's Laboratory Manual for volume requirements.
10. On Study Day 1 collect samples for BKV PCR, antidrug antibodies, and safety labs prior to administration of first dose of MAU868. Refer to the study's Laboratory Manual for collection requirements.
11. After screening, plasma samples should be collected and sent to the central laboratory at each assessment for BKV DNA PCR, possible genotypic resistance testing and a backup sample. During screening, only BKV PCR is required and may be performed by the laboratory used by the site for usual clinical care, or sent to the central lab for testing. Refer to the study's Laboratory Manual for volume requirements.
12. In the event subject undergoes hemodialysis, plasmapheresis, or immunoadsorption treatment, a PK sample should be collected prior to and following the respective treatment.

13. Three PK samples should be collected on Study Day 1 (first dose administration) and Study Day 84 (last dose administration) : within approximately 30 minutes prior to the start of the infusion, within approximately 30 minutes following the end of the infusion and between approximately 3-6 hours after the end of infusion.
14. On Study days 28 and 56 (2^{nd} and 3^{rd} dose administrations), two PK samples should be collected: within 30 minutes prior to the start of infusion and within 30 minutes following the end of infusion.
15. Any anti-donor antibodies collected by the site should be recorded in the eCRF, but collection is not mandatory.
16. Only for females of child-bearing potential. A negative urine or serum pregnancy test performed locally within 96 hours prior to Study Day 1 (Baseline). Local urine dipstick or serum pregnancy testing should be performed before infusions #2 on Day 28, #3 on Day 56 and #4 on Day 84.
17. Vital signs (temperature, blood pressure, heart rate, respiratory rate and oxygen saturation) should be obtained at each visit if the visit is in person. If the visit is not in person vital signs are not required. On drug infusion days, vitals should be taken within 30 minutes before starting the infusion, and then approximately every 30 minutes (+/- 10 minutes) after the start of the infusion until at least 2 hours after completing the infusion.
18. ECGs should be performed prior to dose administration on Study Day 1 and after dose administration on Study Day 84 and on Day 252 (or at the Early Termination Visit)
19. Blood and urine for safety should be collected and sent to the central laboratory. Laboratory tests used in for the management and monitoring of the subject per standard practice may be performed at the local laboratory at the Investigator's discretion.

Appendix B: Clinical Safety Laboratory Analytes

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Bilirubin (total, direct, and indirect)
Total protein	Uric acid

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential [1]	

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Coagulation

Prothrombin time	International normalized ratio (INR)
Activated Partial Thromboplastin Time (aPTT)	

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

2. Microscopy is performed only as needed based on positive dipstick test results.

Other Tests

Urine or serum pregnancy test [1]	

1. Women of childbearing potential only.

Appendix C: PK Sample Schedule

PK Draws	Within ~30min Prior to Infusion	Within ~30min following Infusion End	3-6 hours Post Dose Infusion	Non-Dose Visit PK Draw
Day 1	X	X	X	
Day 7				X
Day 14				X
Day 21				X
Day 28	X	X		
Day 35				
Day 42				
Day 56	X	X		
Day 70				
Day 84	X	X	X	
Day 112				X
Day 140				X
Day 252				X

Samples collected prior to and during infusion should be collected within *approximately* 30 minutes of specified timepoints.

Appendix D: CTCAE 5

Section 3.3.2 of the protocol outlines criteria for discontinuation from study drug. All treatment-related SAEs and certain treatment-related AEs and treatment-related laboratory abnormalities should result in immediate discontinuation from study drug. Re-challenge is not permitted.

Determination of whether an individual treatment related non-serious AE and/or treatment related laboratory abnormality should prompt discontinuation of study drug depends on the severity of the AE and laboratory abnormality based on Common Terminology Criteria for Adverse Events (CTCAE) version 5 grade.

Note that the following requires immediate discontinuation of study drug:

- Treatment-related AEs of Grade 3 or higher (including infusion reactions) except for cytokine release syndrome and serum sickness where a severity grade of 2 or higher should prompt discontinuation. CTCAE criteria for infusion related reactions, cytokine release syndrome, and serum sickness are below. The complete CTCAE criteria for other treatment related AEs may be accessed at the following website: (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

- Clinically significant treatment-related laboratory abnormality Grade 3 or higher. CTCAE criteria for laboratory abnormalities (i.e., investigations) are also displayed below.

INFUSION RELATED REACTION:

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Infusion related reaction	Mild transient reaction; interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption f infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.

CYTOKINE RELEASE SYNDROME:

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% O2	Hypotension managed with one pressor; hypoxia requiring >40% O2	Life-threatening consequences: urgent intervention indicated	Death

Definition: disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.

Navigational Note: Also consider reporting other organ dysfunctions including neurological toxicities such as: Psychiatric disorders: Hallucinations or Confusion; Nervous system disorders: Seizure, Dysphasia, Tremor, or Headache.

SERUM SICKNESS:

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia: fever, rash, urticaria, antihistamines indicated	Sever arthralgia or arthritis; extensive rash; steroids or IV fluids indicated	Live-threatening consequences; pressor or ventilatory support indicated	Death

Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately six to twenty-one days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort and dyspnea.

Navigational Note: -

INVESTIGATIONS:

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Activated partial thromboplastin time prolonged	>ULN – 1.5 x ULN	>1.5 – 2.5 x ULN	>2.5 x ULN; bleeding	-	-

Definition: A finding based on laboratory test results in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.

Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alanine aminotransferase increased	>ULN – 3.0 x ULN if baseline was normal; 1.5 – 3.0 x baseline if baseline was abnormal	>3.0 – 5.0 x ULN if baseline was normal; >3.0-5.0 baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	

Definition: A finding based on laboratory results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.

Navigational Note: Also consider Hepatobiliary disorders: Hepatic failure

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alkaline phosphatase increased	>ULN – 2.5 x ULN if baseline was normal; 2.0 – 2.5 x baseline if baseline was abnormal	>2.5 – 5.0 x ULN if baseline was normal; >2.5-5.0 baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in blood specimen.

Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Aspartate aminotransferase increased	>ULN – 3.0 x ULN if baseline was normal; 1.5-3.0 x baseline if baseline was abnormal	>3.0 – 5.0 x ULN if baseline was normal; >3.0-5.0 baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

Definition: A finding based on laboratory test results that indicate an increase in the level of aminotransferase (ALT or SGPT) in blood specimen.

Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicate		-

Definition: A finding based on laboratory test results that indicate abnormal levels of antidiuretic hormone in the blood specimen.

Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood bicarbonate decrease	<LLN and no intervention initiated	-	-	-	-

Definition: A finding based on laboratory test results that indicate a decrease in levels of bicarbonate in a venous blood specimen.

Navigational Note: Also consider Metabolism and nutrition disorder: Acidosis or Alkalosis

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood bilirubin increased	>ULN – 1.5 x ULN if baseline was normal; > 1.0 – 1.5 x baseline if baseline was abnormal	>ULN – 1.5 -3.0 x ULN if baseline was normal; > 1.5 – 3.0 x baseline if baseline was abnormal	>ULN – 3.0 – 10.0 x ULN if baseline was normal; > 3.0 – 10.0 x baseline if baseline was abnormal	> 10.0 ULN if baseline was normal; > 10.0 x baseline if baseline was abnormal	

Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin ins associated with Jaundice.

Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-

Definition: a finding based on laboratory test results that indicate a decrease in levels of corticotrophin in a blood sample.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood gonadotrophin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL		

Definition: A finding based on laboratory test results that indicate abnormal levels of gonadotrophin hormone in a blood specimen.

Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood lactate dehydrogenase increased	>ULN	-	-	-	-

Definition: A finding based on laboratory test results that indicate increased levels of lactate dehydrogenase in a blood specimen.

Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood prolactin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADLs	-	-	-

Definition: A finding based on laboratory test results that indicate abnormal levels of prolactin hormone in a blood specimen.

Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Carbon monoxide diffusing capacity decrease	3-5 units below LLN; for follow-up, a decrease of 3-5 units (ml/min/mm Hg) below the baseline value; asymptomatic and intervention not indicated	6-8 units below LLN; for follow--up, an asymptomatic decrease of >5 – 8 units (ml/min/mm Hg) below the baseline value; symptomatic and intervention no indicated	Asymptomatic decrease of >8 units drip; >5 units drop along with the presence of pulmonary symptoms (e.g., >Grade 2 hypoxia or >Grade 2 dyspnea); intervention indicated	-	-

Definition: A finding based on lung function test results that indicate a decrease in the lung capacity to absorb carbon monoxide.

Navigational Note: Also consider Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Ejection fraction decreased	-	Resting ejection fraction (EF) 50-40%; 10 -19% drop from baseline	Resting ejection (EF) 39 – 20%; >=20% drop from baseline	Resting ejection fraction (EF) < 20%	-

Definition: The percentage computed when the amount of blood effected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.
Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Electrocardiogram QT corrected interval prolonged	**Average** QTc 450 – 480 ms	**Average** QTc 481 – 500 ms	Average QTc >=501ms; >60 ms change from baseline	Torsade dep pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	-

Definition: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval
Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Electrocardiogram T wave abnormal	T wave flattening	Nonspecific ST segment change	-	-	-

Definition: A disorder characterized by Electrocardiogram T wave amplitude changes.
Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fibrinogen decreased	<1.0 – 0.5 x LLN; if abnormal, <25% decrease from baseline	<0.75 – 0.5 x LLN; if abnormal 25 – 50% decrease from baseline	<0.5 – 0.25 x LLN; if abnormal, 50-75% decrease from baseline	,0.25 x LLN 5% decrease from baseline; absolute value <50mg/dl	-

Definition: A finding based on laboratory test results that indicate a decrease in levels of fibrinogen in a blood specimen.
Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Forced expiratory volume decreased	FEV1% (percentages of observed FEV1 and FVC related to their respective predicted values) 99-70% predicted	FEV1 60-69%	50-59%	<=49%	-

Definition: A finding based on test results that indicate a relative decrease in the fraction of the forced vital capacity that is exhaled in a specific number of seconds.
Navigational Note: Also consider Respiratory, thoracic and mediastinal disorder: Respiratory failure or Dyspnea

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
GGT increased	>ULN – 2.5 x ULN if baseline was normal; 2.0-2.5 x baseline if baseline was abnormal	>ULN – 2.5 – 5.0 x ULN if baseline was normal; 2.5-5.0 x baseline if baseline was abnormal	>ULN – 5.0 – 20.0 x ULN if baseline was normal; > 5.0 – 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

Definition: A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.
Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	-	-	-

Definition: A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen.
Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Haptoglobin decreased	<LLN	-	-	-	-

Definition: A finding based on laboratory test results that indicate a decrease in levels of haptoglobin in a blood specimen.
Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-	-

Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin above normal.
Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
INR increased	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding	-	-

Definition: A finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood.
Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-

Definition: A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen.
Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Lymphocyte count decreased	<LLN -800/mm3; <LLN- 0.8x 10e9/L	<800 - 500/ mm3; <LLN- 0.8 -0.5 x 10e9/L	<500 - 200/ mm3; <0.5 - 0.2 x 10e9/L	<200/mm3; <0.2 x 10e9/L	-

Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.
Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-

Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.
Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophil count decreased	<LLN - 1500/ mm3; <LLN - 1.5 x 0e9/L	<1500 - 1000/ mm3; <1.5 - 1.0 x 10e9/L	<1000 - 500/ mm3; <1.0 - 0.5 x 10e9/L	<500/mm3; <0.5 x 10e9/L	-

Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.
Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-

Definition: A finding based on laboratory test results that indicate a decrease in levels of pancreatic enzymes in a biological specimen.
Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
White Blood cell decreased	<LLN – 3000/ mm3; <LLN – 3.0 x 10e9/L	<3000 – 2000/ mm3; <3.0 – 2.0 x 10e9	<2000 -1000/ mm3; <2.0 – 1.0 x 10e9/L	<1000/mm3; <1.0 x 10e9/L	-

Definition: a finding based on laboratory test results that indicate a decrease in number of white blood cells in a blood specimen.

Navigational Note: -

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Investigations – Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal. Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Sever or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicate; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death