CLINICAL STUDY PROTOCOL

A Randomized, Placebo-Controlled, Phase 2 Study of HB-101, a Bivalent Cytomegalovirus (CMV) Vaccine, in CMV-Seronegative Recipient (R-) Patients Awaiting Kidney Transplantation from Living CMV-Seropositive Donors (D+)

Investigational Product: HB-101
Protocol Number: H-100-002

Sponsor:
Hookipa Biotech GmbH
Helmut-Qualtinger-Gasse 2
1030 Vienna
Austria

IND Number: 017938
EudraCT Number: 2017-005047-32
Version Number: 6.0
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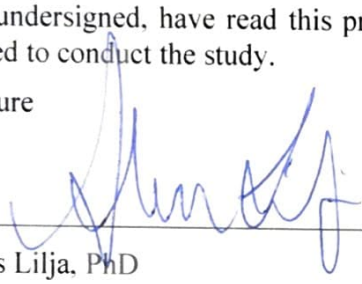
Global Amendment 1: 26 June 2019
Global Amendment 2: 07 November 2019
Global Amendment 3: 09 December 2020

SIGNATURE PAGE

STUDY TITLE: A Randomized, Placebo-Controlled, Phase 2 Study of HB-101, a Bivalent Cytomegalovirus (CMV) Vaccine, in CMV-Seronegative Recipient (R-) Patients Awaiting Kidney Transplantation from Living CMV-Seropositive Donors (D+)

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

Signature



Date

09-Dec-2020

Anders Lilja, PhD
Therapeutic Area Head, Infectious Diseases
Hookipa Biotech GmbH
Telephone: + 43 676846674310

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 Hookipa Biotech GmbH 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 Hookipa Biotech GmbH 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 Hookipa Biotech GmbH, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethics Committee Regulations, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Randomized, Placebo-Controlled, Phase 2 Study of HB-101, a Bivalent Cytomegalovirus (CMV) Vaccine, in CMV-Seronegative Recipient (R-) Patients Awaiting Kidney Transplantation from Living CMV-Seropositive Donors (D+)

PROTOCOL NUMBER: H-100-002

INVESTIGATIONAL PRODUCT: HB-101

PHASE: 2

INDICATION: Prevention of clinically significant CMV infection, defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV preemptive therapy based on documented CMV viremia and the clinical condition of the patient.

TREATMENT ARMS:

Groups 1 and 2 will be *stratified* by treatment intent (as per investigator and institutional standards) regarding the use of anti-CMV anti-virals post-transplantation. Each group will be *randomized* into 2 arms to receive either HB-101 or placebo:

- Group 1: Patients to be followed preemptively post-transplant:
  - Arm 1a: CMV seronegative (-) patients awaiting kidney transplant from a CMV seropositive (+) living donor randomized to receive HB-101 before transplant, and monitoring after transplant.
  - Arm 1b: CMV seronegative (-) patients awaiting kidney transplant from a CMV seropositive (+) living donor randomized to receive placebo before transplant, and monitoring after transplant.
- Group 2: Patients to be treated prophylactically with anti-virals post-transplant:
  - Arm 2a: CMV seronegative (-) patients awaiting kidney transplant from a CMV seropositive (+) living donor to receive HB-101 before transplant, and anti-viral prophylaxis and monitoring after transplant.
  - Arm 2b: CMV seronegative (-) patients awaiting kidney transplant from a CMV seropositive (+) living donor to receive placebo before transplant, and anti-viral prophylaxis and monitoring after transplant.

Group 3 will enroll CMV seropositive (+) patients awaiting kidney transplant from a CMV seropositive (+) or CMV seronegative (-) living donor. Patients will receive HB-101 vaccination(s) prior to their transplant surgery. Post-transplant CMV management will follow either preemptive or prophylactic care as defined at study enrollment by the investigator and institutional standards.

OBJECTIVES:

The study objectives and endpoints are listed in the table below.

Study Objectives	Endpoints
Primary	
To assess the safety and reactogenicity of HB-101	Assessed by treatment group for Groups 1 and 2 and open-label HB-101 for Group 3 and by number of vaccinations: • Incidence and severity of AEs, SAEs, and changes in laboratory values • Incidence and severity of localized or generalized injection site reactions
To assess the immunogenicity of HB-101	Descriptive central statistics will be presented by treatment group for Groups 1 and 2 and open-label HB-101 for Group 3 and by post-transplant CMV management strategy (prevention or preemption) for the following immunogenicity parameters: • CMV neut • CMV ELISPOT pp65 • CMV ELISPOT gB
Secondary	
To assess the efficacy of the administration of at least 2 doses of HB-101 compared to that of placebo in mitigating CMV DNAemia/viremia for CMV seronegative (-) recipients awaiting kidney transplantation from a CMV seropositive (+) donor and followed by CMV preemptive therapy post-transplant	• Incidence and time to clinically significant CMV infection, CMV disease, and CMV syndrome • Incidence and time to CMV viremia requiring anti-viral therapy • Incidence and duration (in days) of anti-CMV therapy courses (at therapeutic doses) required • Incidence and time to quantifiable CMV DNAemia, peak CMV DNAemia level, and duration of CMV DNAemia above the limit of quantitation • Incidence and time to graft failure and organ rejection
To assess the efficacy of the administration of at least 2 doses of HB-101 compared to that of placebo in decreasing the use of anti-virals at treatment dose for CMV seronegative (-) recipients awaiting kidney transplantation from a CMV seropositive (+) donor and to be treated prophylactically for CMV post-transplant	
To assess the efficacy of the administration of at least 2 doses of HB-101 in CMV seropositive (+) recipients awaiting kidney transplant and followed by CMV post-transplant preemptive management or prophylactic anti-viral therapy	
Exploratory	
To assess additional immunogenicity parameters of HB-101	Descriptive central statistics will be presented by treatment group for Groups 1 and 2 and open-label HB-101 for Group 3 and by post-transplant CMV management strategy (prevention or preemption) for the following immunogenicity parameters: • LCMV neutralizing antibody • CMV ICS pp65 • CMV ICS gB • LCMV ELISPOT NP

AE = adverse event; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; ELISPOT = enzyme-linked immunospot; gB = glycoprotein B; ICS = intracellular cytokine staining; LCMV = lymphocytic choriomeningitis virus; neut = neutralization; NP = nucleoprotein; pp65 = phosphoprotein 65 kD; SAE = serious adverse event.

All efforts will be made to assess the immunogenicity analyses listed in the primary and exploratory objectives. There could be circumstances when a decision is made to not conduct or

to discontinue immunogenicity analyses due to practical or strategic reasons (e.g., not enough blood volume collected from the patient).

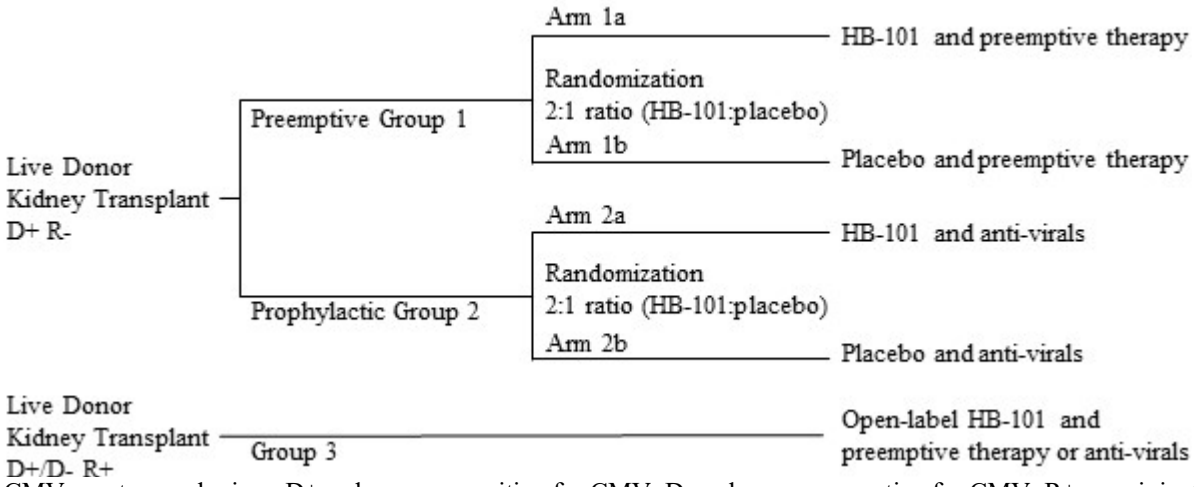
POPULATION:

Adult CMV seronegative (-) patients awaiting kidney transplant from a CMV seropositive (+) living donor (Groups 1 and 2) and adult CMV seropositive (+) patients awaiting kidney transplant from a CMV seropositive (+) or CMV seronegative (-) living donor (Group 3), recruited globally from specified transplant centers. Approximately 150 patients will be enrolled.

STUDY DESIGN AND DURATION:

This Phase 2 study of HB-101, a bivalent CMV vaccine, in patients awaiting kidney transplantation includes a randomized, placebo-controlled portion (Groups 1 and 2) and an open-label portion (Group 3).

High-Level Study Schematic



CMV = cytomegalovirus; D+ = donor seropositive for CMV; D- = donor seronegative for CMV; R+ = recipient seropositive for CMV; R- = recipient seronegative for CMV.

For Groups 1 and 2, adult CMV seronegative (-) patients awaiting kidney transplant from a CMV seropositive (+) living donor will be enrolled according to treatment intent with regard to the method of CMV prevention after transplant (either preemptive or prophylactic) as defined at study enrollment by the investigator and institutional standards.

Patients enrolled into Groups 1 and 2 should have a living donor kidney transplantation ideally planned between 2 to 4 months after the first injection of study drug (HB-101 or placebo).

- Group 1 - The preemptive group will be randomized in a 2:1 ratio (HB-101:placebo) to receive either HB-101 or placebo before transplant. Post-transplant patients will be monitored per preemptive institutional standards.
- Group 2 - The prophylactic group will be randomized in a 2:1 ratio (HB-101:placebo) to receive either HB-101 or placebo before transplant. Post-transplant patients will receive 3 to 6 months of anti-viral prophylaxis following institutional standards.

Enrollment of Group 2 will be limited to no more than 54% of total patients.

For Group 3, adult CMV seropositive (+) patients awaiting kidney transplant from a CMV seropositive (+) or CMV seronegative (-) living donor will be enrolled into Group 3. Post-transplant CMV management will follow either preemptive or prophylactic care as defined at study enrollment by the investigator and institutional standards.

Patients enrolled into Group 3 should have a kidney transplant from a living donor planned between 2 to 4 months after the first injection of HB-101. Patients in Group 3 will receive HB-101 vaccination(s) prior to their transplant surgery. Enrollment of Group 3 will be a minimum of 15% of total patients.

Patients receiving at least 2 doses of study drug before transplant will be included in the statistical analysis of the efficacy endpoints.

The patient will complete and conclude the study on whichever day of the study one of the following events first occurs:

- When the patient completes the study follow-up (12 months post-transplant).
- If for some reason kidney transplant has not occurred by 12 months after the first dose of study drug (HB-101 or placebo).
- If the patient experiences graft failure requiring removal of the transplanted organ or returns to dialysis.
- If the patient is withdrawn or withdraws from the study.
- If the patient is lost to follow-up.
- If the patient dies.

The total duration of the study for each patient participating in the study will be approximately 15 months.

The dosing schedule relative to transplantation is listed in the table titled "Timing of Kidney Transplant vs. Study Drug (HB-101 or Placebo) Injection, Where Day 0 is the Day of First Dose of Study Drug."

Study drug is defined as either HB-101 or placebo.

Timing of Kidney Transplant vs. Study Drug (HB-101 or Placebo) Injection, Where Day 0 is the Day of First Dose of Study Drug

Timing of Kidney Transplant	Number of Injections Planned	Timing of Study Drug Injection
Prior to Day 34	1*	Day 0
Between Day 35 and Day 62	2	Day 0 and Day 28**
Between Day 63 and Day 90 or Between Day 91 and Day 120	3	Day 0, Day 28**, and Day 56** or Day 84**

*Patients who received only 1 dose of study drug will be excluded from the mITT Population for efficacy analysis.
**After Day 0 dose administration, a timeframe of ±7 days from scheduled day of dosing is allowed.
mITT = modified Intent-to-Treat; Day 0 = day of first dose of study drug; Day 28 = 28 days after the first dose of study drug; Day 34 = 34 days after the first dose of study drug; Day 35 = 35 days after the first dose of study drug; Day 56 = 56 days after the first dose of study drug; Day 62 = 62 days after the first dose of study drug; Day 63 = 63 days after the first dose of study drug; Day 84 = 84 days after the first dose of study drug; Day 90 = 90 days after the first dose of study drug; Day 91 = 91 days after the first dose of study drug; Day 120 = 120 days after the first dose of study drug.

In brief, it is the intent of this study to administer up to 3 doses of study drug (HB-101 or placebo) prior to transplantation and within proximity to the time of transplantation. However, 2 doses of

study drug before transplant will be sufficient for the patients to be included in the efficacy analyses if a third dose of study drug is not feasible due to transplantation timelines. Patients will not receive study drug after transplantation.

After Day 0 dose administration, the subsequent study drug administration(s) should be given 28 days (±7 days) apart.

Patients whose planned transplantation is less than 35 days from the planned first study drug (HB-101 or placebo) injection should not be enrolled.

A minimum of 7 days (±2 days) must be planned between the last dose of study drug and transplantation, unless agreed otherwise between the sponsor and investigator on a case-by-case basis.

Patients whose planned transplantation is no longer than 4 months from the time of the first study drug (HB-101 or placebo) injection should be enrolled. Changes in transplantation timelines will not result in patient withdrawal from the study. In case of delayed transplantation, additional study drug injections prior to transplantation can be discussed with the sponsor or sponsor designee (who should be blinded). The maximum allowed number of patients receiving additional study drug injections prior to transplantation will be capped at 10 patients (less than 10% of planned sample size).

For Groups 1 and 2, in the event that the living donor is not available and a kidney from a CMV seropositive (+) deceased donor becomes available, the patient can continue in the study after transplantation. For Group 3, in the event that the living donor is not available and a kidney from a deceased donor becomes available, the patient can continue in the study after transplantation.

The additional study drug booster will be administered at least 7 days (±2 days) prior to the scheduled transplantation. This allows maximal protection against CMV prior to the transplant. Blood collection for immunogenicity will be performed prior to each study drug booster administered. Immunogenicity will not be used to determine the administration of a booster as these results would be unblinding; instead, reactogenicity will be reviewed and the investigator and sponsor may decide not to administer the booster if there is evidence of increasing reactions with increasing number of vaccinations. The number and timing of vaccinations versus transplantation will be described in the descriptive analyses.

RATIONALE:

Cytomegalovirus is a common opportunistic pathogen in patients who have undergone solid organ transplantation (SOT). The majority of recipients who are seronegative acquire primary infection from a seropositive donor organ. Viral replication in the recipient results in viremia, which can progress to end-organ disease. Active CMV infection correlates with a higher risk of other infections, post-transplant lymphoma, organ rejection, and overall morbidity and mortality. To prevent CMV infection and disease, transplant centers routinely employ either a prophylactic or preemptive strategy using ganciclovir or its oral prodrug valganciclovir. The prophylactic approach is effective in preventing end-organ disease while on anti-viral prophylaxis, but patients remain at significant risk of developing viremia and late-onset disease once prophylaxis is stopped. Sometimes, late-onset disease is caused by strains of CMV that have developed resistance to ganciclovir, which requires the use of more toxic second-line therapies. The preemptive approach

requires close monitoring of CMV DNAemia via polymerase chain reaction (PCR) and is thus often limited by practical considerations, given the need for frequent blood draws.

An effective CMV vaccine administered prior to transplantation would overcome the limitations of both the prophylactic and preemptive approaches. Hookipa Biotech GmbH (hereinafter Hookipa Biotech) completed a Phase 1 healthy volunteer study (Study H-100-001) of the predecessor HB-101 (encoding phosphoprotein 65 kD [pp65] and a truncated glycoprotein B [gB] of human cytomegalovirus [HCMV]).

In brief, Hookipa Biotech observed:

- Neutralizing antibodies formed against the antigen after 2 or 3 vaccinations.
- A favorable safety profile.
- CMV-neutralizing antibodies after 3 vaccinations on par with previously studied vaccines.
- gB- and pp65-specific T-cell immunogenicity previously shown to correlate with protection (in adoptive T-cell transfer studies).

Based on this, Hookipa Biotech anticipates that the vaccine should be more effective than previous vaccines tested in the SOT setting.

Based on the available safety data of the H-100-002 study (data cutoff date of 03 September 2019) (see the latest Investigator's Brochure in circulation), H-100-002 protocol amendment Version 5.0 will include Group 3 to explore additional safety, immunogenicity, and efficacy data in CMV seropositive (+) patients awaiting kidney transplant from a CMV seropositive (+) or CMV seronegative (-) donor. The safety, immunogenicity, and efficacy data collected from this patient population will provide critical information for the registration trial based on the broad population of patients who are at intermediate and high risk of developing clinically significant CMV infections post-transplantation.

PATIENT ELIGIBILITY CRITERIA:

Inclusion Criteria:

Patients who meet all of the following inclusion criteria for their respective groups will be eligible to participate in the study:

1. Male or female patients 18 years of age or older.
2. Patients willing and able to give written informed consent for participation in the study.
3. Patients must be eligible to undergo kidney transplantation from a living donor as per institutional standards.
4. For Groups 1 and 2, patients must be CMV immunoglobulin G (IgG) seronegative (-) and will be receiving a kidney for transplantation from donors who are CMV IgG seropositive (+). (If CMV IgG serology is indeterminate, repeat testing is recommended. If the serology for the donor is indeterminate upon repeat testing, it should be considered positive; if the serology for the recipient is indeterminate upon repeat testing, it should be considered negative).
5. For Group 3, patients must be CMV IgG seropositive (+) and will be receiving a kidney for transplantation from donors who are CMV IgG seropositive (+) or CMV IgG seronegative (-).

Group 3 patients must have documentation of a planned transplant that is scheduled to occur between 2 and 4 months after the first study drug injection.

6. Post-transplant CMV management will follow either a preemptive treatment strategy or prophylactic anti-viral medication(s) (e.g., valganciclovir) per institutional standard of practice.
7. Female patients of childbearing potential can participate in the study if they agree to use highly effective contraception. This applies from the time period between signing of the informed consent form (ICF) and up to 12 months after the last study drug (HB-101 or placebo) injection or up to completion of the study, whichever is longer.

   Highly effective contraception methods include:

   - Total abstinence. Abstinence is acceptable only when this is in line with the preferred and usual lifestyle of the patient (e.g., true abstinence). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Male or female sterilization.
   - Combination of any 2 of the following categories (Categories 1+2, 1+3, or 2+3):
     - Category 1: Use of oral, injected, or implanted hormonal methods of contraception.
     - Category 2: Placement of an intrauterine device or intrauterine system.
     - Category 3: Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository. Note: The use of Category 3 is only acceptable when used in combination with Category 1 or 2.
8. Female patients must have a negative serum or urine human chorionic gonadotropin pregnancy test (urine testing limited to patients producing urine daily) prior to each dose of study drug (HB-101 or placebo), unless the pregnancy test is deemed a false positive and clinical evidence is negative for pregnancy after discussion between the sponsor and investigator on a case-by-case basis; or be surgically or biologically sterile or post-menopausal.

   Post-menopausal females are defined as:

   - Age >50 years with amenorrhea for at least 12 months.
   - Age ≤50 years with 6 months of spontaneous amenorrhea and follicle-stimulating hormone level within post-menopausal range (>40 mIU/mL).
   - Permanently sterilized women (hysterectomy or bilateral oophorectomy).
9. Male patients with sexual partners of childbearing potential can participate in the study if they agree to use barrier contraception from the time period between signing of the ICF and through 3 months after the last dose of study drug.
10. Male patients must agree to refrain from sperm donation from the time period between signing of the ICF and through 3 months after the last dose of study drug.

11. Patients who would comply with the requirements of this protocol (e.g., return for follow-up visits), as judged by the investigator.

Exclusion Criteria:

Patients who meet any of the following criteria will be excluded from the study:

1. Patients who are highly sensitized or who are likely to undergo desensitization at time of transplant (e.g., donor-specific antibody titers at the local laboratory >2000).

   Only patients with no risk or low risk of sensitization defined below should be enrolled, owing to tolerance against the relevant HLA epitopes:

   No Risk:

   Patient HLA genotype includes HLA-A2 *and* HLA-A3 *and* HLA-B7.

   Low Risk:

   Patient HLA genotype includes at least one HLA type from each of the following three groups:

A2	A24	A68	A69

   and

A1	A3	A11	A23	A24	A25	A26	A29	A30	A31	A32	A33	A34	A36	A43	A66	A74	A80

   and

B7	B13	B27	B37	B41	B42	B47	B48	B54	B55	B56	B60	B61	B67	B73	B81

2. Patients planning to undergo multi-organ transplantation.
3. Patients participating in another interventional clinical study.
4. Previous vaccination with an investigational CMV vaccine.
5. Patients with known diagnosis of human immunodeficiency virus.
6. Patients who are pregnant, breastfeeding, or planning to become pregnant during the study.
7. Any Screening safety laboratory value of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN), total bilirubin >2 × ULN, absolute neutrophil count <500 cells/µL, or lymphocyte count <200 cells/µL.
8. Any confirmed or suspected immunodeficiency disorder (based on medical history and physical examination) that could interfere with the immune response or that presents a risk for the patient to receive a vaccine candidate in development.
9. Treatment with any chronic immunosuppressive medication or other immuno-modifying drugs within 6 months prior to study entry (unless agreed otherwise between the sponsor and investigator on a case-by-case basis). However, inhaled and topical steroids and low-dose oral corticosteroids (≤10 mg/day of prednisone or equivalent) are allowed.

10. For Groups 1 and 2 only, patients with prior history of CMV disease or CMV infection requiring anti-viral therapy.
11. For Group 3 only, patients with active CMV infection requiring anti-viral therapy within 30 days prior to the first injection of study drug.
12. Patients with a history of severe allergic reactions and/or anaphylaxis that could interfere with the immune response (including an allergy or hypersensitivity to any ingredient found in the study drug [HB-101 or placebo]) or that presents a risk for the patient to receive a vaccine candidate in development.
13. Patients with a severe coagulation abnormality that would preclude intramuscular injection.
14. Patients with a rash, dermatological condition, or tattoo in the area of the injection site(s) that could interfere with administration site reaction rating. (Note: The injection site(s) can be the non-dominant arm [most preferred injection site], dominant arm, or either thigh [least preferred injection site], as judged by the investigator).
15. History or current evidence of medical disorders or conditions that could prevent the successful completion of the study, as judged by the investigator.
16. It is anticipated that the patient will be unavailable to complete the study follow-up.
17. Fever (≥38°C) occurs within 7 days prior to first dose (unless agreed otherwise between the sponsor and investigator on a case-by-case basis).
18. For patients receiving post-transplant CMV prophylactic therapy management only, patients who will be receiving Cytogam® in their post-transplant CMV prophylaxis regimen.

STUDY VACCINE DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Vaccination schedule/site of administration:

Three intramuscular doses of HB-101 will be administered according to the administration schedule as per the table titled "Timing of Kidney Transplant vs. Study Drug (HB-101 or Placebo) Injection, Where Day 0 is the Day of First Dose of Study Drug."

Note that the injection site(s) can be the deltoid muscle of the non-dominant arm (most preferred injection site), deltoid muscle of the dominant arm, or either thigh (least preferred injection site), as judged by the investigator. In circumstances when administration of two 0.5 mL injections are used, the injections should be at different sites (e.g., both shoulders), or if at the same site, separated by at least 5 cm.

Vaccine composition/dose:

HB-101 has been developed by the sponsor.

HB-101 uses replication-deficient lymphocytic choriomeningitis virus (rLCMV) as a vector for a bivalent recombinant vaccine against HCMV. One vector expresses the pp65 protein of HCMV, and one expresses a truncated gB protein of HCMV. The 2 vectors are produced separately. The final drug product is manufactured by mixing 1 batch of rLCMV pp65 and 1 batch of rLCMV gB in a 1:1 ratio based on pp65- and gB-expressing vectors. HB-101 was produced pre-diluted and ready-to-use.

HB-101 is formulated at 1.2×10^8 focus-forming units/mL. The product is filled in 2 mL

single-dose vials containing 0.7 mL of vaccine. The volume of administration of 1 dose of HB-101 is 1.0 mL.

The quality control standards and requirements for HB-101 are described in separate Quality Assurance documents. The required approvals will be obtained.

The vaccine will be labeled and packaged according to applicable regulatory requirements (European Union Good Manufacturing Practice, Annex 13; and Title 21 of the Code of Federal Regulations Part 201).

The components of HB-101 include water for injection, total rLCMV vectors, sodium chloride, HEPES, poloxamer 188 (Pluronic® F68), glycine, and recombinant human serum albumin (Recombumin® Alpha).

STUDY PLACEBO DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Placebo injection schedule/site of administration:

For Groups 1 and 2 only, 3 intramuscular doses of placebo will be administered according to the administration schedule as per the table titled "Timing of Kidney Transplant vs. Study Drug (HB-101 or Placebo) Injection, Where Day 0 is the Day of First Dose of Study Drug." All Group 3 patients will receive open-label HB-101.

Note that the injection site(s) can be the deltoid muscle of the non-dominant arm (most preferred injection site), deltoid muscle of the dominant arm, or either thigh (least preferred injection site), as judged by the investigator. In circumstances when administration of two 0.5 mL injections are used, the injections should be at different sites (e.g., both shoulders), or if at the same site, separated by at least 5 cm.

Placebo composition/dose:

Saline (0.9% w/v sodium chloride) will be used as the placebo and is ready-to-use. The volume of administration of 1 dose of placebo is 1.0 mL.

EFFICACY PARAMETERS:

Cytomegalovirus viremia and the use of anti-virals at treatment dose will be used to assess the efficacy of HB-101. For the purposes of this study, CMV viremia will include all patients with evidence of CMV viremia via PCR **and** who are either asymptomatic, with CMV syndrome (fatigue, fever, leukopenia), and/or end-organ disease as defined by Ljungman (Clin Inf Dis 2017).

CMV viremia/DNAemia:

- The incidence, magnitude, and duration of CMV DNAemia through 12 months after transplant will be assessed.

Use of anti-virals at treatment dose:

- The incidence, duration, and number of courses of CMV anti-viral therapy through 12 months after transplant will be assessed.

IMMUNOGENICITY PARAMETERS:

The patient's blood samples should be drawn and assessed for humoral and cellular immunogenicity (central analysis).

Parameters of Primary Immunogenicity Objective:

Cellular immunogenicity analyses per the table titled "Immunogenicity Analysis and Time Points," and per Appendix A of protocol H-100-002.

- CMV pp65-specific interferon γ (IFN-γ) enzyme-linked immunospot (ELISPOT) assay; (CMV ELISPOT pp65).
- CMV gB-specific IFN-γ ELISPOT assay; (CMV ELISPOT gB).

Humoral immunogenicity analysis per the table titled "Immunogenicity Analysis and Time Points," and per Appendix A of protocol H-100-002.

- CMV neutralization (neut) on MRC-5 cells; (CMV neut).

Parameters of Exploratory Immunogenicity Objective:

Cellular immunogenicity analyses per the table titled "Immunogenicity Analysis and Time Points," and per Appendix A of protocol H-100-002.

- CMV pp65-specific intracellular cytokine staining (ICS) of cluster of differentiation (CD) 4+ and CD8+ T-cells for IFN-γ, interleukin-2 (IL-2), tumor necrosis factor alpha (TNF-α), CD107a, and CD40L; (CMV ICS pp65).
- CMV gB-specific ICS of CD4+ and CD8+ T-cells for IFN-γ, IL-2, TNF-α, CD107a, and CD40L; (CMV ICS gB).
- Lymphocytic choriomeningitis virus (LCMV) nucleoprotein (NP)-specific IFN-γ ELISPOT assay (possible that analyses will not occur at all time points, e.g., insufficient volumes of blood); (LCMV ELISPOT NP).

Humoral immunogenicity analysis per the table titled "Immunogenicity Analysis and Time Points," and per Appendix A of protocol H-100-002.

- LCMV neutralizing antibody.

Immunogenicity Analysis and Time Points

	Pre-Dose 1[1]	Pre-Dose 2[1] (28 Days After Dose 1[2])	Pre-Dose 3[1]	Day of Transplant (Prior to Transplant Procedure)	3 Months After Transplant[3]	6 Months After Transplant[3]	9 Months After Transplant[3]	End of Study Visit
Study Assessments								
Study drug injection	X	X	X	-	-	-	-	-
Immunogenicity Testing								
CMV neut	X	X	X	X	X	X	X	X
LCMV neutralizing antibody	X	-	-	X	-	-	-	X
CMV ELISPOT pp65	X	X	X	X	X	X	X	X
CMV ELISPOT gB	X	X	X	X	X	X	X	X
CMV ICS pp65	X	X	X	X	X	X	X	X
CMV ICS gB	X	X	X	X	X	X	X	X
LCMV ELISPOT NP*	X	X	X	X	X	X	X	X

*Possible that analyses will not occur at all time points, e.g., insufficient volumes of blood.

1. Blood collection for immunogenicity will be performed prior to each study drug booster administration.
2. Time (window) from the last dose of study drug (HB-101 or placebo) is 28 days (±7 days).
3. Time window of follow-up visits after transplant is ±7 days.

CMV = cytomegalovirus; ELISPOT = enzyme-linked immunospot; gB = glycoprotein B; ICS = intracellular cytokine staining; LCMV = lymphocytic choriomeningitis virus; neut = neutralization; NP = nucleoprotein; pp65 = phosphoprotein 65 kD.

SAFETY PARAMETERS:

Safety parameters for all arms of the study will include the following:

- All adverse events should be recorded from the time of the first injection of study drug up through 30 days after the last injection of study drug. Only adverse events considered by the investigator to be related to study drug should be recorded from 31 days after the last injection of study drug up through the End of Study Visit.
- Serious adverse events (SAEs) should be recorded during the entire study.
    - All SAEs that occur from the time of the first injection of study drug up through the End of Study Visit must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence.

      Note that pre-planned, elective procedures for pre-existing condition(s) (such as biopsies or dialysis) leading to hospitalization or prolonging hospitalization are NOT considered SAEs.
- Potential signs/symptoms of reactogenicity will be assessed after each study drug administration.
- Adverse events of special interest (graft rejection, CMV syndrome, and CMV disease) post-transplant should be recorded after transplant up to the End of Study Visit.
- Vital signs (body temperature, heart rate, diastolic blood pressure, systolic blood pressure, and respiratory rate) will be recorded during the study.

- Physical examination (general assessment based on the complaints of the patient and on the investigator's judgment) and local assessment of the study drug injection site will be conducted during the study. Results of the physical examination will be captured in study sources, clinically significant abnormalities will be reported as patient medical history prior to randomization (for Groups 1 and 2) or dosing (for Group 3), and adverse events for worsening or emerging findings after randomization (for Groups 1 and 2) or dosing (for Group 3).
- During the study, safety blood collection tests will include the following (analysis will be conducted centrally):
    - Complete blood count with differential: white blood cell count with differential (neutrophils, lymphocytes, eosinophils, monocytes, and basophils), red blood cell count, hemoglobin, hematocrit, reticulocyte count, and platelet count.
    - Liver function tests and enzymes: albumin, ALT, AST, direct bilirubin, total bilirubin, γ-glutamyl transpeptidase, and alkaline phosphatase.
    - Renal function tests: blood urea nitrogen, Chronic Kidney Disease Epidemiology Collaboration for glomerular filtration rate, and serum creatinine.

STATISTICAL ANALYSES:

This Phase 2 study plans to enroll approximately 150 patients. The Intent-to-Treat (ITT) Population will include all patients who are enrolled.

The modified Intent-to-Treat (mITT) Population will include all patients who receive a kidney transplant and at least 2 doses of study drug prior to kidney transplant. The mITT Population will be used for all efficacy analyses.

The Immunogenicity Population will include all patients who receive at least 1 dose of study drug and who have at least 1 post-dose immunogenicity measurement.

The Safety Population will include all patients in the ITT Population who receive any study drug.

Within each population, results will be presented according to treatment arm for Groups 1 and 2 and open-label HB-101 for Group 3.

A primary objective is to assess the safety and reactogenicity of HB-101 in CMV seronegative (-) patients who are awaiting a kidney transplant from a CMV seropositive (+) living donor (Groups 1 and 2) and to assess the safety and reactogenicity of HB-101 in CMV seropositive (+) patients who are awaiting a kidney transplant from a CMV seropositive (+) or CMV seronegative (-) living donor (Group 3). This objective will be assessed by treatment group for Groups 1 and 2 and open-label HB-101 for Group 3 and by number of vaccinations for the following endpoints:

- Incidence and severity of adverse events, SAEs, and changes in laboratory values
- Incidence and severity of localized or generalized injection site reactions

All safety analyses will be performed on the Safety Population. Analyses will be based on adverse events, vital signs, and clinical laboratory assessments. Safety analyses will be descriptive and will be presented in tabular format with the appropriate summary statistics. The percentage of patients reporting any adverse events of special interest will also be summarized.

A primary objective is to assess the immunogenicity of HB-101. Descriptive central statistics will be presented by treatment group for Groups 1 and 2 and open-label HB-101 for Group 3 and by post-transplant CMV management strategy (prevention or preemption) for the following immunogenicity parameters:

- CMV neut
- CMV ELISPOT pp65
- CMV ELISPOT gB

An exploratory objective is to assess additional immunogenicity parameters. Descriptive central statistics will be presented by treatment group for Groups 1 and 2 and open-label HB-101 for Group 3 and by post-transplant CMV management strategy (prevention or preemption) for the following immunogenicity parameters:

- LCMV neutralizing antibody
- CMV ICS pp65
- CMV ICS gB
- LCMV ELISPOT NP

For purposes of the primary objective, the total ELISPOT gB+pp65 AND CMV-neutralizing antibody titers will be used. Other assays will be used for exploratory objectives.

Immunogenicity analyses will be performed based on the Immunogenicity Population. Immunogenicity parameters will be summarized descriptively by treatment arm for Groups 1 and 2 and open-label HB-101 for Group 3 and by post-transplant CMV management strategy (prevention or preemption).

The secondary objectives are to assess the following:

- The efficacy of the administration of at least 2 doses of HB-101 compared to that of placebo in mitigating CMV DNAemia/viremia for CMV seronegative (-) recipients awaiting kidney transplantation from CMV seropositive (+) donor and followed by CMV preemptive therapy post-transplant
- The efficacy of the administration of at least 2 doses of HB-101 compared to that of placebo in decreasing the use of anti-virals at treatment dose for CMV seronegative (-) recipients awaiting kidney transplantation from CMV seropositive (+) donor and to be treated prophylactically for CMV post-transplant
- The efficacy of the administration of at least 2 doses of HB-101 in CMV seropositive (+) recipients prior to transplant and followed by CMV post-transplant preemptive management or prophylactic anti-viral therapy

The incidence, duration, and number of courses of CMV anti-viral therapy through 12 months after transplant will also be summarized descriptively.

These objectives will be assessed by the following endpoints:

- Incidence and time to clinically significant CMV infection, CMV disease, and CMV syndrome

- Incidence and time to CMV viremia requiring anti-viral therapy
- Incidence and duration (in days) of anti-CMV therapy courses (at therapeutic doses) required
- Incidence and time to quantifiable CMV DNAemia, peak CMV DNAemia level, and duration of CMV DNAemia above the limit of quantitation
- Incidence and time to graft failure and organ rejection

Demographic characteristics (age, gender, etc.) and other baseline characteristics will be tabulated using descriptive statistics: frequency tables, including N, n for each category, and percentage for each category, will be generated for categorical variables; and mean, median, standard deviation, minimum, and maximum will be provided for continuous variables. Transplant characteristics will be summarized. These data will be tabulated for all patients by treatment arm for Groups 1 and 2 and open-label HB-101 for Group 3.

SAMPLE SIZE DETERMINATION:

A total sample size of approximately 150 patients is planned for the study. Patients in Groups 1 and 2 will be randomized with a 2:1 ratio for active versus placebo. Patients in Group 3 will be enrolled to receive open-label HB-101. The sample size has been set for an initial assessment of the safety and immunogenicity of the vaccine candidate, which will provide for approximately 100 patients exposed to the HB-101 vaccine. No formal statistical assessment for sample size determination has been conducted. The sample size is considered adequate to provide the necessary safety and immunogenicity data and help with the determination of point estimates of clinical efficacy endpoints (clinically significant CMV infection as defined by the Food and Drug Administration “Guidance for Industry: Cytomegalovirus in Transplantation: Developing Drugs to Treat or Prevent Disease”) to design and adequately statistically power Phase 3 trials.

SITES: Approximately 25 to 40 global sites.

SPONSOR:

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CMV	Cytomegalovirus
CRA	Clinical research associate
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
EC	Ethics Committee
eCRF	Electronic case report form
EDC	Electronic data capture
ELISPOT	Enzyme-linked immunospot
FDA	Food and Drug Administration
FFU	Focus-forming units
gB	Glycoprotein B
GCP	Good Clinical Practice
GP	Glycoprotein
hCG	Human chorionic gonadotropin
HCMV	Human cytomegalovirus
HLA	Human leukocyte antigen
ICF	Informed consent form
ICH	International Council for Harmonisation
ICS	Intracellular cytokine staining
IFN-γ	Interferon γ
IgG	Immunoglobulin G
IL-2	Interleukin-2
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LCMV	Lymphocytic choriomeningitis virus
mITT	Modified Intent-to-Treat
NaCl	Sodium chloride
neut	Neutralization
NIMP	Non-investigational medical product
NP	Nucleoprotein
PCR	Polymerase chain reaction
pp65	Phosphoprotein 65 kD

Abbreviation	Definition
RCV	Replication-competent virus
rHSA	Recombinant human serum albumin
rLCMV	Replication-deficient lymphocytic choriomeningitis virus
RNA	Ribonucleic acid
SAE	Serious adverse event
SOT	Solid organ transplantation
TEAE	Treatment-emergent adverse event
TNF-α	Tumor necrosis factor alpha
ULN	Upper limit of normal

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background

Human cytomegalovirus (HCMV), also referred to as human herpesvirus 5, is a virus of the betaherpesvirinae subfamily. Infection by cytomegalovirus (CMV) is common and is acquired by contact with bodily fluids. In healthy immunocompetent subjects, primary infection typically presents with subclinical symptoms, though it can result in infectious mononucleosis. The primary infection invariably becomes latent and can reactivate, especially during periods of immune suppression. According to the National Health and Nutrition Examination Survey data from 1999 to 2004, the overall age-adjusted CMV seroprevalence among individuals in the United States aged 6 to 49 years was 50.4%.[1]

In immunosuppressed transplant recipients, primary infection, superinfection, or reactivation may cause severe disease such as pneumonitis, retinitis, hepatitis, nephritis, and encephalitis. Vaccination-mediated prevention of CMV infection in solid organ and stem cell transplant subjects, particularly in seronegative subjects receiving solid organ transplants from seropositive donors, and in seropositive stem cell transplant recipients, represents a significant medical need.

Immunity acquired through natural infection helps contain CMV in a latent state and reduces the clinical consequences of re-infections and reactivations. Neutralizing antibodies against the virus contribute to protection. This has been demonstrated by protection of the fetus by transplacental maternal antibodies and by passive transfer of immunoglobulin-containing CMV antibodies to transplant subjects. The effect of passive immunoglobulin in prevention of congenital infection and resulting disease remains less clear and is still under investigation. T-cell-mediated immunity has been shown to also prevent reactivation and to aid in recovery from CMV infection, with multiple supporting lines of evidence, including adoptive transfer of cytotoxic T-cells to transplant recipients.[2]

There is currently no commercially available vaccine against CMV, though multiple vaccine candidates are in clinical development. Most candidate vaccines incorporate variations of the HCMV glycoprotein B ([gB], encoded by UL55) to induce virus-neutralizing antibodies. Glycoprotein B is often combined with phosphoprotein 65 kD ([pp65], encoded by UL83) as a key target of cellular immunity. The potential utility of gB and pp65 as HCMV vaccine antigens can be inferred from the natural history of infection. Neutralizing antibodies specific for gB[3,4] and cluster of differentiation (CD) 8+ cytotoxic T lymphocytes specific for pp65[5] have been isolated from subjects following HCMV infection. Furthermore, pp65-specific T-cells isolated from donors can be transferred to hematopoietic stem cell transplant recipients, resulting in clearance of HCMV infection or a reduction of viral load.[6]

The utility of gB and pp65 as monovalent HCMV vaccine antigens was demonstrated in previous clinical studies. A canarypox vector expressing full length gB was well tolerated but evidenced only limited immunogenicity.[7] A subunit protein gB formulated with MF59 adjuvant was safe, well tolerated, immunogenic, and showed signs of moderate clinical efficacy in post-partum women and in solid organ transplant recipients.[8,9,10] A second subunit protein gB vaccine formulated with a different adjuvant has completed a safety and immunogenicity study, but the results have not yet been reported.[11] A canarypox vector expressing full-length pp65 was safe and immunogenic,[12] but was not further pursued. An adjuvanted human leukocyte antigen (HLA)-A* 0201-restricted pp65 peptide vaccine was well tolerated, immunogenic, and

significantly reduced mortality and viremia in stem cell transplant recipients with hematological illnesses.[13] It is noteworthy that this vaccine induced significant adverse reactions in healthy subjects.[14] Moreover, pp65 is 1 of 3 antigens expressed in a modified vaccinia Ankara-vectored vaccine candidate that recently completed a Phase 1 safety and immunogenicity study in healthy adults.[15]

Two multivalent vaccine candidates expressing gB and pp65 have been evaluated in the clinic. A deoxyribonucleic acid (DNA) vaccine containing 2 plasmids expressing a truncated version of gB in combination with a mutated pp65 was well tolerated and safe in hematopoietic stem cell transplant recipients.[16,17] The immunogenicity data suggested that the vaccine functioned primarily through pp65-specific T-cells. In the stem cell recipient population, the vaccine appeared to lower the viral load but did not reduce the need for anti-viral therapy. A non-replicating alphavirus replicon particle vaccine expressing a truncated isoform of gB and a pp65-IE1 fusion protein was safe, well tolerated, and immunogenic in a Phase 1 study but has not, to this date, been developed further.[18]

Different forms of the gB and pp65 antigens have been used in clinical studies without safety concerns surfacing (except the adjuvanted pp65 peptide vaccine in healthy subjects).[14] These proteins are immunogenic in humans and a bivalent vaccine eliciting strong humoral immune responses to gB and robust cellular immunity to pp65 would act synergistically to benefit vaccinees.

1.1.1 Lymphocytic Choriomeningitis Virus

Lymphocytic choriomeningitis virus (LCMV) is the prototype member of the arenavirus family. It is an enveloped, bisegmented negative single-strand ribonucleic acid (RNA) virus with an ambisense coding strategy. The genome codes for 4 proteins: the surface glycoprotein (GP), the nucleoprotein (NP), the RNA-dependent RNA polymerase L, and a zinc finger protein Z. Lymphocytic choriomeningitis virus particles are pleomorphic, with a mean diameter of approximately 110 to 130 nm.

Lymphocytic choriomeningitis is a rodent-borne infectious disease that presents as aseptic meningitis, encephalitis, or meningoencephalitis. The disease is caused by the LCMV. The natural host of LCMV is the mouse, though it can infect other rodents, or accidentally (albeit rarely) be transmitted to primates and humans. It is a rare human pathogen, and, with the rare exception of vertical transmission and transplant-associated transmission, there are, to Hookipa Biotech GmbH's (hereinafter Hookipa Biotech) knowledge, no documented cases of human-to-human transmission. In humans, LCMV can cause a variety of symptoms from malaise to meningitis, though postnatal subjects nearly always recover without sequelae. Congenital infection more frequently results in clinical disease.[19] Seroprevalence in humans is very low in most geographic regions and does not exceed 5% of the human population.[20]

An acute infection in adult mice is controlled by a vigorous cellular immune response. In contrast, virus-neutralizing serum activity is undetectable, or found only late after virus control. The majority of the antibody response targets the NP but does not neutralize the virus. Lymphocytic choriomeningitis virus-neutralizing antibodies are directed against the only surface GP of the virus.[21]

1.1.2 Replication-Deficient Lymphocytic Choriomeningitis Virus Vectors

Non-replicating viral vectors of LCMV have been constructed by deletion of the GP protein and insertion of foreign genes, including model antigens (e.g., ovalbumin) and microbial antigens from mycobacterium tuberculosis, vesicular stomatitis virus, simian immunodeficiency virus, and influenza virus. These recombinant, non-propagating vectors have been studied in mice and non-human primates and have been shown to induce potent humoral and cellular immunity.[22,23]

As a replication-deficient vector, replication-deficient lymphocytic choriomeningitis virus (rLCMV) has the following features of interest for vaccine applications:

- Safety: The non-replicating virus is anticipated to infect target cells in the vaccine, replicate the genomic RNA, and express the foreign antigen, but not produce infectious virus due to absence of the essential GP gene in the vector genome. Thus, this vector is -propagation deficient in any cell, except engineered production cell lines. Because of this safety profile, it has the potential to be used in healthy subjects of all ages, as well as in persons with underlying health conditions.
- Immunogenicity: In animal models, non-replicating rLCMV vectors that express foreign antigens induce strong functional antibodies against these antigens. The humoral response is combined with potent cytotoxic CD8+ T-cell responses, owing to intracellular processing of endogenously synthesized proteins and direct presentation via the major histocompatibility complex class 1 pathway.
- Utility: Successive homologous boosts should be possible because of a low prevalence of pre-existing immunity to LCMV in the human population, and no to low virus-neutralizing immune response induced by the vector.

1.2 Rationale

Cytomegalovirus is a common opportunistic pathogen in patients who have undergone solid organ transplantation (SOT). The majority of recipients who are seronegative acquire primary infection from a seropositive donor organ. Viral replication in the recipient results in viremia, which can progress to end-organ disease. Active CMV infection correlates with a higher risk of other infections, post-transplant lymphoma, organ rejection, and overall morbidity and mortality. To prevent CMV infection and disease, transplant centers routinely employ either a prophylactic or preemptive strategy using ganciclovir or its oral prodrug valganciclovir. The prophylactic approach is effective in preventing end-organ disease while on anti-viral prophylaxis, but patients remain at significant risk of developing viremia and late-onset disease once prophylaxis is stopped. Sometimes, late-onset disease is caused by strains of CMV that have developed resistance to ganciclovir, which requires the use of more toxic second-line therapies. The preemptive approach requires close monitoring of CMV DNAemia via polymerase chain reaction (PCR) and is thus often limited by practical considerations, given the need for frequent blood draws.

An effective CMV vaccine administered prior to transplantation would overcome the limitations of both the prophylactic and preemptive approaches. Hookipa Biotech completed a Phase 1 healthy volunteer study (Study H-100-001) of the predecessor HB-101 (encoding pp65 and a truncated gB of HCMV).

In brief, Hookipa Biotech observed:

- Neutralizing antibodies formed against the antigen after 2 or 3 vaccinations.
- A favorable safety profile.
- CMV-neutralizing antibodies after 3 vaccinations on par with previously studied vaccines.
- gB- and pp65-specific T-cell immunogenicity previously shown to correlate with protection (in adoptive T-cell transfer studies).

Based on this, Hookipa Biotech anticipates that the vaccine should be more effective than previous vaccines tested in the SOT setting.

1.2.1 Rationale for Including Cytomegalovirus Seropositive Kidney Transplant Recipients

Based on the available safety data of the H-100-002 study (data cutoff date of 03 September 2019) (see the latest Investigator's Brochure in circulation), H-100-002 protocol amendment Version 5.0 will include Group 3 to explore additional safety, immunogenicity, and efficacy data in CMV seropositive (+) patients awaiting kidney transplant from a CMV seropositive (+) or CMV seronegative (-) donor. The safety, immunogenicity, and efficacy data collected from this patient population will provide critical information for the registration trial based on the broad population of patients who are at intermediate and high risk of developing clinically significant CMV infections -post transplantation.

1.3 Risk/Benefit

Cytomegalovirus is an important pathogen for women of childbearing age and for allograft recipients, 2 populations in which development of a vaccine has been rated as a high priority. The life-long latency and ability to re-infect despite pre-existing natural immunity make the production of a vaccine against CMV challenging.[10]

In a setting that lacked an effective CMV vaccine, alternative strategies were devised to reduce the risk of CMV infection and disease. Hand and environmental hygiene is an essential part of every infection control program and could reduce the transmission rate of CMV. Infection by CMV in the first 3 years of life is followed by viral excretion in urine and saliva for up to 42 months. Accordingly, CMV seronegative (-) mothers of CMV-infected children are at 20% to 25% higher risk of primary CMV infection compared with CMV seronegative (-) mothers of uninfected children and become infected with a probability of at least 50% within 1 year after the child acquires the infection.[24]

The success of SOT and hematopoetic stem cell transplantations adds another growing group of patients at risk of CMV disease. In particular, CMV seronegative (-) transplant recipients who receive graft from a CMV seropositive (+) donor are at a high risk of severe CMV disease. In the allograft recipient, viremic dissemination can cause end-organ disease, such as hepatitis, pneumonitis, gastroenteritis, and retinitis, and can predispose to transplant rejection.[10] Anti-viral prophylactic strategies are limited by toxicities, drug-drug interactions, and development of anti-viral resistance.[25]

Patients enrolled in this study will be vaccinated while they await transplantation and are not currently receiving immunosuppression, per Exclusion Criteria 5, 8, and 9. The minimum time between vaccination and transplantation will be 7 days (±2 days) per study protocol.

The recombinant vaccine used in this study is replication-deficient. The non-replicating virus infects target cells (e.g., dendritic cells), where it replicates the genomic RNA and expresses the foreign antigen, but does not produce infectious virus due to absence of the essential GP gene in the vector genome. Thus, this vector is propagation-deficient and as such has the potential to be used in healthy subjects of all ages, as well as in persons with underlying health conditions.

In animal studies performed in mice, Hookipa Biotech has demonstrated that the vector administered via all routes, including dedicated intracranial route administration, causes no pathology (including in the brain, which is devoid of resident immune defense). Biodistribution studies in immunocompetent mice indicated that the vector material can be found in multiple tissues after immunization, but was not associated with pathologic sequelae in any tissues 56 to 90 days after inoculation. In addition, toxicity studies in rats supplement these safety data. Research studies using analogous vectors (encoding different antigens) were performed in guinea pigs, rabbits, and non-human primates and no apparent toxicities were observed in any of these studies.

Furthermore, HB-101 was well tolerated in healthy adults in the Phase 1 clinical trial. No severe adverse reactions or possible severe adverse reactions to HB-101 have been reported. In sum, the risks to patients from HB-101 administration are considered low, while the benefits could include the prevention of CMV infection and disease in solid organ transplant patients.

Patients enrolled in the study will receive the standard of care CMV management post-transplant that they would have received outside of the clinical trial and are not put at increased risk of developing clinically significant CMV infection.

The immune memory cells will be responsible for the mounting of an anamnestic response should the subject be exposed to the CMV antigen after transplantation (in case of CMV primary infection from the graft or the environment). This was observed in 1 of the healthy volunteers who developed a strong immune response as a result of a primary infection after a decrease in the circulating CD4 and CD8 populations.

The inclusion of recipients with indeterminate CMV immunoglobulin titers is based on the current international guidelines for the management of CMV infection post-transplantation as defined by Kotton et al (Transplantation 2018).[26] Indeterminate titers are not unknown titers of anti-CMV immunoglobulin, they are low-level titers that can result from a waning immunity or passive immunity (i.e., in recipients after transfusion). For the purpose of the most conservative management of CMV risk after transplant, recipients with an indeterminate result for CMV serology are assumed to be negative (if any active immunity exists, it is weak) and indeterminate results for donor are assumed to be positive (while immunity might be old, the graft may still be infected by latent CMV infection).

1.3.1 Risks

The risks to which subjects could be exposed in the clinical development program can be separated into 2 categories: those typical of administration of a vaccine and its route of delivery, and those possibly related to the administration of predecessor HB-101 or HB-101 in particular. Predecessor HB-101 and HB-101-specific risks are the vector, the antigens, the formulation, and the mode of action.

At the time of the writing of this protocol amendment, no serious adverse reaction (i.e., drug-related serious adverse event [SAE]) has been reported; therefore, no events are considered

expected. However, for a current list of expected adverse reactions, the investigator should refer to the most up-to-date version of the Investigator's Brochure.

1.3.1.1 Risks related to administration of vaccine

Possible risks that are frequently associated with intramuscular vaccination include the occurrence of local reactions such as edema, induration and erythema, transient local pain, and reddening or tenderness at the injection site. Other adverse effects could include mild to moderate headache, myalgia, flu-like symptoms, malaise, or fatigue (as documented for commercial vaccines [EPAR FLUARIX, 2015; EPAR HAVRIX, 2015]).

Any vaccine could cause allergic and anaphylactic reactions, in addition to the described local reactions at the vaccination site, and systemic flu-like reactions.

Needles during blood sampling could cause local reactions such as edema.

There is a possible risk of sensitization (donor sensitization and increased HLA sensitization) prior to transplantation. The sensitization risk can be mitigated by considering the patients' HLA genotypes (see Exclusion Criteria, below). It has been reported that as many of 4% of dialysis patients awaiting kidney transplantation become sensitized.[28] Other clinical studies have shown that this risk of sensitization following vaccination may be as high as 7.5%. [29]

1.3.1.2 Specific risks related to predecessor HB-101 and HB-101

Vector

Lymphocytic choriomeningitis is a rodent-borne infectious disease that presents as aseptic meningitis, encephalitis, or meningoencephalitis. The disease is caused by the LCMV. Central nervous system involvement in the form of aseptic meningitis or meningoencephalitis represents a rare complication and resolves without sequelae. The natural host of LCMV is the mouse, though it can infect other rodents, or accidentally (albeit rarely) be transmitted to primates and humans. It is a rare human pathogen, and with the rare exception of vertical transmission and transplant-associated transmission, there are, to Hookipa Biotech's knowledge, no documented cases of human to human transmission. In humans, LCMV can cause a variety of symptoms from malaise to meningitis, though postnatal subjects nearly always recover without sequelae. Hookipa Biotech has developed a rLCMV vector platform.

The risk presented by the vector is pathogenicity in the vaccine recipient. The primary mitigation is the deletion of the essential GP from the genome, which makes the vector unable to propagate outside of engineered packaging cell lines. Therefore, infection of the individual target cell is a self-limiting event and the number of cells affected correlates with the dose administered.

The vector has no theoretical risk of forming replication-competent virus (RCV). This was accomplished by designing the vectors with no sequence homology between the vector and the GP gene in the *trans*-complementing production cell line. This eliminates the chance of gain-of-function genetic rearrangements. Furthermore, during the manufacture of predecessor HB-101 and HB-101, the lack of RCV was demonstrated in vitro for the master seed viruses and bulk drug substances. Finally, 3 biosafety studies in mice using research grade material comparable to vaccine demonstrated that injection of large doses of the vector into the brain or peritoneum of immune-compromised mice failed to produce pathology or infectious virus titers in the animals.

Therefore, the design and testing of the vectors mitigate the risk of replicating vectors. Clinical data showed no signs or symptoms of systemic disease.

During the passive phase of Study H-100-001 (Month 4 + 1 day of the first subject from Cohort 1, to the Month 12 visit for the last subject from Cohort 3), it was noted that, owing to a strong increase of humoral and cellular immunity to HCMV after the conclusion of the active phase of the study, a primary HCMV infection was suspected in 1 subject in Cohort 2 before Month 6. The subject did not report any symptoms.

During Study H-100-001, 1 subject (7%) developed a neutralizing antibody response during the study against the vector after 3 administrations of the high dose, which returned to baseline at Month 12.

Antigens

The 2 antigens, pp65 and gB, are derived from HCMV, a relatively benign pathogen for healthy adults. Antigen gB is the viral fusion protein that promotes fusion of the HCMV envelope with the target cell membrane and pp65 is a phosphoprotein with kinase activity that has been shown to interfere with innate immune-signaling pathways in HCMV-infected cells. Predecessor HB-101 and HB-101 expressed a truncated isoform of gB that is lacking the long cytoplasmic tail and an unmodified isoform of pp65. Various isoforms of both antigens, including isoforms similar to those expressed by predecessor HB-101 and HB-101, have been used in previous clinical studies of candidate HCMV vaccines without safety concerns.

Formulation

Predecessor HB-101 (the HB-101 product used in clinical Study H-100-001) contained a 1:1 ratio of HCMV gB- and HCMV pp65-expressing infectious particles with a combined titer of 5.14×10^8 focus-forming units (FFU)/mL formulated in 10 mM HEPES, 150 mM sodium chloride (NaCl), 20 mM glycine, 0.1% (w/v) poloxamer 188, 2% (w/v) recombinant human serum albumin (rHSA), pH 7.4.

In the current Phase 2 clinical study, HB-101 was produced by mixing HCMV gB- and HCMV pp65-expressing infectious particles in a 1:1 ratio followed by a 2.6-fold dilution in 10 mM HEPES, 150 mM NaCl, 20 mM glycine, pH 7.4. Therefore, the Phase 2 HB-101 is formulated with a combined titer of 1.2×10^8 FFU/mL in 10 mM HEPES, 150 mM NaCl, 20 mM glycine, 0.8% (w/v) rHSA, 0.04% (w/v) poloxamer 188, pH 7.4. Each 1.0 mL dose delivers 1.2×10^8 FFU, 2.4 mg HEPES, 8.8 mg NaCl, 1.5 mg glycine, 0.4 mg poloxamer 188, and 8.0 mg rHSA.

None of the components of either predecessor HB-101 or current HB-101 are anticipated to pose a risk to the recipients. Poloxamer 188 and rHSA are used in other licensed or investigational medicinal products.

Mode of action

The vectors infect target cells in the vaccine recipient, replicate the genome, and express the encoded vector proteins and vaccine antigens, which are presented to B- and T-cells to elicit an immune response. The antigens have been tested in other clinical trials without signs of immunopathology. The non-replicating nature of the vector limits the amount and duration of vector-specific antigen expression and reduces the risk of immunopathology caused by vector proteins. Animal studies have not indicated any adverse effects due to the mode of action.

Diagnostic sensitivity

Because the vaccine contains genetic sequences of CMV and CMV PCR is used to monitor patients for CMV infection post-transplantation, the CMV PCR assays at each site will be reviewed to ensure the primer for the PCR assay does not overlap with the vaccine genetic sequences. This will eliminate the risk of false positive PCR results related to the administration of the vaccine.

1.3.2 Benefits

HB-101 is being developed to prevent CMV infection. The target populations of the clinical development program of HB-101 are adolescent girls, pre-pregnant women, and recipients of SOT or hematopoietic stem cell transplants.

Non-clinical data demonstrate that predecessor HB-101 is safe and elicits humoral and cellular immune responses against gB and pp65. Predecessor HB-101 has been tested in immunogenicity models in mice and rabbits for immunogenicity and in female guinea pigs for immunogenicity and efficacy. These animal studies have demonstrated that predecessor HB-101 induces strong humoral and cellular immune responses against gB and pp65 and sero-neutralization against HCMV. The guinea pig congenital guinea pig CMV infection model demonstrated that vaccination of female guinea pigs with predecessor HB-101 followed by mating, gestation, and challenge with CMV protected pups against mortality.

Study H-100-001 assessed the safety and immunogenicity of predecessor HB-101 in healthy subjects serologically negative for HCMV.

In brief, Hookipa Biotech observed:

- Neutralizing antibodies formed against the antigen after 2 or 3 vaccinations.
- A favorable safety profile.
- CMV-neutralizing antibodies after 3 vaccinations on par with previously studied vaccines.
- gB- and pp65-specific T-cell immunogenicity previously shown to correlate with protection (in adoptive T-cell transfer studies).

Based on this, Hookipa Biotech anticipates that the vaccine should be more effective than previous vaccines tested in the SOT setting.

Safety data from Study H-100-001 indicate a favorable tolerability profile from the vaccine with side effects typically limited to headache, influenza-like illness, myalgia, upper respiratory tract infections, and gastroenteritis.

Although the proposed populations for the HB-101 clinical development program include adolescent girls and recipients of solid organ or hematopoietic stem cells, to date, no specific studies have been conducted to determine the effect of HB-101 in pediatric subjects or recipients of hematopoietic stem cells. Such studies will be planned in the future.

The population of Study H-100-002 is a subset of recipients of SOT. Immunogenicity results of Study H-100-001 support that levels of protective immunity could be reached and could protect from clinically significant CMV infections, defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV preemptive therapy based on documented CMV viremia and the clinical condition of the patient, post-transplantation.

2 STUDY OBJECTIVES

The study objectives and endpoints are listed in Table 1.

Table 1. Study Objectives and Endpoints

Study Objectives	Endpoints
Primary	
To assess the safety and reactogenicity of HB-101	Assessed by treatment group for Groups 1 and 2 and open-label HB-101 for Group 3 and by number of vaccinations: • Incidence and severity of AEs, SAEs, and changes in laboratory values • Incidence and severity of localized or generalized injection site reactions
To assess the immunogenicity of HB-101	Descriptive central statistics will be presented by treatment group for Groups 1 and 2 and open-label HB-101 for Group 3 and by post-transplant CMV management strategy (prevention or preemption) for the following immunogenicity parameters: • CMV neut • CMV ELISPOT pp65 • CMV ELISPOT gB
Secondary	
To assess the efficacy of the administration of at least 2 doses of HB-101 compared to that of placebo in mitigating CMV DNAemia/viremia for CMV seronegative (-) recipients awaiting kidney transplantation from a CMV seropositive (+) donor and followed by CMV preemptive therapy post-transplant	• Incidence and time to clinically significant CMV infection, CMV disease, and CMV syndrome • Incidence and time to CMV viremia requiring anti-viral therapy • Incidence and duration (in days) of anti-CMV therapy courses (at therapeutic doses) required • Incidence and time to quantifiable CMV DNAemia, peak CMV DNAemia level, and duration of CMV DNAemia above the limit of quantitation • Incidence and time to graft failure and organ rejection
To assess the efficacy of the administration of at least 2 doses of HB-101 compared to that of placebo in decreasing the use of anti-virals at treatment dose for CMV seronegative (-) recipients awaiting kidney transplantation from a CMV seropositive (+) donor and to be treated prophylactically for CMV post-transplant	
To assess the efficacy of the administration of at least 2 doses of HB-101 in CMV seropositive (+) recipients awaiting kidney transplant and followed by CMV post-transplant preemptive management or prophylactic anti-viral therapy	
Exploratory	
To assess additional immunogenicity parameters of HB-101	Descriptive central statistics will be presented by treatment group for Groups 1 and 2 and open-label HB-101 for Group 3 and by post-transplant CMV management strategy (prevention or preemption) for the following immunogenicity parameters: • LCMV neutralizing antibody • CMV ICS pp65 • CMV ICS gB • LCMV ELISPOT NP

AE = adverse event; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; ELISPOT = enzyme-linked immunospot; gB = glycoprotein B; ICS = intracellular cytokine staining; LCMV = lymphocytic choriomeningitis virus; neut = neutralization; NP = nucleoprotein; pp65 = phosphoprotein 65 kD; SAE = serious adverse event.

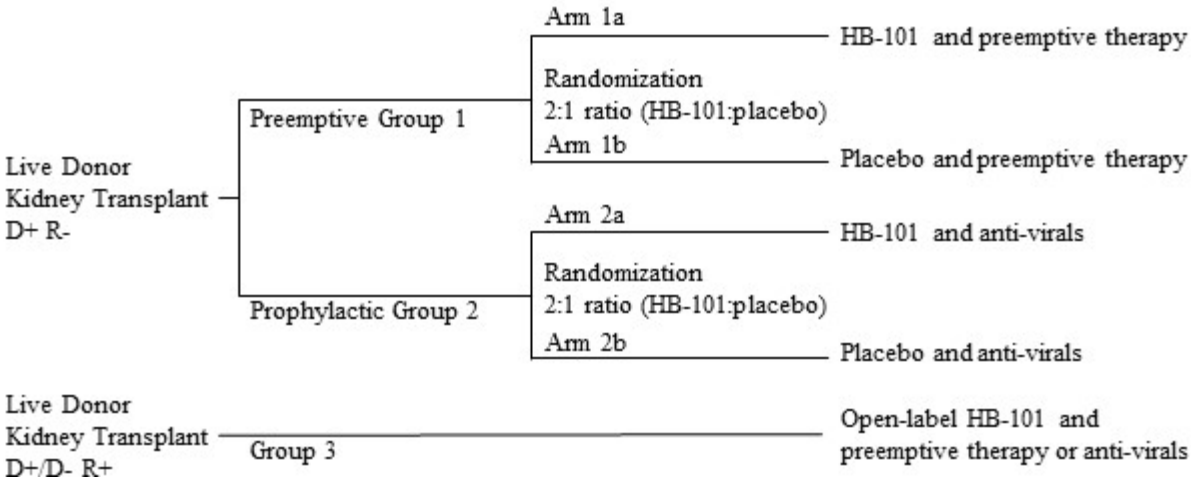
3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 2 study of HB-101, a bivalent CMV vaccine, in patients awaiting kidney transplantation and includes a randomized, placebo-controlled portion (Groups 1 and 2) and an open-label portion (Group 3). Approximately 150 patients recruited globally from specified transplant centers will be enrolled. The study will occur at approximately 25 to 40 global sites.

A high-level study schematic of Study H-100-002 is presented in Figure 1.

Figure 1. High-Level Study Schematic



CMV = cytomegalovirus; D+ = donor seropositive for CMV; D- = donor seronegative for CMV; R+ = recipient seropositive for CMV; R- = recipient seronegative for CMV.

For Groups 1 and 2, adult CMV seronegative (-) patients awaiting kidney transplant from a CMV seropositive (+) living donor will be enrolled according to treatment intent with regard to the method of CMV prevention after transplant (either preemptive or prophylactic) as defined at study enrollment by the investigator and institutional standards.

Patients enrolled into Groups 1 and 2 should have a living donor kidney transplantation ideally planned between 2 to 4 months after the first injection of study drug (HB-101 or placebo).

- Group 1 - The preemptive group will be randomized in a 2:1 ratio (HB-101:placebo) to receive either HB-101 or placebo before transplant. Post-transplant patients will be monitored per preemptive institutional standards.
- Group 2 - The prophylactic group will be randomized in a 2:1 ratio (HB-101:placebo) to receive either HB-101 or placebo before transplant. Post-transplant patients will receive 3 to 6 months of anti-viral prophylaxis following institutional standards.

Enrollment of Group 2 will be limited to no more than 54% of total patients.

For Group 3, adult CMV seropositive (+) patients awaiting kidney transplant from a CMV seropositive (+) or CMV seronegative (-) living donor will be enrolled into Group 3. Post-transplant CMV management will follow either preemptive or prophylactic care as defined at study enrollment by the investigator and institutional standards.

Patients enrolled into Group 3 should have a kidney transplantation from a living donor planned between 2 to 4 months after the first injection of HB-101. Patients in Group 3 will receive HB-101 vaccination(s) prior to their transplant surgery. Enrollment of Group 3 will be a minimum of 15% of total patients.

Patients receiving at least 2 doses of study drug before transplant will be included in the statistical analysis of the efficacy endpoints.

The total duration of the study for each patient participating in the study will be approximately 15 months.

The dosing schedule relative to transplantation is listed in Table 2.

Study drug is defined as either HB-101 or placebo.

Table 2. Timing of Kidney Transplant vs. Study Drug (HB-101 or Placebo) Injection, Where Day 0 is the Day of First Dose of Study Drug

Timing of Kidney Transplant	Number of Injections Planned	Timing of Study Drug Injection
Prior to Day 34	1*	Day 0
Between Day 35 and Day 62	2	Day 0 and Day 28**
Between Day 63 and Day 90 or Between Day 91 and Day 120	3	Day 0, Day 28**, and Day 56** or Day 84**

*Patients who received only 1 dose of study drug will be excluded from the mITT Population for efficacy analysis.
**After Day 0 dose administration, a timeframe of ±7 days from scheduled day of dosing is allowed.
mITT = modified Intent-to-Treat; Day 0 = day of first dose of study drug; Day 28 = 28 days after the first dose of study drug; Day 34 = 34 days after the first dose of study drug; Day 35 = 35 days after the first dose of study drug; Day 56 = 56 days after the first dose of study drug; Day 62 = 62 days after the first dose of study drug; Day 63 = 63 days after the first dose of study drug; Day 84 = 84 days after the first dose of study drug; Day 90 = 90 days after the first dose of study drug; Day 91 = 91 days after the first dose of study drug; Day 120 = 120 days after the first dose of study drug.

In brief, it is the intent of this study to administer up to 3 doses of study drug (HB-101 or placebo) prior to transplantation and within proximity to the time of transplantation. However, 2 doses of study drug before transplant will be sufficient for the patients to be included in the efficacy analyses if a third dose of study drug is not feasible due to transplantation timelines. Patients will not receive study drug after transplantation.

After Day 0 dose administration, the subsequent study drug administration(s) should be given 28 days (±7 days) apart.

Patients whose planned transplantation is less than 35 days from the planned first study drug (HB-101 or placebo) injection should not be enrolled.

A minimum of 7 days (±2 days) must be planned between the last dose of study drug and transplantation, unless agreed otherwise between the sponsor and investigator on a case-by-case basis.

Patients whose planned transplantation is no longer than 4 months from the time of the first study drug (HB-101 or placebo) injection should be enrolled. Changes in transplantation timelines will not result in patient withdrawal from the study. In case of delayed transplantation, additional study drug injections prior to transplantation can be discussed with the sponsor or sponsor designee (who should be blinded). The maximum allowed number of patients receiving additional study drug injections prior to transplantation will be capped at 10 patients (less than 10% of planned sample size).

For Groups 1 and 2, in the event that the living donor is not available and a kidney from a CMV seropositive (+) deceased donor becomes available, the patient can continue in the study after transplantation. For Group 3, in the event that the living donor is not available and a kidney from a deceased donor becomes available, the patient can continue in the study after transplantation.

The additional study drug booster will be administered at least 7 days (±2 days) prior to the scheduled transplantation. This allows maximal protection against CMV prior to the transplant. Blood collection for immunogenicity will be performed prior to each study drug booster administered. Immunogenicity will not be used to determine the administration of a booster as these results would be unblinding; instead, reactogenicity will be reviewed and the investigator and sponsor may decide not to administer the booster if there is evidence of increasing reactions with increasing number of vaccinations. The number and timing of vaccinations versus transplantation will be described in the descriptive analyses.

3.2 Study Indication

Prevention of clinically significant CMV infection, defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV preemptive therapy based on documented CMV viremia and the clinical condition of the patient.

3.3 Definition of the End of the Study

End of the study will be upon completion of the post-transplant Follow-up Period for the last patient as described in Section 6.3 and the study completion of the electronic case report form (eCRF) for the last patient.

3.4 Early Study Termination

The study can be terminated at any time for any reason by the sponsor. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 6.4 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) of the early termination of the trial. The sponsor or designee will inform competent authorities according to local regulations, including the reason for early termination of the study.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

Patients who meet all of the following inclusion criteria for their respective groups will be eligible to participate in the study:

1. Male or female patients 18 years of age or older.
2. Patients willing and able to give written informed consent for participation in the study.
3. Patients must be eligible to undergo kidney transplantation from a living donor as per institutional standards.
4. For Groups 1 and 2 only, patients must be CMV immunoglobulin G (IgG) seronegative (-) and will be receiving a kidney for transplantation from donors who are CMV IgG seropositive (+). (If CMV IgG serology is indeterminate, repeat testing is recommended. If the serology for the donor is indeterminate upon repeat testing, it should be considered positive; if the serology for the recipient is indeterminate upon repeat testing, it should be considered negative).
5. For Group 3 only, patients must be CMV IgG seropositive (+) and will be receiving a kidney for transplantation from donors who are CMV IgG seropositive (+) or CMV IgG seronegative (-). Group 3 patients must have documentation of a planned transplant that is scheduled to occur between 2 and 4 months after the first study drug injection.
6. Post-transplant CMV management will follow either a preemptive treatment strategy or prophylactic anti-viral medication(s) (e.g., valganciclovir) per institutional standard of practice.
7. Female patients of childbearing potential can participate in the study if they agree to use highly effective contraception. This applies from the time period between signing of the informed consent form (ICF) and up to 12 months after the last study drug (HB-101 or placebo) injection or up to completion of the study, whichever is longer.

   Highly effective contraception methods include:

   - Total abstinence. Abstinence is acceptable only when this is in line with the preferred and usual lifestyle of the patient (e.g., true abstinence). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Male or female sterilization.
   - Combination of any 2 of the following categories (Categories 1+2, 1+3, or 2+3):
     - Category 1: Use of oral, injected, or implanted hormonal methods of contraception.
     - Category 2: Placement of an intrauterine device or intrauterine system.
     - Category 3: Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository. Note: The use of Category 3 is only acceptable when used in combination with Category 1 or 2.

8. Female patients must have a negative serum or urine human chorionic gonadotropin (hCG) pregnancy test (urine testing limited to patients producing urine daily) prior to each dose of study drug (HB-101 or placebo), unless the pregnancy test is deemed a false positive and clinical evidence is negative for pregnancy after discussion between the sponsor and investigator on a case-by-case basis; or be surgically or biologically sterile or post-menopausal.

   Post-menopausal females are defined as:

   - Age >50 years with amenorrhea for at least 12 months.
   - Age ≤50 years with 6 months of spontaneous amenorrhea and follicle-stimulating hormone level within post-menopausal range (>40 mIU/mL).
   - Permanently sterilized women (hysterectomy or bilateral oophorectomy).

9. Male patients with sexual partners of childbearing potential can participate in the study if they agree to use barrier contraception from the time period between signing of the ICF and through 3 months after the last dose of study drug.
10. Male patients must agree to refrain from sperm donation from the time period between signing of the ICF and through 3 months after the last dose of study drug.
11. Patients who would comply with the requirements of this protocol (e.g., return for follow-up visits), as judged by the investigator.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Patients who are highly sensitized or who are likely to undergo desensitization at time of transplant (e.g., donor-specific antibody titers at the local laboratory >2000).

   Only patients with no risk or low risk of sensitization defined below should be enrolled, owing to tolerance against the relevant HLA epitopes:

   <u>No Risk:</u>

   Patient HLA genotype includes HLA-A2 *and* HLA-A3 *and* HLA-B7.

   <u>Low Risk:</u>

   Patient HLA genotype includes at least one HLA type from each of the following three groups:

A2	A24	A68	A69

and

A1	A3	A11	A23	A24	A25	A26	A29	A30	A31	A32	A33	A34	A36	A43	A66	A74	A80

and

B7	B13	B27	B37	B41	B42	B47	B48	B54	B55	B56	B60	B61	B67	B73	B81

2. Patients planning to undergo multi-organ transplantation.
3. Patients participating in another interventional clinical study.
4. Previous vaccination with an investigational CMV vaccine.
5. Patients with known diagnosis of human immunodeficiency virus.
6. Patients who are pregnant, breastfeeding, or planning to become pregnant during the study.
7. Any Screening safety laboratory value of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN), total bilirubin >2 × ULN, absolute neutrophil count <500 cells/μL, or lymphocyte count <200 cells/μL.
8. Any confirmed or suspected immunodeficiency disorder (based on medical history and physical examination) that could interfere with the immune response or that presents a risk for the patient to receive a vaccine candidate in development.
9. Treatment with any chronic immunosuppressive medication or other immuno-modifying drugs within 6 months prior to study entry (unless agreed otherwise between the sponsor and investigator on a case-by-case basis). However, inhaled and topical steroids and low-dose oral corticosteroids (≤10 mg/day of prednisone or equivalent) are allowed.
10. For Groups 1 and 2 only, patients with prior history of CMV disease or CMV infection requiring anti-viral therapy.
11. For Group 3 only, patients with active CMV infection requiring anti-viral therapy within 30 days prior to the first injection of study drug.
12. Patients with a history of severe allergic reactions and/or anaphylaxis that could interfere with the immune response (including an allergy or hypersensitivity to any ingredient found in the study drug [HB-101 or placebo]) or that presents a risk for the patient to receive a vaccine candidate in development.
13. Patients with a severe coagulation abnormality that would preclude intramuscular injection.
14. Patients with a rash, dermatological condition, or tattoo in the area of the injection site(s) that could interfere with administration site reaction rating. (Note: The injection site(s) can be the non-dominant arm [most preferred injection site], dominant arm, or either thigh [least preferred injection site], as judged by the investigator).
15. History or current evidence of medical disorders or conditions that could prevent the successful completion of the study, as judged by the investigator.
16. It is anticipated that the patient will be unavailable to complete the study follow-up.
17. Fever (≥38°C) occurs within 7 days prior to first dose (unless agreed otherwise between the sponsor and investigator on a case-by-case basis).
18. For patients receiving post-transplant CMV prophylactic therapy management only, patients who will be receiving Cytogam® in their post-transplant CMV prophylaxis regimen.

4.3 Study Drug Discontinuation

This study consists of a pre-transplant Treatment Period (Section 6.2) and it is the intent of this study to administer up to 3 doses of study drug prior to transplantation. Patients will not receive

study drug post-transplantation. If a patient needs to discontinue study drug during the pre-transplant Treatment Period (Section 6.2), the patient should remain on the study and be followed for safety.

For Groups 1 and 2, if a patient is paired to a CMV seronegative (-) kidney donor after study drug administration, the patient will discontinue study drug and will be evaluated for 30 days after last study drug administration.

Administration of study drug during the pre-transplant Treatment Period (Section 6.2) will be stopped and no further administration will be made to any of the patients following the Withdrawal Criteria (Section 4.4).

4.4 Withdrawal Criteria

Participation of a patient in this clinical study can be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason and without prejudice.
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient 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 that continued participation is not in the best interest of the patient.
- Pregnancy.
- Requirement of prohibited concomitant medication.
- Patient failure to comply with protocol requirements or study-related procedures.
- Termination of the study by the sponsor or the regulatory authority.

If a patient withdraws prematurely from the study due to criteria listed above or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the End of Study Visit during pre-transplant (if patient withdraws from the study before transplant) or the End of Study Visit during post-transplant (if patient withdraws from the study after transplant). If a patient withdraws consent, no additional study-related activities are required. The reason for patient withdrawal must be documented in the eCRF.

A premature withdrawal visit is not considered as the end of the study participation. At a minimum, all patients who discontinue study drug during the Treatment Period will be contacted to return 30 days after the last administration of the study drug for safety follow-up evaluations according to Table 5.

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

Withdrawn patients will not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Arms

5.1.1 Groups 1 and 2

Groups 1 and 2 will be *stratified* by treatment intent (as per investigator and institutional standards) regarding the use of anti-CMV anti-virals post-transplantation. Each group will be *randomized* into 2 arms to receive either HB-101 or placebo (Figure 1):

- Group 1: Patients to be followed preemptively post-transplant:
  - Arm 1a: CMV seronegative (-) patients awaiting kidney transplant from a CMV seropositive (+) living donor randomized to receive HB-101 before transplant, and monitoring after transplant.
  - Arm 1b: CMV seronegative (-) patients awaiting kidney transplant from a CMV seropositive (+) living donor randomized to receive placebo before transplant, and monitoring after transplant.
- Group 2: Patients to be treated prophylactically with anti-virals post-transplant:
  - Arm 2a: CMV seronegative (-) patients awaiting kidney transplant from a CMV seropositive (+) living donor to receive HB-101 before transplant, and anti-viral prophylaxis and monitoring after transplant.
  - Arm 2b: CMV seronegative (-) patients awaiting kidney transplant from a CMV seropositive (+) living donor to receive placebo before transplant, and anti-viral prophylaxis and monitoring after transplant.

5.1.2 Group 3

Group 3 will enroll CMV seropositive (+) patients awaiting kidney transplant from a CMV seropositive (+) or CMV seronegative (-) living donor. Patients will receive HB-101 vaccination(s) prior to their transplant surgery. Post-transplant CMV management will follow either preemptive or prophylactic care as defined at study enrollment by the investigator and institutional standards.

5.2 Rationale for Dosing

An effective CMV vaccine administered prior to transplantation would overcome the limitations of both the prophylactic and preemptive approaches. Hookipa Biotech completed a Phase 1 healthy volunteer study (Study H-100-001) of the predecessor HB-101 (encoding pp65 and a truncated gB of HCMV).

In brief, Hookipa Biotech observed:

- Neutralizing antibodies formed against the antigen after 2 or 3 vaccinations.
- A favorable safety profile.
- CMV-neutralizing antibodies after 3 vaccinations on par with previously studied vaccines.
- gB- and pp65-specific T-cell immunogenicity previously shown to correlate with protection (in adoptive T-cell transfer studies).

Based on this, Hookipa Biotech anticipates that the vaccine should be more effective than previous vaccines tested in the SOT setting.

5.3 Justification of Selected Dose

In the Phase 1 healthy volunteer study (Study H-100-001), the HB-101 dose of 2.6×10^7 FFU was found to be as immunogenic as a dose of 2.6×10^8 FFU, with the maximum immunogenicity attained more quickly with 2 doses of 2.6×10^8 FFU. The final concentration of HB-101 to be used in this study (H-100-002) is 1.2×10^8 FFU/mL. Each vial of HB-101 contains 0.7 mL of vaccine. Therefore, to achieve a dose that is closer to the highest dose used in the Phase 1 study, patients will be administered 2 vials (1.0 mL total injection volume) for a total dose of 1.2×10^8 FFU/mL per administration. Based on the Phase 1 study, this dose should attain maximum immunogenicity with minimal number of administrations.

The intent of this study is to attain maximum immunogenicity as quickly as possible prior to transplantation by administering 3 doses of HB-101. The dosing schedule for the 3 doses is planned for 0, 1, and 3 months (see Section 3.1). Patients enrolled should have a kidney transplantation ideally planned between 2 and 4 months after the first injection of study drug. This should ensure that patients receive at least 2 doses of HB-101; however, unanticipated changes in transplantation timelines may not allow for 2 doses of HB-101 to be administered. As vaccination post-transplantation is not allowed as part of this protocol, these patients will receive 1 dose of HB-101. This is not the intent of this study, but is a potential consequence of unanticipated changes in transplantation timelines.

5.4 Randomization and Blinding

5.4.1 Groups 1 and 2

Adult CMV seronegative (-) patients awaiting kidney transplant from a CMV seropositive (+) living donor will be enrolled into Groups 1 or 2 according to treatment intent with regard to the method of CMV prevention after transplant (either preemptive or prophylactic) as defined at study enrollment by the investigator and institutional standards.

- Group 1 - The preemptive group will be randomized in a 2:1 ratio (HB-101:placebo) to receive either HB-101 or placebo before transplant. Post-transplant patients will be monitored per preemptive institutional standards.
- Group 2 - The prophylactic group will be randomized in a 2:1 ratio (HB-101:placebo) to receive either HB-101 or placebo before transplant. Post-transplant patients will receive 3 to 6 months of anti-viral prophylaxis following institutional standards.

Patients will be randomized via a centralized Interactive Response Technology (IRT) system. Enrollment of Group 2 will be limited to no more than 54% of total patients.

The study is double blind for Groups 1 and 2; patients and investigators will be blinded to treatment assignment.

At each site, the pharmacy staff will include unblinded personnel. Based on the treatment assignment from the automated randomization system (i.e., IRT), an unblinded pharmacist or designee at each site will prepare the study drug injection syringe. Syringes containing study drug

will be prepared per instructions in the Investigational Medicinal Product Manual, independent of clinical staff, and delivered to the clinical team for blinded administration.

Syringes, syringe labels, and translucent colored tape are supplied with the study drug. The syringe labels are not translucent and therefore, the syringe label masks the color of the solution (as the placebo and active vaccine differ slightly in color) in the syringe to avoid potential unblinding. Furthermore, the syringe with placebo is also stored at 2ºC to 8ºC (35.6ºF to 46.4ºF) to mimic HB-101 in syringes to avoid potential unblinding to the dose administrator (who is blinded).

The syringe will be distributed to the blinded investigator or their designee with the syringe label in place covering the entire volume of the drug to be administered. The label will not allow the blinded investigator or their designee to differentiate between the placebo or study drug liquid but still be able to see that the amount of liquid is 1 mL and safely administer it to the patient. The clinical monitoring team will also be blinded to treatment assignment. An independent unblinded team will monitor drug accountability and protocol compliance at the pharmacy.

5.4.2 Group 3

Group 3 will be open label. In Group 3, CMV seropositive (+) patients awaiting kidney transplant from a CMV seropositive (+) or CMV seronegative (-) donor will be enrolled to receive HB-101 vaccination(s) prior to their transplant surgery.

There will be no randomization or blinding for patients in Group 3. Enrollment of Group 3 will be a minimum of 15% of total patients.

5.5 Breaking the Blind (Groups 1 and 2 Only)

Unblinding by request of an investigator should only occur in the event of an emergency or adverse event for which it is necessary to know the treatment assignment of an individual patient. If the investigator must identify the treatment assignment of an individual patient, the investigator or qualified designee should request the medication information from the IRT system and promptly contact the sponsor or sponsor designee. The documentation from the IRT system indicating the code break must be retained with the patient's source documents in a secure manner so as not to unblind the treatment assignment to other site or sponsor personnel.

Hookipa Biotech study team members will be unblinded after each patient receives their last dose of study drug and undergoes his/her kidney transplantation. Medpace, the investigator, and study site personnel will remain blinded for the entire study with the exception of the study site pharmacist or research nurse who prepares the study drug for administration.

5.6 Drug Supplies

5.6.1 Formulation and Packaging

5.6.1.1 HB-101

HB-101 has been developed by the sponsor.

HB-101 uses rLCMV as a vector for a bivalent recombinant vaccine against HCMV. One vector expresses the pp65 protein of HCMV, and one expresses a truncated gB protein of HCMV. The 2 vectors are produced separately. The final drug product is manufactured by mixing 1 batch of

rLCMV pp65 and 1 batch of rLCMV gB in a 1:1 ratio based on pp65- and gB-expressing vectors. HB-101 was produced pre-diluted and ready-to-use.

HB-101 is formulated at 1.2×10^8 FFU/mL. The product is filled in 2 mL single-dose vials containing 0.7 mL of vaccine.

The quality control standards and requirements for HB-101 are described in separate Quality Assurance documents. The required approvals will be obtained.

The vaccine will be labeled and packaged according to applicable regulatory requirements (European Union Good Manufacturing Practice, Annex 13; and Title 21 of the Code of Federal Regulations [CFR] Part 201).

The components of HB-101 include water for injection, total rLCMV vectors, NaCl, HEPES, poloxamer 188 (Pluronic® F68), glycine, and rHSA (Recombumin® Alpha).

Table 3. HB-101 Formulation for Clinical Use

Manufacturer	Hookipa Biotech.
Vial description	2 mL single dose vials.
HB-101 volume per vial	0.7 mL fill volume.
Composition in vial	Solution containing water for injection, total rLCMV vectors, sodium chloride, HEPES, poloxamer 188 (Pluronic® F68), glycine, and recombinant human serum albumin (Recombumin® Alpha).
Administration	• HB-101 vials are pre-diluted and ready-to-use. • Volume for each dose of study drug is 1.0 mL. • The total dose of HB-101 is 1.2×10^8 FFU.
Diluent for administration	None needed.
Storage of HB-101 vials	≤-65°C or ≤-85°F.
FFU = focus-forming units; rLCMV = replication-deficient lymphocytic choriomeningitis virus.	

5.6.1.2 Placebo

Saline (0.9% w/v NaCl) will be used as the placebo. The sponsor will supply this saline for the study.

5.6.2 Study Drug Preparation and Dispensing

Syringes, syringe labels, translucent colored tape, and filter needles will be supplied with the study drug.

Syringes containing HB-101 or placebo to be administered will be prepared by an unblinded pharmacist or designee per instructions in the Investigational Medicinal Product Manual, independent of clinical staff, and delivered to the clinical team for blinded administration.

5.6.2.1 HB-101

HB-101 was produced pre-diluted and ready-to-use.

Trace amounts of small product-derived particles may be observed in the vaccine. HB-101 will be drawn into the syringe using a filter needle, and then will be administered via the intramuscular route in a hospital setting, followed by a 60-minute observation period.

HB-101 prepared syringe should be stored at 2°C to 8°C for up to 4 hours until administration. HB-101 will be administered via the intramuscular route in a clinic setting, followed by a 60-minute observation period.

5.6.2.2 Placebo

Sodium chloride (0.9% w/v) will be used as the placebo and is ready-to-use.

5.6.3 Study Drug Administration

The volume of administration of 1 dose of study drug is 1.0 mL. Study drug will be injected with a syringe as a single injection of 1.0 mL or as 2 separate injections of 0.5 mL each for administration, per discretion of the investigator.

Three intramuscular doses of study drug will be administered according to the administration schedule as per Table 2.

Note that the injection site(s) can be the deltoid muscle of the non-dominant arm (most preferred injection site), deltoid muscle of the dominant arm, or either thigh (least preferred injection site), as judged by the investigator. In circumstances when administration of two 0.5 mL injections are used, the injections should be at different sites (e.g., both shoulders), or if at the same site, separated by at least 5 cm.

5.6.4 Treatment Compliance

Study drug will only be administered by study site personnel.

5.6.5 Storage and Accountability

HB-101 vials should be stored at ≤-65°C or ≤-85°F and placebo should be stored according to the manufacturer's instructions.

Study drug should be stored in a safe and locked place with no access for unauthorized personnel.

Any significant temperature deviation (according to Investigational Medicinal Product Manual) should be reported to the sponsor or sponsor's designee as soon as detected. Following an exposure to a temperature deviation, study drug should not be used until written approval is given by the sponsor.

5.7 Prior and Concomitant Medications and Vaccinations

5.7.1 Excluded Prior Medications and Vaccinations

The following medications and vaccinations are prohibited:

- Treatment with any chronic immunosuppressive medication or other immune-modifying drugs within 6 months prior to study entry (unless agreed otherwise between the sponsor and investigator on a case-by-case basis). Immunosuppressive medication necessary to prevent acute rejection of a previous kidney transplant is allowed.
- Previous vaccination with an investigational CMV vaccine.

5.7.2 Allowed Prior Medications and Vaccinations

Inhaled and topical steroids and low-dose oral corticosteroids (≤10 mg/day of prednisone or equivalent) are allowed.

5.7.3 Documentation of Prior and Concomitant Medication and Vaccination Use

At every study visit and contact, the investigator should question the patient regarding any medication taken and treatment received by the patient.

The investigator will review the following criteria at each study visit subsequent to the first study drug administration. If any criterion becomes pertinent during the study, it may not require withdrawal of the patient from the study but could impact whether a patient could be assessed in sensitivity analyses:

- Use of any investigational or non-registered product (drug/vaccine) other than the study drug during the study period.
- Receipt of routine commercial vaccinations (with the exception of seasonal influenza vaccination) within 5 months after study entry.
- Administration of more than 7 days of immunosuppressants or other immune-modifying drugs prior to transplantation. For corticosteroids, this would mean prednisone ≥0.125 mg/kg/day (maximum 10 mg/day), or equivalent. Inhaled and topical steroids and low-dose oral corticosteroids (≤10 mg/day of prednisone or equivalent) are allowed. Immunosuppressive medication necessary to prevent acute rejection of a previous kidney transplant is allowed.

During the study, all concomitant medications, including changes in chronic medication (with the exception of vitamins and/or dietary supplements), should be recorded in the eCRF from Day 0 up through 30 days after the last dose of study drug, or on the Day of Transplant, whichever occurs first. The process additionally applies to any medication the patient received to treat an adverse event. Chronic medication is defined as medication taken regularly by the patient for a minimum of 6 months before the study start (e.g., contraceptive pill).

If the patient withdraws from the study before transplant, concomitant medications considered by the investigator to be related to SAEs and taken by patients before transplant should be recorded in the eCRF.

Similarly, concomitant medications considered by the investigator to be related to SAEs and taken by patients after transplant should be recorded in the eCRF after transplant up to the End of Study Visit. Standard immunosuppression post-transplantation is allowed, including induction regimen for immunosuppression (e.g., antithymocyte globulin).

5.7.4 Documentation of Concomitant Medications of Special Interest

Concomitant medications of special interest should be documented at time points per Table 6.

Concomitant medications of special interest within 7 days prior to and after transplant are anti-virals and immunosuppressants (including induction regimen, e.g., antithymocyte globulin), non-study vaccines, granulocyte colony-stimulating factor, erythropoietin, and transfusions of blood product. Concomitant medications of special interest, taken by patients within 7 days prior to transplant and throughout the study after transplant, should be recorded in the eCRF.

6 STUDY PERIOD

6.1 Clinical Screening

The Screening Period starts after a patient has signed and dated the written informed consent form (ICF) to participate in the study and concludes on the day of randomization (for Groups 1 and 2) or dosing (for Group 3). The Screening Period should be within 56 days of Day 0. After 56 days, if the patient has not withdrawn from the study, he/she will be rescreened with sponsor approval.

The patient must sign and date the written ICF prior to study procedures.

The following Screening assessments can be conducted for up to 14 days prior to Day 0:

- Inclusion/exclusion criteria reviewed.
- Patient's relevant medical history recorded.
- Patient's medication/vaccination history recorded.
- Safety blood collection (complete blood count with differential, liver function tests and enzymes, and renal function tests) at the local or central laboratory.
- Pregnancy test (serum or urine hCG test, urine testing limited to patients producing urine daily) (for females of childbearing potential).
- Serum follicle-stimulating hormone (for all females aged ≤50 years with 6 months of spontaneous amenorrhea).
- Physical examination.

The following Screening assessment can be conducted for up to 56 days prior to Day 0:

- Patient signs and dates written ICF.
- Patient demographics recorded.
- CMV serology sample.

During Screening, information collected on screen failures should be recorded on the eCRF.

Clinical Screening study assessments are listed in Table 5.

If the kidney transplant recipient is identified to be CMV seronegative (-) and an HLA-matched CMV seropositive (+) donor is identified (listed) and has passed the first visit of eligibility, then there is a reasonable likelihood that the recipient will be paired with a living kidney donor, and the transplant recipient can be screened for enrollment into Group 1 or 2 and dosed in the study.

If after study drug administration, the CMV seronegative (-) transplant recipient is paired with a kidney donor who is CMV seronegative (-):

- The patient will discontinue from further study drug administration and will be evaluated for 30 days post-dose from last study drug safety monitoring per protocol.
- If the patient has an ongoing adverse event suspected to be related to study drug, the patient will continue to be monitored until the adverse event resolves completely or to baseline, whichever occurs first.

If the kidney transplant recipient is identified to be CMV seropositive (+) and an HLA-matched CMV seropositive (+) or CMV seronegative (-) donor is identified (listed) and has passed the first visit of eligibility, and has a transplantation planned between 2 and 4 months after the first study drug injection, then the transplant recipient can be screened for enrollment into Group 3 and dosed in the study.

6.1.1 Information to be Collected on Screen Failures

Patients who sign the study ICF but who fail to be started on study drug prior to transplant for any reason will be considered screen failures. The reason for a patient not being started on study drug will be entered on the Screen Fail eCRF and every patient's demographic information will be recorded on the Demography eCRF. No other data will be entered into the clinical database for patients who are screen failures.

6.2 Pre-Transplant: Treatment Period

During the study, the pre-transplant Treatment Period starts on Day 0 on the first day of dosing and lasts up to the time of kidney transplant or End of Study Visit.

First dose of study drug (Day 0) is scheduled when the patient in Groups 1 or 2 has a confirmed CMV seropositive (+) kidney donor identified or when the patient in Group 3 has a confirmed CMV seropositive (+) or CMV seronegative (-) kidney donor identified, and there is a plan and/or date to transplant.

Prior to patients receiving first dose of study drug on Day 0, the patient's inclusion/exclusion criteria should be reviewed again. Patients in Groups 1 and 2 will be randomized prior to or on Day 0 pre-dose.

Each study drug administration should be given 28 days (±7 days) apart. Dosing of study drug will occur according to the administration schedule as per Table 2.

A minimum of 7 days (±2 days) must be planned between the last dose of study drug and transplantation, unless agreed otherwise between the sponsor and investigator on a case-by-case basis.

Study assessments during the pre-transplant Treatment Period are listed in Table 5.

In some cases, patients could receive the last dose of study drug before their kidney transplant, but their post-injection follow-up visits (7 and 30 days after the last dose of study drug) will occur after their transplant. These post-injection follow-up visits should be scheduled based on the date of the last (final) study drug administration, NOT by transplantation date. It is possible that the time window of post-injection follow-up visit assessments will be redundant to a visit in the post-transplant period. If the time window is ±2 weeks, assessments should NOT be duplicated. Study assessments are listed in Table 5 and Table 6.

6.3 Post-Transplant: Follow-Up Period for Efficacy

During the study, the post-transplant Follow-up Period for Efficacy of the study is the follow-up period that starts after a patient receives a kidney transplant and concludes when the patient either completes the study or is withdrawn or withdraws from the study.

Patients will not receive study drug during the post-transplant Follow-up Period for Efficacy.

Follow-up visits to the clinical study site will be per institutional standard of care for post-transplant CMV preemptive or anti-viral prophylaxis management. Post-transplant study assessments will be conducted at the follow-up visits.

Study assessments during the post-transplant Follow-up Period for Efficacy are listed in Table 6.

6.4 End of Study Visit (Including Study Completion and Study Withdrawal)

The patient will complete and conclude the study on whichever day of the study one of the following events first occurs:

- When the patient completes the study follow-up (12 months post-transplant).
- If for some reason kidney transplant has not occurred by 12 months after the first dose of study drug.
- If the patient experiences graft failure requiring removal of the transplanted organ or returns to dialysis.
- If the patient is withdrawn or withdraws from the study.
- If the patient is lost to follow-up.
- If the patient dies.

If a patient completes the study or is withdrawn or withdraws from the study, a study visit should be scheduled within 14 days, at which time all study assessments listed for the End of Study Visit should be conducted.

During post-transplant, study assessments for the End of Study Visit are listed in Table 6.

Dosing during the study will end when all enrolled patients have completed their planned doses of study drug. The study will end when the last patient last visit post-transplantation is completed.

If a patient does not receive study drug prior to transplant, the End of Study Visit is not necessary (screen failure). The patient would be withdrawn from the study.

7 STUDY ASSESSMENTS

There is a ±3 day window on assessments during the pre-transplant Treatment Period and a ±7 day window on assessments during the post-transplant Follow-up Period, to take into account public or religious holidays or weather, **if not explicitly specified otherwise**.

In some cases, patients could receive the last dose of study drug before their kidney transplant, but their post-injection follow-up visits (7 and 30 days after the last dose of study drug) will occur after their transplant. There is a ±3 day window on assessments of their post-injection follow-up visits (7 and 30 days after last dose of study drug).

Prior to transplant, patients will be assessed per the phone calls/study visits listed in Table 5. In the event that the patient cannot return to the site for the study visit occurring 7 days after study drug administration (Visits 3, 5, and 7 in Table 5), the assessments should be collected via phone call. These assessments include study drug injection site examinations, concomitant medications, adverse events, and SAEs. In addition, every effort should be made to collect local safety blood collection tests and enter these into the eCRF, as well as assess for clinical significance by the investigator.

After transplant, all patients of the study who received study drug will be assessed per the study visits listed in Table 6. Patients who received last dose of study drug and will have their post-injection visit(s) after transplant will be assessed per the study visits listed in Table 5. Remaining pre-transplant phone calls/study visits will occur post-transplant and will not be protocol deviations. Patients will not receive study drug after transplant.

During the study, it is possible that the time windows of study visits and assessments will be redundant. If the time window is ±2 weeks, assessments should NOT be duplicated.

Table 5 and Table 6 list study assessments.

8 EFFICACY ASSESSMENTS

Cytomegalovirus viremia and the use of anti-virals at treatment dose will be used to assess the efficacy of HB-101. For the purposes of this study, CMV viremia will include all patients with evidence of CMV viremia via PCR **and** who are either asymptomatic, with CMV syndrome (fatigue, fever, leukopenia), and/or end organ- disease as defined by Ljungman (Clin Inf Dis 2017).[26]

CMV viremia/DNAemia:

- The incidence, magnitude, and duration of CMV DNAemia through 12 months after transplant will be assessed.

Use of anti-virals at treatment dose:

- The incidence, duration, and number of courses of CMV anti-viral therapy through 12 months after transplant will be assessed.

CMV disease and CMV syndrome:

Incidence and time to clinically significant CMV disease and CMV syndrome.

8.1 Cytomegalovirus Polymerase Chain Reaction (CMV PCR) Test

After transplant, at the time points listed in Table 6, the patient's blood sample will be collected for CMV PCR. Plasma CMV PCR will be assessed at the central laboratory retrospectively. Patient management will follow institutional standards and be based on local laboratory CMV results. Cytomegalovirus DNAemia is defined as CMV virus load in the patient's blood as measured per central PCR testing.

The time points when the patient's blood sample for CMV PCR should be drawn post-transplant are different in patients receiving preemptive and prophylactic care. Section 8.1.1 and Section 8.1.2 list the time points at which the patient's blood sample should be drawn for CMV PCR post-transplant.

The analysis of CMV DNAemia at the central laboratory will be conducted in batches retrospectively. Study sites should still conduct local CMV DNAemia via PCR analysis and follow their institutional guideline regarding thresholds to initiate anti-viral treatment.

The study site will record their local CMV viremia level in the eCRF.

Only CMV PCR testing time points will differ between patients receiving preemptive and prophylactic care. All other study assessments should be conducted within 12 months in all patients.

8.1.1 Local CMV PCR Testing for Patients Receiving Preemptive Care

The patient's blood sample should be drawn and assessed for CMV PCR testing at the following time points:

- Weekly for the first 16 weeks after transplant.
- 6 months after transplant.
- 9 months after transplant.

- 12 months after transplant or at End of Study.
- Additional time points following the institution's standard of care.
- If the patient has clinically significant signs or symptoms of CMV disease or infection.

The CMV PCR testing should be conducted at the institution if it corresponds to the institution's standard of care follow-up visit or at a commercial laboratory.

If the patient has clinically significant signs or symptoms of CMV disease or infection at any time during the follow-up, the patient's blood should be drawn and tested for CMV PCR.

8.1.2 Local CMV PCR Testing for Patients Receiving Prophylactic Care

While on anti-viral prophylaxis treatment, the patient's blood sample should be drawn and assessed for CMV PCR testing at the following time points:

- 3 months after transplant.
- 6 months after transplant.
- 9 months after transplant.
- 12 months after transplant or at End of Study.
- Additional time points following institution's standard of care.
- If the patient has clinically significant signs or symptoms of CMV disease or infection.

The CMV PCR testing should be conducted at the institution if it corresponds to the institution's standard of care follow-up visit or at a commercial laboratory.

If the patient has clinically significant signs or symptoms of CMV disease or infection at any time during the follow-up, the patient's blood should be drawn and tested for CMV PCR.

8.1.3 Central CMV PCR Testing

At the time points when CMV PCR testing is conducted at the institution, the study site personnel will draw the patient's blood sample for central CMV PCR analysis, unless agreed otherwise between the sponsor and investigator on a case-by-case basis.

8.2 Graft Rejection Assessments

After transplant, as listed in Table 6, the investigator will assess the patient for graft rejection per institutional standards of the study site. During the study, the patient's graft rejection assessment data should be recorded on the graft rejection page of the eCRF.

Appendix D lists the scale/score/grade system of graft rejection assessments during the study.

8.3 Cytomegalovirus Disease and Syndrome Assessments Post-Transplant

After transplant, as listed in Table 6, CMV disease (see Appendix F for definition of CMV disease) and CMV syndrome (see Appendix E for definition of CMV syndrome) will be assessed per the institutional standards of the study site.

The patient's CMV disease and syndrome assessments post-transplant should be recorded on the CMV event page of the eCRF.

9 IMMUNOGENICITY ASSESSMENTS

The patient's blood samples should be drawn and assessed for humoral and cellular immunogenicity (central analysis).

All efforts will be made to assess the immunogenicity analyses listed in the primary and exploratory objectives. There could be circumstances when a decision is made to not conduct or to discontinue immunogenicity analyses due to practical or strategic reasons (e.g., not enough blood volume collected from the patient).

9.1 Parameters of Primary Immunogenicity Objective

Cellular immunogenicity analyses per Table 4, Table 5, and Table 6.

- CMV pp65-specific interferon γ (IFN-γ) enzyme-linked immunospot (ELISPOT) assay; (CMV ELISPOT pp65).
- CMV gB-specific IFN-γ ELISPOT assay; (CMV ELISPOT gB).

Humoral immunogenicity analysis per Table 4, Table 5, and Table 6.

- CMV neutralization (neut) on MRC-5 cells; (CMV neut).

9.2 Parameters of Exploratory Immunogenicity Objective

Cellular immunogenicity analyses per Table 4, Table 5, and Table 6.

- CMV pp65-specific intracellular cytokine staining (ICS) of CD4+ and CD8+ T-cells for IFN-γ, interleukin-2 (IL-2), tumor necrosis factor alpha (TNF-α), CD107a, and CD40L; (CMV ICS pp65).
- CMV gB-specific ICS of CD4+ and CD8+ T-cells for IFN-γ, IL-2, TNF-α, CD107a, and CD40L; (CMV ICS gB).
- LCMV NP-specific IFN-γ ELISPOT assay (possible that analyses will not occur at all time points, e.g., insufficient volumes of blood); (LCMV ELISPOT NP).

Humoral immunogenicity analysis per Table 4, Table 5, and Table 6.

- LCMV neutralizing antibody.

Table 4. Immunogenicity Analysis and Time Points

	Pre-Dose 1[1]	Pre-Dose 2[1] (28 Days After Dose 1[2])	Pre-Dose 3[1]	Day of Transplant (Prior to Transplant Procedure)	3 Months After Transplant[3]	6 Months After Transplant[3]	9 Months After Transplant[3]	End of Study Visit
Study Assessments								
Study drug injection	X	X	X	-	-	-	-	-
Immunogenicity Testing								
CMV neut	X	X	X	X	X	X	X	X
LCMV neutralizing antibody	X	-	-	X	-	-	-	X
CMV ELISPOT pp65	X	X	X	X	X	X	X	X
CMV ELISPOT gB	X	X	X	X	X	X	X	X
CMV ICS pp65	X	X	X	X	X	X	X	X
CMV ICS gB	X	X	X	X	X	X	X	X
LCMV ELISPOT NP*	X	X	X	X	X	X	X	X

*Possible that analyses will not occur at all time points, e.g., insufficient volumes of blood.

1. Blood collection for immunogenicity will be performed prior to each study drug booster administration.
2. Time (window) from the last dose of study drug (HB-101 or placebo) is 28 days (±7 days).
3. Time window of follow-up visits after transplant is ±7 days.

CMV = cytomegalovirus; ELISPOT = enzyme-linked immunospot; gB = glycoprotein B; ICS = intracellular cytokine staining; LCMV = lymphocytic choriomeningitis virus; neut = neutralization; NP = nucleoprotein; pp65 = phosphoprotein 65 kD.

10 SAFETY ASSESSMENTS

10.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a 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 an investigational medicinal product, whether or not related to the investigational medicinal product. 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 recorded from the time of the first injection of study drug up through 30 days after the last injection of study drug. Only adverse events considered by the investigator to be related to study drug should be recorded from 31 days after the last injection of study drug up through the End of Study Visit.

During the study, adverse events of special interest post-transplant should be recorded after transplant up to the End of Study Visit. Adverse events of special interest after kidney transplant are graft rejection, CMV syndrome, and CMV disease. Physical examination (general assessment based on the complaints of the patient and on the investigator's judgment) and local assessment of the study drug injection site will be conducted during the study. Results of the physical examination will be captured in study sources, clinically significant abnormalities will be reported as patient medical history prior to randomization (for Groups 1 and 2) or dosing (for Group 3), and adverse events for worsening or emerging findings after randomization (for Groups 1 and 2) or dosing (for Group 3). Patients should be instructed to report any adverse event that they experience to the investigator. From the time of first dose of study drug, 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.

Any medical condition already present at Screening should not be reported as an adverse event unless the medical condition or signs or symptoms present at Day 0 changes in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as adverse events. The investigator will exercise his/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. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

10.1.1 Adverse (Drug) Reaction

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

10.1.2 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 predecessor HB-101, the reference safety information is included in the Investigator's Brochure currently in force. The reference safety information will be reviewed annually and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

10.1.3 Assessment of Adverse Events by the Investigator

The investigator will assess the severity (intensity) of each adverse event, and will 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 except reactogenicity (see Section 10.6) should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

For those adverse events not listed in the CTCAE, the following grading system should be used:

- Mild (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with patient's daily activities.
- Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with patient's usual activities, but still acceptable.
- Severe (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the patient's daily activities, unacceptable.
- Life-threatening (CTCAE Grade 4): Life-threatening or disabling adverse event.
- Death (CTCAE Grade 5): Death-related adverse event.
- For the assessment of local and systemic injection site reactions (reactogenicity), the Food and Drug Administration (FDA) "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" should be used. See Section 10.6.

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 (unrelated, not related, no relation) – 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 (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 patient may have.
- Concomitant drug-
  - The other drugs the patient is taking or the treatment the patient 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 pharmacokinetics of the study drug-
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

Assessment of Outcomes:

The outcome of any non-serious adverse event or any SAE is to be assessed as:

- Recovered/resolved.
- Not recovered/not resolved.
- Recovering/resolving.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

10.2 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 patient 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: Pre-planned, elective procedures for pre-existing condition(s) (such as biopsies or dialysis) leading to hospitalization or prolonging hospitalization are NOT considered SAEs. However, hospitalizations for procedures conducted for the diagnosis of CMV disease (i.e., biopsy, endoscopy), are considered events of special interest and will be collected as SAEs.
    - NOTE: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room 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. 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) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- An important medical event.
    - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient 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.
- Is a Grade 4 adverse event considered related to the study drug.

10.3 Serious Adverse Event Reporting – Procedures for Investigators

Initial Reports

Serious adverse events should be recorded during the entire study.

All SAEs that occur from the time of the first injection of study drug up through the End of Study Visit must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria).

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 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 and fax or email the completed paper SAE form to Medpace 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.

The back-up SAE form and SAE instructions form list Safety Contact Information for SAE reporting.

Follow-Up Reports

The investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient 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 (e.g., 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 steps outlined above for initial reporting of SAEs.

10.4 Pregnancy Reporting

If the patient or partner of a patient participating in the study becomes pregnant following dosing of study drug during the study or within 30 days of discontinuing study drug, the investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure In Utero form to the investigator for completion.

A patient becoming pregnant while on study drug will immediately be withdrawn from the study and early withdrawal study procedures will be performed.

The patient or partner should be followed by the investigator until completion of the pregnancy. Patients who become pregnant during the study will be consented to collect information on the outcome of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, stillbirth, neonatal death, spontaneous abortion, or congenital anomaly), the investigator should follow the steps for reporting an SAE.

10.5 Expedited Reporting

The sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the FDA, applicable competent authorities in all the Member States concerned, and to the Central EC, and in any case no later than 7 days after knowledge by the sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA, applicable competent authorities concerned, and to the Central EC concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor.

The sponsor will also inform all investigators as required. The investigators will report suspected unexpected serious adverse reactions to the IRB/Local EC as appropriate.

Expedited reporting of suspected unexpected serious adverse reactions related to non-investigational medical products (NIMPs) will not be necessary. Listings of cases related to NIMPs will be included in the Development Safety Update Report.

10.6 Reactogenicity

10.6.1 60-Minute On-Site Post-Injection Observation

On days patients receive study drug, the patients will be observed on site for at least 60 minutes after study drug administration, and potential signs/symptoms of reactogenicity will be noted by the investigator or designee, as listed in Table 5. Potential signs/symptoms of reactogenicity will be recorded in the adverse event section of the eCRF. If 2 injections were used to administer a dose, both injection sites should be monitored and findings should identify local reactions by site.

Local and general symptoms of reactogenicity will be assessed according to the FDA “Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (see Appendix C), after each study drug administration, as listed in Table 5.

10.6.2 Study Drug Injection Site Examination

Local and general symptoms of reactogenicity will be assessed according to the FDA “Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (see Appendix C), after each study drug administration, as listed in Table 5.

If a patient is not able to come to the clinic 7 days after each study drug administration (Visits 3, 5, and 7 in Table 5) for the reactogenicity and vital sign assessments, the sponsor or their designee needs to be contacted as soon as possible to discuss.

The sponsor or their designee can allow patients with Day 0 reactogenicity symptom grading of mild to moderate (Grade 1 to 2) to have the 7 days after study drug administration assessments performed by the site remotely, via a phone call with the patient.

Source documents generated from the phone call will need to include all data required per the protocol to enable assessments per FDA guidelines (Appendix C). Signs or symptoms that cannot be collected remotely will need to be specified in the source documents as missing and entered in the eCRF as missing data.

Patients with Day 0 reactogenicity symptom grading of severe or higher will have to be monitored on site until resolution or at least Grade 2 (or lower), and per local standards.

If 2 injections were used to administer a dose, both injection sites should be monitored and findings should identify local reactions by site.

The following local symptoms will be assessed after each study drug administration at each injection site:

- Administration site pain.
- Administration site tenderness.
- Administration site induration.
- Administration site erythema/redness.
- Administration site pruritus.
- Administration site swelling.

The following general symptoms will be assessed after each study drug administration:

- Malaise.
- Fatigue.
- Body temperature.
- Generalized myalgia.
- Nausea/vomiting.
- Diarrhea.
- Headache.
- Myalgia.
- Illness or clinical adverse event.

10.7 Adverse Events of Special Interest Post-Transplant

During the study, adverse events of special interest post-transplant should be recorded after transplant up to the End of Study Visit. Adverse events of special interest after kidney transplant are graft rejection, CMV syndrome, and CMV disease.

Adverse events of special interest post-transplant should be recorded at the time points listed in Table 6.

10.8 Safety Blood Collection

The patient blood samples should be drawn (prior to study drug administration on study drug dosing days) for complete blood count with differential, liver function tests and enzymes, and renal function tests per the time points listed in Table 5. Analysis of safety blood collection tests will be conducted centrally, but there may be circumstances for safety analysis to be tested locally. Results of the safety blood analysis tested locally for eligibility confirmation should be recorded on the Unscheduled Local Laboratory page of the eCRF.

During the study, safety blood collection tests will include the following (analysis will be conducted centrally):

- Complete blood count with differential: white blood cell count with differential (neutrophils, lymphocytes, eosinophils, monocytes, and basophils), red blood cell count, hemoglobin, hematocrit, reticulocyte count, and platelet count.
- Liver function tests and enzymes: albumin, ALT, AST, direct bilirubin, total bilirubin, γ-glutamyl transpeptidase, and alkaline phosphatase.
- Renal function tests: blood urea nitrogen, Chronic Kidney Disease Epidemiology Collaboration for glomerular filtration rate, and serum creatinine.

For the second and third dose of study drug (Visits 4 and 6), the study drug administration can proceed as long as the blood sample is collected for central safety lab analysis prior to study drug administration. Results of the safety lab analysis do not need to be available prior to the second and third dose administration.

10.9 Cytomegalovirus Serology

Cytomegalovirus serology is to be tested locally during Screening up to 56 days prior to Day 0.

10.10 Vital Signs

Vital signs (body temperature, heart rate, diastolic blood pressure, systolic blood pressure, and respiratory rate) will be recorded (prior to study drug administration on study drug dosing days) at the time points listed in Table 5.

10.11 Physical Examinations

Physical examination (general assessment based on the complaints of the patient and on the investigator's judgment) will be conducted (prior to study drug administration on study drug dosing days) at the time points listed in Table 5 and Table 6.

Results of physical examination will be captured in study sources, clinically significant abnormalities will be reported as patient medical history prior to randomization (for Groups 1 and 2) or dosing (for Group 3), and adverse events for worsening or emerging findings after randomization (for Groups 1 and 2) or dosing (for Group 3).

10.12 Reproductive Testing

Pregnancy tests (serum or urine hCG, urine testing limited to patients producing urine daily) will be conducted on females of childbearing potential at the time points listed in Table 5 and Table 6.

Follicle-stimulating hormone tests will be conducted on females, aged ≤50 years with 6 months of spontaneous amenorrhea, up to 14 days prior to Day 0 (as listed in Table 5).

10.13 Demographic Data

Patient demographic data (e.g., gender, race, ethnicity, birth date/year [to infer age], and weight and height [to calculate body mass index]) should be recorded during Screening up to 56 days prior to Day 0.

The patient's relevant medical history, including the patient's pre-existing conditions or signs and/or symptoms present prior to the start of study should be recorded up to 14 days prior to Day 0. Changes in the patient's medical history from Screening should be recorded on Day 0 pre-dose.

The patient's medication/vaccination history should be recorded up to 14 days prior to Day 0.

10.14 Transplant Characteristics

At the time of transplant, transplant characteristics will be collected, including degree of HLA mismatch, use of induction therapy and nature, donor characteristics (including CMV serology conducted at the institution or obtained from medical records), warm ischemia time, cold ischemia time, laparoscopy, and kidney side.

The patient's transplant characteristics should be collected as listed in Table 5 and recorded on the eCRF for transplant characteristics.

11 BIOMARKER ASSESSMENTS

11.1 Exploratory Biomarker Assessments

If the patient consents, exploratory biomarker research may be conducted on any blood samples collected during the study. These additional investigations could extend the search for other potentially relevant biomarkers for the HB-101 effect and/or safety. This may also include research to help develop ways to detect, monitor, or treat CMV infection. These additional investigations would be dependent upon clinical outcome, reagent, and sample availability. Additional consent will be obtained in the case of genetic testing being performed as part of the exploratory biomarker assessments. If the patient does not consent to the exploratory biomarker assessments, the patient will still be allowed to participate in the study.

11.2 Additional Exploratory Biomarker Assessment Using Remaining Biomarker Samples

If the patient consents, their remaining blood samples may be stored for up to 15 years for additional research related to HB-101 and CMV disease or other study treatments. This may also include research to help develop ways to detect, monitor, or treat CMV infection. A decision to perform such exploratory biomarker research studies would be based on outcome data or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

12 STATISTICS

12.1 Analysis Populations

This Phase 2 study plans to enroll approximately 150 patients. The Intent-to-Treat (ITT) Population will include all patients who are enrolled.

The modified Intent-to-Treat (mITT) Population will include all patients who receive a kidney transplant and at least 2 doses of study drug prior to kidney transplant. The mITT Population will be used for all efficacy analyses.

The Immunogenicity Population will include all patients who receive at least 1 dose of study drug and who have at least 1 post-dose immunogenicity measurement.

The Safety Population will include all patients in the ITT Population who receive any study drug.

Within each population, results will be presented according to treatment arm for Groups 1 and 2 and open-label HB-101 for Group 3.

12.2 Statistical Methods

Continuous variables will be summarized by using the number of non-missing observations, arithmetic mean, standard deviation, median, minimum, and maximum values as descriptive statistics. Categorical variables will be summarized by using the frequency count and the percentage of patients in each category as descriptive statistics.

The results of the study will be analyzed descriptively. However, should the results be favorable, subgroup analyses and additional analyses may be performed based on patient characteristics, transplant characteristics, number and timing of vaccinations, or use of immunosuppression to identify factors influencing vaccine response. Such exploratory analyses will be described in the Statistical Analysis Plan.

12.2.1 Patient Characteristics

Demographic characteristics (age, gender, etc.) and other baseline characteristics will be tabulated using descriptive statistics: frequency tables, including N, n for each category, and percentage for each category, will be generated for categorical variables; and mean, median, standard deviation, minimum, and maximum will be provided for continuous variables. Transplant characteristics will be summarized.

These data will be tabulated for all patients by treatment arm for Groups 1 and 2 and open-label HB-101 for Group 3.

12.2.2 Analysis of Efficacy

The secondary objectives are to assess the following:

- The efficacy of the administration of at least 2 doses of HB-101 compared to that of placebo in mitigating CMV DNAemia/viremia for CMV seronegative (-) recipients awaiting kidney transplantation from CMV seropositive (+) donor and followed by CMV preemptive therapy post-transplant
- The efficacy of the administration of at least 2 doses of HB-101 compared to that of placebo in decreasing the use of anti-virals at treatment dose for CMV seronegative (-)

recipients awaiting kidney transplantation from CMV seropositive (+) donor and to be treated prophylactically for CMV post-transplant

- The efficacy of the administration of at least 2 doses of HB-101 in CMV seropositive (+) recipients prior to transplant and followed by CMV post-transplant preemptive management or prophylactic anti-viral therapy

The incidence, magnitude, and duration of CMV DNAemia through 12 months after transplant will be summarized. The incidence, duration, and number of courses of CMV anti-viral therapy through 12 months after transplant will also be summarized descriptively.

These objectives will be assessed by the following endpoints:

- Incidence and time to clinically significant CMV infection, CMV disease, and CMV syndrome
- Incidence and time to CMV viremia requiring anti-viral therapy
- Incidence and duration (in days) of anti-CMV therapy courses (at therapeutic doses) required
- Incidence and time to quantifiable CMV DNAemia, peak CMV DNAemia level, and duration of CMV DNAemia above the limit of quantitation
- Incidence and time to graft failure and organ rejection

12.2.3 Analysis of Immunogenicity

A primary objective is to assess the immunogenicity of HB-101. Descriptive central statistics will be presented by treatment group for Groups 1 and 2 and open-label HB-101 for Group 3 and by post-transplant CMV management strategy (prevention or preemption) for the following immunogenicity parameters:

- CMV neut
- CMV ELISPOT pp65
- CMV ELISPOT gB

An exploratory objective is to assess additional immunogenicity parameters. Descriptive central statistics will be presented by treatment group for Groups 1 and 2 and open-label HB-101 for Group 3 and by post-transplant CMV management strategy (prevention or preemption) for the following immunogenicity parameters:

- LCMV neutralizing antibody
- CMV ICS pp65
- CMV ICS gB
- LCMV ELISPOT NP

For purposes of the primary objective, the total ELISPOT gB+pp65 AND CMV-neutralizing antibody titers will be used. Other assays will be used for the exploratory objectives.

Immunogenicity analyses will be performed based on the Immunogenicity Population. Immunogenicity parameters will be summarized descriptively by treatment arm for Groups 1 and 2 and open-label HB-101 for Group 3 and by post-transplant CMV management strategy (prevention or preemption).

12.2.4 Analysis of Safety

A primary objective is to assess the safety and reactogenicity of HB-101 in CMV seronegative (-) patients who are awaiting a kidney transplant from a CMV seropositive (+) living donor (Groups 1 and 2) and to assess the safety and reactogenicity of HB-101 in CMV seropositive (+) patients who are awaiting a kidney transplant from a CMV seropositive (+) or CMV seronegative (-) living donor (Group 3). This objective will be assessed by treatment group for Groups 1 and 2 and open-label HB-101 for Group 3 and by number of vaccinations for the following endpoints:

- Incidence and severity of adverse events, SAEs, and changes in laboratory values
- Incidence and severity of localized or generalized injection site reactions

All safety analyses will be performed on the Safety Population. Analyses will be based on adverse events, vital signs, and clinical laboratory assessments. Safety analyses will be descriptive and will be presented in tabular format with the appropriate summary statistics.

A treatment-emergent adverse event (TEAE) is defined as an adverse event with a start date and time on or after the administration of study drug. The number and percentage of patients with TEAEs will be tabulated by System Organ Class and Preferred Term for each treatment group and by severity and relationship to treatment. Serious adverse events and adverse events leading to discontinuation from study drug will be summarized by treatment group. Listings will also be generated for SAEs and adverse events leading to discontinuation of study drug. The percentage of patients reporting any adverse events of special interest will also be summarized.

Descriptive statistics will be provided for clinical laboratory data and vital signs data, presented as both actual values and changes from Day 0 over time.

12.2.5 Sample Size Determination

A total sample size of approximately 150 patients is planned for the study. Patients in Groups 1 and 2 will be randomized with a 2:1 ratio for active versus placebo. Patients in Group 3 will be enrolled to receive open-label HB-101. The sample size has been set for an initial assessment of the safety and immunogenicity of the vaccine candidate, which will provide for approximately 100 patients exposed to the HB-101 vaccine. No formal statistical assessment for sample size determination has been conducted. The sample size is considered adequate to provide the necessary safety and immunogenicity data and help with the determination of point estimates of clinical efficacy endpoints (clinically significant CMV infection as defined by the FDA “Guidance for Industry: Cytomegalovirus in Transplantation: Developing Drugs to Treat or Prevent Disease”) to design and adequately statistically power Phase 3 trials.

13 DATA MANAGEMENT AND RECORD KEEPING

13.1 Data Management

13.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (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 have been accounted for.

13.1.2 Computer Systems

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

13.1.3 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 user name and password in order to enter, review, or correct study data. These procedures must comply with 21 CFR Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

13.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

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

13.1.5 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.

13.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are 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.

14 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

14.1 Ethical Conduct of the Study

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

14.2 Institutional Review Board/Independent Ethics Committee

For United States study sites:

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

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB.

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

For European study sites:

It is the responsibility of the sponsor or their designee (i.e., Medpace) to obtain the approval of the responsible ECs according to the national regulations.

The study will only start at the respective sites once the respective committee's written approval has been given.

14.3 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/EC 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 patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The investigator will obtain written informed consent from each patient 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/EC, and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

14.4 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 (European study sites), applicable regulatory requirements, and the Declaration of Helsinki, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA'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 patient in this study, the sponsor or their designee will review with the investigator and site personnel the following documents: protocol, Investigator's Brochure, 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 are 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 CRA 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.

14.5 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/EC as appropriate. Patients 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.

14.6 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 patients (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.

14.7 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.

14.8 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.

14.9 Insurance and Indemnity

In accordance with the relevant national regulations, the sponsor has taken out subject liability insurance for all patients who give 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.

14.10 Legal Aspects

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

The study will commence (i.e., initiation of study centers) when the approvals from the regulatory authorities and the biosafety committees are in place and favorable Ethics opinions have been received.

15 STUDY ADMINISTRATIVE INFORMATION

15.1 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/EC, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/EC within 5 working days.

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APPENDIX A: SCHEDULE OF EVENTS

Table 5. Study Events Pre-Transplant

Pre-Transplant Study Visit[1,2,3,4,5,6]	**Reference to Section**	**1**	**2**	**Phone Call**	**3**	**4**	**Phone Call**	**5**	**6**	**Phone Call**	**7**	**8**	**9**
Time frame of study assessment from study drug injection		**Screening[7]**	**Day 0 Dose 1**	**3 Days After Dose 1[8]**	**7 Days After Dose 1[9]**	**28 Days After Dose 1[10,16] Dose 2**	**3 Days After Dose 2[8]**	**7 Days After Dose 2[9,11]**	**Dose 3[10,16]**	**3 Days After Dose 3[8]**	**7 Days After Dose 3[9,11]**	**Day of Transplant (Prior to Transplant Procedure)**	**30 Days After Last Dose of Study Drug (HB-101 or placebo)[11]**
Study Assessments													
Informed consent	6.1	X[14]											
CMV serology	10.9	X[14]											
Inclusion/exclusion criteria	4.1 and 4.2	X[13]	X[12]										
Demographics	10.13	X[14]											
Pregnancy test (serum or urine hCG) (for females of childbearing potential)[21]	10.12	X[13]	X[12]			X[12]			X[12]			X	X
Serum FSH[19]	10.12	X[13]											
Relevant medical history	10.13	X[13]	X[12]										
Medication/vaccination history	10.13	X[13]											
Vital signs (SBP, DBP, heart rate, respiratory rate, and body temperature)	10.10		X[12]		X	X[12]		X	X[12]		X	X	X
Physical examination	10.11	X[13]	X[12]			X[12]			X[12]			X	X
Randomization (Groups 1 and 2 only)	6.2 and 5.4		X[12,15]										
Study drug (HB-101 or placebo) injection	3.1 and 5.6.3		X			X			X				
On-site post-injection observation (60 minutes)	10.6.1		X			X			X				
Study drug (HB-101 or placebo) injection site examination for reactogenicity (assessment of local and general symptoms)	10.6.2		X		X[17]	X		X[17]	X		X[17]		
Patient's blood sample for humoral immunogenicity	9.1 and 9.2		X[12]			X[12]			X[12]			X	

Table 5. Study Events Pre-Transplant (Continued)

Pre-Transplant Study Visit[1,2,3,4,5,6]	Reference to Section	1	2	Phone Call	3	4	Phone Call	5	6	Phone Call	7	8	9
Time frame of study assessment from study drug injection		**Screening[7]**	**Day 0 Dose 1**	**3 Days After Dose 1[8]**	**7 Days After Dose 1[9]**	**28 Days After Dose 1[10,16] Dose 2**	**3 Days After Dose 2[8]**	**7 Days After Dose 2[9,11]**	**Dose 3[10,16]**	**3 Days After Dose 3[8]**	**7 Days After Dose 3[9,11]**	**Day of Transplant (Prior to Transplant Procedure)**	**30 Days After Last Dose of Study Drug (HB-101 or placebo)[11]**
Patient's blood sample for cellular immunogenicity	9.1 and 9.2		X[12]			X[12]			X[12]			X	
Safety blood collection (CBC with differential, liver function tests and enzymes, renal function tests)	10.8	X[13]	X[12]		X[18]	X[12]		X[18]	X[12]		X[18]	X	X
All concomitant medications	5.7.3		X	X	X[17]	X	X	X[17]	X	X	X[17]	X	X[20]
Record adverse events	10.1		X	X	X[17]	X	X	X[17]	X	X	X[17]	X	X
Record SAEs	10.3		X	X	X[17]	X	X	X[17]	X	X	X[17]	X	X
Transplant characteristics	10.14											X	

1. After transplant, patients will be assessed per the study visits in Table 6 (all patients of the study who receive study drug). Remaining pre-transplant phone calls/study visits will occur post-transplant and will not be protocol deviations.
2. During the study, it is possible that the time windows of study visits and assessments will be redundant. If the time window is ±2 weeks, assessments should NOT be duplicated.
3. If kidney transplant occurs prior to Day 34, the patient will be administered study drug (HB-101 or placebo) at Day 0 only. A minimum of 7 days (±2 days) must be planned between the last dose of study drug and transplantation.
4. If kidney transplant occurs between Day 35 and Day 62, the patient will be administered study drug (HB-101 or placebo) at Day 0 and Day 28. A minimum of 7 days (±2 days) must be planned between the last dose of study drug and transplantation.
5. If kidney transplant occurs between Day 63 and Day 90 or between Day 91 and Day 120, the patient will be administered study drug (HB-101 or placebo) at Day 0, Day 28, and Day 56 or Day 84. A minimum of 7 days (±2 days) must be planned between the last dose of study drug and transplantation.
6. There is a ±3 day window on assessments during the pre-transplant Treatment Period, to take into account public or religious holidays or weather, **if not explicitly specified otherwise.**
7. During the study, the Screening Period should be within 56 days of Day 0.
8. Time (window) from the last dose of study drug (HB-101 or placebo) is 3 days (±1 day).
9. Time (window) from the last dose of study drug (HB-101 or placebo) is 7 days (±3 days).
10. Time (window) of study drug (HB-101 or placebo) is 28 days (±7 days) from Dose 1 to Dose 2 and 28 or 56 days (±7 days) from Dose 2 to Dose 3 (depending on the transplant date).
11. In some cases, the post-injection follow-up visits will occur post-transplant.
12. Assessments occur prior to study drug (HB-101 or placebo) injection.
13. Assessments can be conducted for up to 14 days prior to Day 0.
14. Assessments can be conducted for up to 56 days prior to Day 0.
15. Randomization will only occur for patients in Groups 1 and 2 and should occur prior to or on Day 0 pre-dose.
16. After Day 0 dose administration, a timeframe of ±7 days from scheduled day of dosing is allowed.

Footnotes continue on next page.

17. In the event that the patient cannot return to the site for the study visit, the assessments will be collected via phone call.
18. In the event that the patient cannot return to the site for the study visit, every effort should be made to collect local safety blood collection tests and enter these into the eCRF, as well as assess for clinical significance by the investigator.
19. Only for female patients aged ≤50 years with 6 months of spontaneous amenorrhea.
20. If the 30-day post-injection follow-up visit occurs post-transplant, then only concomitant medications of special interest and those related to SAEs need to be recorded.
21. Urine pregnancy test will be limited to patients producing urine daily.

CBC = complete blood count; CMV= cytomegalovirus; Day 0 = day of first dose of study drug; Day 28 = 28 days after the first dose of study drug; Day 34 = 34 days after the first dose of study drug; Day 35 = 35 days the first dose of study drug; Day 56 = 56 days after the first dose of study drug; Day 62 = 62 days after the first dose of study drug; Day 63 = 63 days after the first dose of study drug; Day 84 = 84 days after the first dose of study drug; Day 90 = 90 days after the first dose of study drug; Day 91 = 91 days after the first dose of study drug; Day 120 = 120 days after the first dose of study drug; DBP = diastolic blood pressure; eCRF = electronic case report form; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; SAE = serious adverse event; SBP = systolic blood pressure.

Table 6. Study Events Post-Transplant (All Patients of Study Who Received Study Drug)

	Reference to Section	Follow-Up Visits[2] Monthly				Follow-Up Visit 3 Months After Transplant[1]	Follow-Up Visit 6 Months After Transplant[1]	Follow-Up Visit 9 Months After Transplant[1]	End of Study Visit[3]
		Week 1	Week 2	Week 3	Week 4				
Study Assessments[4,5]									
Pregnancy test (serum or urine hCG) (for females of childbearing potential)[7]	10.12					X	X	X	X
Physical examination	10.11					X	X	X	X
Patient's blood sample for humoral immunogenicity	9.1 and 9.2					X	X	X	X
Patient's blood sample for cellular immunogenicity	9.1 and 9.2					X	X	X	X
Record adverse events -Adverse events, regardless of causality, should be recorded up through 30 days after the last injection of study drug. -Adverse events considered related to the study drug should be recorded from 31 days after the last injection of study drug up through the End of Study Visit.	10.1	< ----------X ----------> Ongoing during study.				< ----------X----------> Ongoing during study.			
Record SAEs	10.3	< ----------X ----------> Ongoing during study.				< ----------X----------> Ongoing during study.			
Concomitant medications related to SAEs	5.7.3	< ----------X ----------> Ongoing during study.				< ----------X----------> Ongoing during study.			
Concomitant medications of special interest -Anti-virals and immunosuppressants, non-study vaccines, granulocyte colony-stimulating factor, erythropoietin, and transfusions of blood product taken 7 days prior to and after transplant.	5.7.4	< ----------X ----------> Ongoing during study.				< ----------X----------> Ongoing during study.			
Record adverse events of special interest:	10.7	< ----------X ----------> Ongoing during study.				< ----------X----------> Ongoing during study.			
Graft rejection assessments	8.2	Transplant Follow-up visits per institutional standard.							X
CMV disease and syndrome assessments	8.3	Transplant Follow-up visits per institutional standard.							X
Blood sample for CMV PCR local testing:[6]									
Patients to be followed preemptively post-transplant **for the first 16 weeks after transplant**.	8.1.1	X	X	X	X	X	X	X	X
Patients to be treated prophylactically with anti-virals post-transplant.	8.1.2	Time points following institution's standard of care.				X	X	X	X
Blood sample for central CMV PCR analysis	8.1.3	Study site personnel will draw the patient's blood sample for central CMV PCR analysis when local CMV PCR testing is conducted at the institution.				X	X	X	X

Footnotes on next page.

1. Time window of follow-up visits after transplant is ±7 days.
2. Follow-up visits will occur per institutional standards of post-transplant clinical monitoring after discussion with the sponsor.
3. Per Section 6.4, the End of Study Visit is also the 12 months post-transplant follow-up visit.
4. During the study, it is possible that the time windows of study visits and assessments will be redundant. If time window is ±2 weeks, assessments should NOT be duplicated.
5. There is a ±7 day window on assessments during the post-transplant Follow-Up Period, to take into account public or religious holidays or weather, **if not explicitly specified otherwise.**
6. Only 1 post-transplant CMV management strategy will be followed (preemptively or prophylactically).
7. Urine pregnancy test will be limited to patients producing urine daily.

CMV = cytomegalovirus; hCG = human chorionic gonadotropin; PCR = polymerase chain reaction; SAE = serious adverse event.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Liver Function Tests and Enzymes

Albumin
Alanine aminotransferase
Direct bilirubin
γ-glutamyl transpeptidase
Alkaline phosphatase
Aspartate aminotransferase
Total bilirubin

Endocrinology

Follicle-stimulating hormone [1]

1. Follicle-stimulating hormone would be conducted for all females aged ≤50 years, with 6 months of spontaneous amenorrhea, up to 14 days prior to Day 0.

Serum or urine human chorionic gonadotropin [2]

2. Serum or urine human chorionic gonadotropin would be conducted for all female patients of childbearing potential during the study. Urine testing will be limited to patients producing urine daily.

Hematology

Hematocrit
Hemoglobin
Platelet count
Red blood cell count
White blood cell count with differential [3]
Reticulocyte count

3. Neutrophils, lymphocytes, eosinophils, monocytes, and basophils.

Renal Function Tests

Blood urea nitrogen
Serum creatinine
Chronic Kidney Disease Epidemiology Collaboration [4,5]

4. Defined as glomerular filtration rate = $141\times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black] where: S_{cr} is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1.
5. Central laboratory would calculate glomerular filtration rate.

APPENDIX C: GUIDANCE FOR INDUSTRY: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

For details on Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, see the online reference at: https://www.fda.gov/downloads/BiologicsBloodVaccines/ucm091977

For a quick reference guide of local and systemic (general) reactions to study drug injection, see Table 7 and Table 8, respectively.

Table 7. Local Reaction to Study Drug Injection

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/redness[1]	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/swelling[2]	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

1. In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
2. Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

ER = emergency room.

Table 8. Systemic (General) Reaction to Study Drug Injection

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Malaise	No interference with activity	Some interference with activity	Prevents daily activity and requires medical intervention	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Prevents daily activity and requires medical intervention	ER visit or hospitalization
Body temperature/fever[1]	38.0-38.4ºC 100.4-101.4ºF	38.5-38.8ºC 101.2-102.0ºF	39.0-40.0ºC 102.1-104.0ºF	>40ºC >104ºF ER visit or hospitalization
Generalized myalgia[2]	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Nausea or vomiting	No interference with activity or 1-3 episodes/24 hours	Some interruption with activities or >2 episodes in 24 hours	Prevents daily activities and requires IV hydration	ER hospitalization for hypotensive shock
Diarrhea	2-3 loose stools or <400 gms/24 hours	4-5 loose stools or 400-800 gms/24 hours	6 or more watery stools or >800 gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Myalgia[2]	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

1. The temperature, not the grade, is captured in the eCRF.
2. If myalgia is localized, use the myalgia grading scale, not the generalized myalgia grading scale.

eCRF = electronic case report form; ER = emergency room; IV = intravenous.

APPENDIX D: GRADING SYSTEM OF GRAFT REJECTION ASSESSMENTS

The grading system of graft rejection assessments should be per Banff kidney rejection grading (Loupy, et al. 2017).

For a quick reference of the grading system of graft rejection assessments per Banff kidney rejection grading, see Table 9 and Table 10.

Reference:

Loupy A, Haas M, Racusen L, Glotz D, Seron D, Nankivell BJ, Colvin RB, Afrouzian M, Akalin R, Alachkar N, Bagnasco S, Becker JU, Cornell L, Drachenberg C, Dragun D, de Kort H, Gibson IW, Kraus ES, Lefaucheur C, Legendre C, Liapis H, Muthukumar R, Nickeleit V, Orandi B, Park W, Rabant M, Randhawa P, Reed EF, Roufosse C, Seshan SV, Sis B, Singh HK, Schinstock C, Tambur A, Zeevi A, Mengel M. The Banff 2015 Kidney Meeting Report: Current Challenges in Rejection Classification and Prospects for Adopting Molecular Pathology. Am J Transplant. 2017 Jan;17(1):28-41.

Table 9. Updated 2015 Banff Classification Categories

Category 1: Normal biopsy or nonspecific changes	
Category 2: Antibody-mediated changes	
Acute/active ABMR	All 3 features must be present for diagnosis. Biopsies showing histological features plus evidence of current/recent antibody interaction with vascular endothelium or DSA, but not both, may be designated as suspicious for acute/active ABMR. Lesions may be clinically acute or smoldering or may be subclinical; it should be noted if the lesion is C4d-positive or C4d-negative, based on the following criteria: 1. Histologic evidence of acute tissue injury, including one or more of the following: • Microvascular inflammation (g >0 in the absence of recurrent or de novo glomerulonephritis, and/or ptc >0) • Intimal or transmural arteritis (v >0)[1] • Acute thrombotic microangiopathy in the absence of any other cause • Acute tubular injury in the absence of any other apparent cause 2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following: • Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections or C4d >0 by IHC on paraffin sections) • At least moderate microvascular inflammation ([g + ptc] ≥2), although in the presence of acute TCMR, borderline infiltrate, or infection; ptc ≥2 alone is not sufficient, and g must be ≥1 • Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated 3. Serologic evidence of DSAs (HLA or other antigens): • Biopsies suspicious for ABMR on the basis of meeting criteria 1 and 2 should prompt expedited DSA testing
Chronic active ABMR[2]	All 3 features must be present for diagnosis. As with acute/active ABMR, biopsies showing histological features plus evidence of current/recent antibody interaction with vascular endothelium or DSA, but not both, may be designated as suspicious, and it should be noted if the lesion is C4d-positive or C4d-negative, based on the criteria listed: 1. Histologic evidence of chronic tissue injury, including one or more of the following: • TG (cg >0), if no evidence of chronic thrombotic microangiopathy; includes changes evident by EM only (cg1a; see Table 10) • Severe peritubular capillary basement membrane multilayering (requires EM)[3] • Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor chronic ABMR if there is no prior history of biopsy-proven TCMR with arterial involvement but are not required 2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following: • Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d >0 by IHC on paraffin sections) • At least moderate microvascular inflammation ([g + ptc] ≥2), although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥2 alone is not sufficient and g must be ≥1 • Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated 3. Serologic evidence of DSAs (HLA or other antigens): • Biopsies suspicious for ABMR on the basis of meeting criteria 1 and 2 should prompt expedited DSA testing

Table 9. Updated 2015 Banff Classification Categories (Continued)

Category 2: Antibody-mediated changes (continued)	
C4d staining without evidence of rejection	All 3 features must be present for diagnosis[4] 1. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d >0 by IHC on paraffin sections) 2. g = 0, ptc = 0, cg = 0 (by light microscopy and by EM if available), v = 0; no TMA, no peritubular capillary basement membrane multilayering, no acute tubular injury (in the absence of another apparent cause for this) 3. No acute cell-mediated rejection (Banff 1997 type 1A or greater) or borderline changes
Category 3: Borderline changes	
Suspicious for acute TCMR	• Foci of tubulitis (t1, t2, or t3) with minor interstitial inflammation (i0 or i1) or interstitial inflammation (i2, i3) with mild (t1) tubulitis; retaining the i1 threshold for borderline from Banff 2005 is permitted although this must be made transparent in reports and publications • No intimal arteritis (v = 0)
Category 4: TCMR	
Acute TCMR Grade	IA. Significant interstitial inflammation (>25% of nonsclerotic cortical parenchyma, i2, or i3) and foci of moderate tubulitis (t2) IB. Significant interstitial inflammation (>25% of nonsclerotic cortical parenchyma, i2, or i3) and foci of severe tubulitis (t3) IIA. Mild to moderate intimal arteritis (v1) with or without interstitial inflammation and tubulitis IIB. Severe intimal arteritis comprising >25% of the luminal area (v2) with or without interstitial inflammation and tubulitis III. Transmural arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)
Chronic active TCMR	Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neointima); note that such lesions may represent chronic active ABMR as well as TCMR; the latter may also be manifest in the tubulointerstitial compartment
Category 5: Interstitial fibrosis and tubular atrophy	
Grade	I. Mild interstitial fibrosis and tubular atrophy (≤25% of cortical area) II. Moderate interstitial fibrosis and tubular atrophy (26-50% of cortical area) III. Severe interstitial fibrosis and tubular atrophy (>50% of cortical area)
Category 6: Other changes not considered to be caused by acute or chronic rejection	
	BK virus nephropathy Posttransplant lymphoproliferative disorders Calcineurin inhibitor nephrotoxicity Acute tubular injury Recurrent disease De novo glomerulopathy (other than transplant glomerulopathy) Pyelonephritis Drug-induced interstitial nephritis

1. It should be noted that these arterial lesions may be indicative of ABMR, TCMR, or mixed ABMR/TCMR. The v lesions are only scored in arteries having a continuous media with 2 or more smooth muscle layers.
2. Lesions of chronic, active ABMR can range from primarily active lesions with early TG evident only by EM (cg1a) to those with advanced TG and other chronic changes in addition to active microvascular inflammation. In the absence of evidence of current/recent antibody interaction with the endothelium, the term "active" should be omitted; in such cases, DSAs may be present at the time of biopsy or at any previous time after transplantation.
3. Seven or more layers in 1 cortical peritubular capillary and 5 or more in 2 additional capillaries, avoiding portions cut tangentially.
4. The clinical significance of these findings may be quite different in grafts exposed to anti-blood group antibodies (ABO-incompatible allografts), in which they do not appear to be injurious to the graft and may represent accommodation; however, with anti-HLA antibodies, such lesions may progress to chronic ABMR and more outcome data are needed.

ABMR = antibody-mediated rejection; cg = glomerular double contours; DSA = donor-specific antibody; EM = electron microscopy; g = glomerulitis; HLA = human leukocyte antigen; i = inflammation; IF = immunofluorescence; IHC = immunohistochemistry; ptc = peritubular capillaritis; t = tubulitis; TCMR = T cell-mediated rejection; TG = transplant glomerulopathy; TMA = thrombotic microangiopathy; v = intimal arteritis.

Table 10. Banff Lesion Grading System

Lesions	
Quantitative criteria for inflammation: i score	
i0	No inflammation or in <10% of unscarred cortical parenchyma
i1	Inflammation in 10-25% of unscarred cortical parenchyma
i2	Inflammation in 26-50% of unscarred cortical parenchyma
i3	Inflammation in >50% of unscarred cortical parenchyma
Quantitative criteria for tubulitis: t score	
t0	No mononuclear leukocytes in tubules
t1	Foci with 1 to 4 leukocytes per tubular cross-section (or 10 tubular cells)
t2	Foci with 5 to 10 leukocytes per tubular cross-section (or 10 tubular cells)
t3	Foci with >10 leukocytes per tubular cross-section or the presence of 2 or more areas of tubular basement membrane destruction accompanied by i2/i3 inflammation and t2 elsewhere
Quantitative criteria for intimal arteritis: v score	
v0	No arteritis
v1	Mild to moderate intimal arteritis in at least 1 arterial cross-section
v2	Severe intimal arteritis with at least 25% luminal area lost in at least 1 arterial cross-section
v3	Transmural arteritis and/or arterial fibrinoid change and medial smooth muscle necrosis with lymphocytic infiltrate in vessel
Quantitative criteria for glomerulitis: g score	
g0	No glomerulitis
g1	Glomerulitis in <25% of glomeruli
g2	Segmental or global glomerulitis in 25-75% of glomeruli
g3	Glomerulitis in >75% of glomeruli
Quantitative criteria for peritubular capillaritis: ptc score	
ptc0	At least 1 leukocyte in <10% of cortical PTCs and/or maximum number of leukocytes <3
ptc1	At least 1 leukocyte cell in ≥10% of cortical PTCs with 3 to 4 leukocytes in most severely involved PTC
ptc2	At least 1 leukocyte in ≥10% of cortical PTCs with 5 to 10 leukocytes in most severely involved PTC
ptc3	At least 1 leukocyte in ≥10% of cortical PTCs with >10 leukocytes in most severely involved PTC
Quantitative criteria for total inflammation: ti score	
ti0	No or trivial interstitial inflammation (<10% of total cortical parenchyma)
ti1	10-25% of total cortical parenchyma inflamed
ti2	26-50% of total cortical parenchyma inflamed
ti3	>50% of total cortical parenchyma inflamed
Quantitative criteria for inflammation in area of interstitial fibrosis and tubular atrophy: i-IFTA score	
i-FTA0	No inflammation or <10% of scarred cortical parenchyma
i-IFTA1	Inflammation in 10-25% of scarred cortical parenchyma
i-IFTA2	Inflammation in 26-50% of scarred cortical parenchyma
i-IFTA3	Inflammation in >50% of scarred cortical parenchyma
Quantitative criteria for C4d score	
C4d0	No staining of PTCs (0%)
C4d1	Minimal C4d staining (>0 but <10% of PTCs)
C4d2	Focal C4d staining (10-50% of PTCs)
C4d3	Diffuse C4d staining (>50% of PTCs)
Quantitative criteria for double contour: cg score	
cg0	No GBM double contours by light microscopy or EM
cg1a	No GBM double contours by light microscopy but GBM double contours (incomplete or circumferential) in at least 3 glomerular capillaries by EM, with associated endothelial swelling and/or subendothelial electron-lucent widening
cg1b	Double contours of the GBM in 1-25% of capillary loops in the most affected nonsclerotic glomerulus by light microscopy; EM confirmation is recommended if EM is available
cg2	Double contours affecting 26-50% of peripheral capillary loops in the most affected glomerulus
cg3	Double contours affecting >50% of peripheral capillary loops in the most affected glomerulus
Quantitative criteria for mesangial matrix expansion: mm score	
mm0	No more than mild mesangial matrix increase in any glomerulus
mm1	At least moderate mesangial matrix increase up to 25% of nonsclerotic glomeruli
mm2	At least moderate mesangial matrix increase in 26-50% of nonsclerotic glomeruli
mm3	At least moderate mesangial matrix increase in >50% of nonsclerotic glomeruli

Table 10. Banff Lesion Grading System (Continued)

Lesions	
Quantitative criteria for arteriolar hyalinosis: ah score	
ah0	No PAS-positive hyaline arteriolar thickening
ah1	Mild to moderate PAS-positive hyaline thickening in at least 1 arteriole
ah2	Moderate to severe PAS-positive hyaline thickening in more than 1 arteriole
ah3	Severe PAS-positive hyaline thickening in many arterioles
Alternative quantitative criteria for hyaline arteriolar thickening: aah score	
aah0	No typical lesions of calcineurin inhibitor-related arteriolopathy
aah1	Replacement of degenerated smooth muscle cells by hyaline deposits in only 1 arteriole, without circumferential involvement
aah2	Replacement of degenerated smooth muscle cells by hyaline deposits in more than 1 arteriole, without circumferential involvement
aah3	Replacement of degenerated smooth muscle cells by hyaline deposits with circumferential involvement, independent of the number of arterioles involved
Quantitative criteria for vascular fibrous intimal thickening: cv score	
cv0	No chronic vascular changes
cv1	Vascular narrowing of up to 25% luminal area by fibrointimal thickening
cv2	Vascular narrowing of 26-50% luminal area by fibrointimal thickening
cv3	Vascular narrowing of >50% luminal area by fibrointimal thickening
Quantitative criteria for interstitial fibrosis: ci score	
ci0	Interstitial fibrosis in up to 5% of cortical area
ci1	Interstitial fibrosis in 6-25% of cortical area (mild interstitial fibrosis)
ci2	Interstitial fibrosis in 26-50% of cortical area (moderate interstitial fibrosis)
ci3	Interstitial fibrosis in >50% of cortical area (severe interstitial fibrosis)
Quantitative criteria for tubular atrophy: ct score	
ct0	No tubular atrophy
ct1	Tubular atrophy involving up to 25% of the area of cortical tubules (mild tubular atrophy)
ct2	Tubular atrophy involving 26-50% of the area of cortical tubules (moderate tubular atrophy)
ct3	Tubular atrophy involving in >50% of the area of cortical tubules (severe tubular atrophy)

aah = hyaline arteriolar thickening; ah = arteriolar hyalinosis; cg = glomerular double contours; ci = interstitial fibrosis; ct = tubular atrophy; cv = vascular fibrous intimal thickening; EM = electron microscopy; g = glomerulitis; GBM = glomerular basement membrane; i = inflammation; i-IFTA = interstitial inflammation in areas of interstitial fibrosis and tubular atrophy; mm = mesangial matrix expansion; PAS = periodic acid-Schiff; ptc = peritubular capillaritis; PTC = peritubular capillary; t = tubulitis; ti = total inflammation; v = intimal arteritis.

APPENDIX E: THE DEFINITION OF CYTOMEGALOVIRUS SYNDROME

Cytomegalovirus Syndrome Definition

Cytomegalovirus (CMV) syndrome is defined as CMV viremia identified by quantitative polymerase chain reaction (or phosphoprotein 65 kD antigenemia and other sponsor-approved CMV assays) and at least 1 of the following criteria: a fever ≥38°C; new onset severe malaise; leukopenia on 2 successive measurements separated by at least 24 hours (defined as white blood cell [WBC] count of <3500 cells/μL if presymptomatic count was ≥4000 cells/μL or a decrease in WBC of >20% if the presymptomatic count was <4000 cells/μL); atypical lymphocytosis of ≥5%; thrombocytopenia (defined as a platelet count of <100,000 cells/μL if the prior count was ≥115,000 cells/μL or a decrease of >20% if the prior count was <115,000 cells/μL); or elevation of hepatic transaminases to ≥2 × upper limit of normal.

APPENDIX F: THE DEFINITION OF CYTOMEGALOVIRUS DISEASE

Cytomegalovirus Disease Definition

Reference:

Ljungman P, Boeckh M, Hirsch HH, Josephson F, Lundgren J, Nichols G, Pikis A, Razonable RR, Miller V, Griffiths PD, Disease Definitions Working Group of the Cytomegalovirus Drug Development Forum. Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials. Clin Infect Dis. 2017;64(1):87-91.