STATISTICAL ANALYSIS PLAN

Protocol 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
Protocol Version/Date:	6.0/09 December 2020
Investigational Product:	HB-101
Sponsor:	Hookipa Biotech GmbH Helmut-Qualtinger-Gasse 2 1030 Vienna Austria
SAP Version/Date:	1.0/26 Jul 2022

SIGNATURE PAGE

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VERSION HISTORY

Version	Version Date	Description
1.0	26Jul2022	Initial approved version.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ATC	Anatomical therapeutic chemical
BMI	Body Mass Index
CMV	Cytomegalovirus
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
ELISPOT	Enzyme-linked Immunospot
FDA	Food and Drug Administration
gB	Glycoprotein B
HCMV	Human Cytomegalovirus
HLA	Human leukocyte antigen
ICS	Intracellular Cytokine Staining
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
neut	Neutralization
NP	Nucleoprotein
NTA	Neutralization antibody titers
PCR	Polymerase chain reaction
pp65	phosphoprotein 65 kD
rLCMV	Replication-deficient Lymphocytic Choriomeningitis Virus
SAE	Serious adverse event
SAP	Statistical Analysis Plan
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number H-100-002. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objectives

- To assess the safety and reactogenicity of HB-101.
- To assess the immunogenicity of HB-101.

2.1.2 Secondary Objectives

- 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.
- 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.

2.1.3 Exploratory Objectives

To assess additional immunogenicity parameters of HB-101.

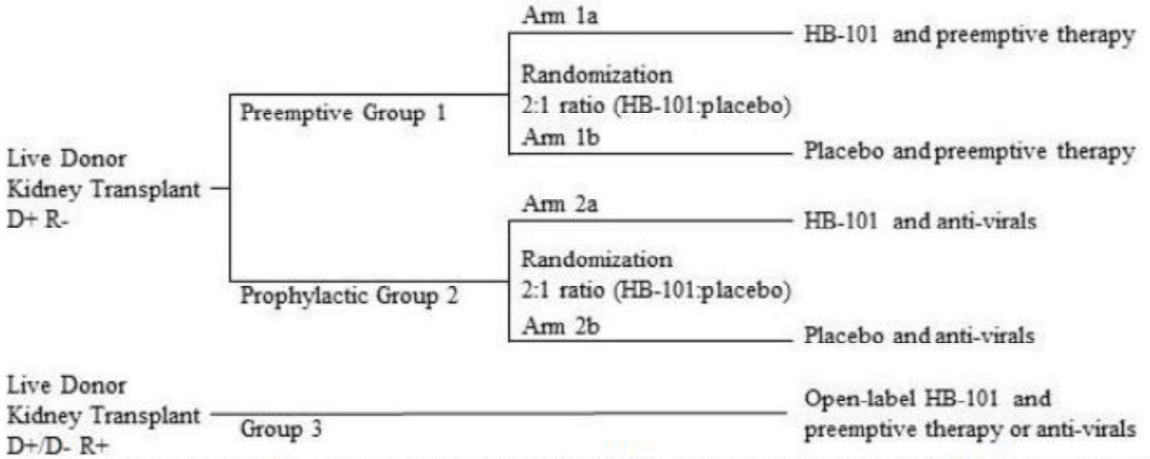
2.2 Study Design

2.2.1 Overview

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 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 Table 1.

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

Table 1 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.

The schedule of events and Immunogenicity analysis and time points are listed in Appendix A.

2.2.2 Randomization and Blinding

For 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.

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.

Hookipa Biotech study team members may 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 designee or research nurse at each site who prepares the study drug for blinded administration.

2.2.3 Study Drug

HB-101 uses replication-deficient lymphocytic choriomeningitis virus (rLCMV) as a vector for a bivalent recombinant vaccine against Human Cytomegalovirus (HCMV). One vector expresses the pp65 protein of HCMV, and one expresses a truncated glycoprotein B (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. Sodium chloride (0.9% w/v) will be used as the placebo. The sponsor will supply this saline for the study.

2.2.4 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 (FDA) "Guidance for Industry: Cytomegalovirus in Transplantation: Developing Drugs to Treat or Prevent Disease") to design and adequately statistically power Phase 3 trials.

2.3 Study Endpoints

2.3.1 Primary Endpoints

For objective of assessing the safety and reactogenicity of HB-101, the primary endpoints are

- Incidence and severity of Adverse events (AEs), serious adverse events (SAEs), and changes in laboratory values
- Incidence and severity of localized or generalized injection site reactions

For objective of assessing the immunogenicity of HB-101, the primary endpoints are descriptive central statistics of the following immunogenicity parameters:

- CMV Neutralization (neut)
- CMV Enzyme-linked immunospot (ELISPOT) phosphoprotein 65 Kd (pp65)
- CMV ELISPOT gB

2.3.2 Secondary Efficacy Endpoints

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

2.3.3 Exploratory Efficacy Endpoints

Descriptive central statistics of the following immunogenicity parameters:

- CMV Intracellular cytokine staining (ICS) pp65
- CMV ICS gB
- LCMV ELISPOT nucleoprotein (NP)

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis and Study Days

Analysis day will be calculated from the date of kidney transplant. The day of kidney transplant will be Analysis Day 1, and the day immediately before Analysis Day 1 will be Analysis Day -1. There will be no Analysis Day 0.

Study Day may also be calculated based on the date of first dose of study drug. The day of the first dose of study drug will be Study Day 0, and the day immediately before Study Day 0 will be Study Day -1.

3.1.2 Definition of Baseline

Unless otherwise defined, baseline is defined as the last measurement prior to the first dose of study drug. Some analyses may also use the date of kidney transplant as the reference point for pre- and post-transplant analyses.

3.1.3 Summary Statistics

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. All data will also be listed.

Within each population, results will be presented according to treatment arm and total for Groups 1 and 2 and open-label HB-101 for Group 3 and total for all the three groups unless specified otherwise. Results from Groups 1 and 2 and results from Group 3 will be displayed in separate outputs unless specified otherwise.

3.1.4 Hypothesis Testing

There is no formal hypothesis testing for this study. This study is for an initial assessment of the safety and immunogenicity of the vaccine candidate.

3.1.5 Handling of Dropouts and Missing Data

In general, data will be analyzed and presented as observed and will not be imputed for the analysis of efficacy and safety.

In case the start and end dates for adverse events and concomitant medications/procedures are missing or incomplete, the missing component(s) will be assumed as the most conservative value possible. For example, Adverse Events (AEs) with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study treatment or ended prior to the start of study treatment. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original case report forms (CRFs) will be presented in the data listings.

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

3.1.6 COVID-19 pandemic

The COVID-19 pandemic may impact the conduct of the study from different aspects including quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations if site personnel or trial patients become infected with COVID-19. Study procedures affected by the COVID-19 pandemic are recorded, as are reasons for study discontinuation/screen failure, protocol deviations, and adverse events. All such data will be listed, and any summaries of this data are mentioned below.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population will include all patients who are enrolled. For Group 1 and Group 2, enrolled will be defined as being randomized and patients will be analyzed by their randomized treatment group. For Group 3, enrolled will be defined as receiving at least one dose of study drug.

3.2.2 Modified Intent-to-Treat (mITT) Population

The modified Intent-to-Treat (mITT) Population will include all ITT 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 and analyzed in the same fashion as the ITT Population.

3.2.3 Immunogenicity Population

The Immunogenicity Population will include all ITT patients who receive at least 1 dose of study drug and who have at least 1 post-dose immunogenicity measurement. The Immunogenicity Population will be analyzed in the same fashion as the ITT Population.

3.2.4 Safety Population

The Safety Population will include all patients in the ITT Population who receive any study drug and will be analyzed by their actual treatment group (if different than randomized).

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of patients who were screened (signed informed consent), discontinued early during screening (screen failures), and randomized/enrolled will be summarized in total based on all screened patients. Reasons for screen failure will also be summarized, including those due to the COVID-19 pandemic.

Counts and percentages of patients who were randomized to Group 1 and Group 2 and enrolled to Group 3, discontinued early from the study, and completed the study will be summarized

based on the ITT Population. Reasons for early discontinuation will also be summarized, including those due to the COVID-19 pandemic.

3.3.2 Protocol Deviations

Counts and percentages of patients with CSR-reportable protocol deviations by deviation category will be summarized based on the ITT Population. Protocol deviations related to COVID-19 may also be summarized.

3.3.3 Analysis Populations

Counts and percentages of patients in each analysis population will be summarized based on the ITT Population. Reasons for exclusion from each analysis population may also be summarized.

3.3.4 Demographic and Baseline Characteristics

Demographic characteristics (age, gender, etc.) and other baseline characteristics, including transplant characteristics, will be summarized for the ITT Population and repeated for other analysis populations (if different than the ITT Population).

The following demographic and baseline characteristics will be summarized:

- Age (years) at Informed Consent
- Sex
- Childbearing potential
- Race
- Ethnicity
- Height at screening (cm)
- Weight at screening (kg)
- Body mass index (BMI) (kg/m^2) at screening and BMI categories (<30 kg/m^2, ≥ 30 kg/m^2)
- Baseline CMV quantitative PCR result
- Degree of human leukocyte antigen mismatch
- Use of induction therapy or not
- Relation of donor to patient
- Donor CMV serology
- ABO incompatibility
- Donor living status
- Warm ischemia time
- Cold ischemia time and unit
- Use of laparoscopy or not
- Side of kidney

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. Counts and percentages of patients with medical history by system organ class and preferred term will be summarized based on the Safety Population for all medical history that did end prior to 14 days before Day 0.

3.3.6 Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the World Health Organization (WHO) Drug Dictionary version March 2019G B3. For summary purposes, medications will be considered prior medications if they stopped within 14 day of Day 0 and prior to the first dose of study drug, and concomitant medications if they were taken at any time after the first dose of study drug (i.e. started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

Counts and percentages of patients taking prior and concomitant medications by ATC class and preferred term will be summarized based on the Safety Population.

3.3.7 Study Drug Exposure

The number of doses of study drug taken (0, 1, 2, 3+) will be summarized for the Safety Population.

3.4 Endpoint Assessment

The mITT Population will be used for all endpoint analyses related to efficacy, the Safety Population for all endpoint analyses related to safety, and the Immunogenicity Population for all endpoint analyses related to immunogenicity. 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.

3.4.1 Primary Endpoints

3.4.1.1 Adverse Events (AEs)

AEs will be captured from the date of informed consent through study completion. All AEs will be coded to system organ class and preferred term using the MedDRA version 22.0 and analyzed using the Safety Population. A treatment-emergent adverse event (TEAE) is defined as an adverse event with a start date and time on or after the first administration of study drug and up to 30 days past the last administration of study drug, or after 30 days past last dose and meeting one of the following criteria:

- Serious AE (SAE)
- AE of special interest post-transplant
- AE related to study medication
- AE related to HLA sensitization

Adverse events of special interest post-transplant are graft rejection, CMV syndrome, and CMV disease.

An overview of AEs will be provided including counts and percentages of patients with the following:

- Any AEs
- Any TEAEs
- Any Grade 3 (severe) or higher TEAEs
- Any Grade 3 (severe) or higher TEAEs related to study medication

- Any TEAEs related to study medication
- Any TEAEs of special interest post-transplant
- Any TEAEs of special interest post-transplant and related to study medication
- Any serious AEs (SAEs)
- Any treatment-emergent serious AEs (TE-SAEs)
- Any TEAEs leading to discontinuation of study medication
- Any TEAEs related to study medication leading to discontinuation of study medication
- Any TEAEs related to COVID-19
- Most frequently reported adverse events related to study medication

Both the pre-transplant and post-transplant adverse events and adverse events of above categories will be included in the table summary. The post-transplant adverse event will be summarized by treatment group for Groups 1 and 2 and open-label HB-101 for Group 3.

Counts and percentages of patients will also be presented by system organ class and preferred term for each of the categories in the overview. Counts and percentages of most frequently reported adverse events and most frequently reported adverse events related to study medication may also be displayed in separate tables.

Listings will be presented specifically for SAEs and TEAEs leading to discontinuation of study drug.

3.4.1.2 Clinical Laboratory Data

Descriptive statistics will be provided for clinical laboratory data including CMV viremia, presented as both actual values and changes from baseline over time, for the Safety Population. A shift analysis from baseline to the highest post-baseline value for the liver function tests may also be presented. A list of laboratory analytes is included in Appendix B.

3.4.1.3 Injection Site Reactions

For assessing the safety and reactogenicity of HB-101, the incidence and severity of localized or generalized injection site reactions will be summarized by symptom type and by injection site and symptom type for the Safety Population.

3.4.1.4 Immunogenicity

To assess the immunogenicity of HB-101, descriptive central statistics will be presented for the following immunogenicity parameters using the Immunogenicity Population:

- CMV neut
- CMV ELISPOT pp65
- CMV ELISPOT gB

The summary will also be based on the number of doses of medication or placebo received (only for 2 and 3 doses). For CMV ELISPOT pp65, CMV ELISPOT gB, and the combination of CMV ELISPOT pp65 and gB, counts and percentages of positive responses will be displayed in addition to the descriptive central statistics. A Wilcoxon signed-rank test will be performed by each treatment and dose group versus the Pre-Dose 1 values from that group. A Mann-Whitney U test of HB-101 versus the corresponding Placebo at each time point will also be performed. The CMV neut parameter will undergo all tests and summaries of the other parameters with the

addition of a 95% confidence interval of the geometric mean titer and a categorical summary of the increase of titer result from Pre-Dose 1 based on the following ranges:

- >2-fold
- >3-fold
- >4-fold

The CMV neut parameter summarization will also be repeated by viremia status (with or without) at Pre-Dose 1 (Group 3 only) and day of transplant.

The result of CMV ELISPOT pp65, CMV ELISPOT gB, pp65 together with gB, and CMV neut result will be plotted against the time of dose received and day of transplant by study medication, dose, and group. The boxplot of CMV neut result by treatment and dose will be provided. The plot of seroconversion rates by dose and treatment will be plotted against the time of dose received and day of transplant. The CMV neutralization antibody titers (NTA) responses and CMV viremia will be plotted by treatment, dose, and viremia status against the time of dose received and day of transplant.

The pre- and post-transplant immunosuppressant use will be summarized by preferred term for all post-transplant randomized patients.

The CMV serology information will be summarized for transplant recipient and kidney donor.

For patients who developed HLA sensitization, the pre- and post-dose sample and recipient genotype information will be listed.

3.4.2 Secondary Endpoints

The incidence, duration, and number of courses of CMV anti-viral therapy through 12 months after transplant will be summarized descriptively for the mITT Population, as will the following:

- 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

The post-transplant CMV syndrome, disease, infection, infection requiring anti-viral therapy, post-transplant anti-viral therapy use will also be summarized in separate tables by syndrome and disease type according to the dose of vaccines or placebos received and for all post-transplant patients regardless of dose of medications.

3.4.2.1 Secondary Endpoint Definitions

- CMV infection is defined as quantifiable local CMV PCR test results above the lower limit of quantification (LLOQ).
- CMV syndrome is defined as CMV infection with at least one syndrome symptom present.
- CMV syndrome disease is defined as CMV infection with (CMV syndrome OR at least one end-organ disease category present).

- CMV infection requiring anti-viral therapy is defined as the triggered start of anti-virals as entered on Local CMV PCR results CRF.
- Time to infection is defined as the date of the first quantifiable result above LLOQ – transplant date.
- Duration above LLOQ is the number of consecutive days with a quantifiable result above LLOQ, starting with the first such value.
- Anti-viral therapy use is defined as the recorded use of flagged anti-viral therapies on the concomitant medication CRF following the triggered start of anti-virals as entered on the Local CMV PCR results CRF.
- Time to anti-viral therapy use is defined as the date of the first post-transplant anti-viral use – transplant date.
- Duration of anti-viral therapy use is the total number of days of recorded post-transplant anti-viral use.
- Number of anti-viral therapy courses is the sum of unique recorded post-transplant anti-viral entries on the concomitant medication CRF.
- Time to rejection is defined as first date of biopsy with rejection recorded – transplant date.

3.4.3 Exploratory Endpoints

To assess additional immunogenicity parameters, descriptive central statistics will be presented for the following immunogenicity parameters for the Immunogenicity Population:

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

3.4.4 Subgroups

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. These can be done by summary table using additional stratification factors.

3.5 Safety Assessment

These additional safety data will be summarized based on the Safety Population.

3.5.1 Vital Signs

Vital signs including height, weight, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, body temperature will be summarized by descriptive statistics for each treatment group. Both actual values and changes from baseline over time will be summarized.

3.5.2 Physical Examinations

The overall physical examination result at each time point will be summarized with counts and percentages.

4 ANALYSIS TIMING

4.1 Interim Analysis

An interim analysis may take place for this study at a timepoint determined by the Sponsor.

Derivations and definitions for the interim analysis will be based on those required for the final analysis contained in this analysis plan, unless deviations are stated within the text. The list of outputs provided with the full set of output templates (planned for the final analysis) will highlight which of these outputs will also be provided for the interim analysis.

Methods for handling the interim analysis are same as the final analysis discussed in Section 3.

5 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in patient data listings which will be sorted by patient and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: SCHEDULE OF EVENTS

Study Events Pre-Transplant

Pre-Transplant Study Visit[1,2,3,4,5,6]	**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 Dose3** [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	X[14]											
CMV serology	X[14]											
Inclusion/exclusion criteria	X[13]	X[12]										
Demographics	X[14]											
Pregnancy test (serum or urine hCG) (for females of childbearing potential)[21]	X[13]	X[12]			X[12]			X[12]			X	X
Serum FSH[19]	X[13]											

Pre-Transplant Study Visit[1,2,3,4,5,6]	**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 Dose3** [9,11]	**Day of Transplant (Prior to Transplant Procedure)**	**30 Days After Last Dose of Study Drug (HB-101 or placebo)**[11]
Relevant medical history	X[13]	X[12]										
Medication/vaccination history	X[13]											
Vital signs (SBP, DBP, heart rate, respiratory rate, and body temperature)		X[12]		X	X[12]		X	X[12]		X	X	X
Physical examination	X[13]	X[12]			X[12]			X[12]			X	X
Randomization (Groups 1 and 2 only)		X[12,15]										
Study drug (HB-101 or placebo) injection		X			X			X				
On-site post-injection observation (60 minutes)		X			X			X				
Study drug (HB-101 or placebo) injection site examination for reactogenicity		X		X[17]	X		X[17]	X		X[17]		

Pre-Transplant Study Visit[1,2,3,4,5,6]	**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 Dose3 [9,11]**	**Day of Transplant (Prior to Transplant Procedure)**	**30 Days After Last Dose of Study Drug (HB-101 or placebo)[11]**
(assessment of local and general symptoms)												
Patient's blood sample for humoral immunogenicity		X[12]			X[12]			X[12]			X	
Safety blood collection (CBC with differential, liver function tests and enzymes, renal function tests)	X[13]	X[12]		X[18]	X[12]		X[18]	X[12]		X[18]	X	X
All concomitant medications		X	X	X[17]	X	X	X[17]	X	X	X[17]	X	X[20]
Record adverse events		X	X	X[17]	X	X	X[17]	X	X	X[17]	X	X
Record SAEs		X	X	X[17]	X	X	X[17]	X	X	X[17]	X	X
Transplant characteristics											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.
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.

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

	Follow-Up Visit[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]					X	X	X	X
Physical examination					X	X	X	X
Patient's blood sample for humoral immunogenicity					X	X	X	X
Patient's blood sample for cellular immunogenicity					X	X	X	X
Record adverse events 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.	<----------X----------> Ongoing during study				<----------X----------> Ongoing during study			
Record SAEs	<----------X----------> Ongoing during study				<----------X----------> Ongoing during study			
Concomitant medications related to SAEs	<----------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.	<----------X----------> Ongoing during study				<----------X----------> Ongoing during study			
Record adverse events of special interest:	<----------X----------> Ongoing during study				<----------X----------> Ongoing during study			
Graft rejection assessments	Transplant Follow-up visits per institutional standard.							X

CMV disease and syndrome assessments	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.	X	X	X	X	X	X	X	X
Patients to be treated prophylactically with anti-virals post-transplant.	Time points following institution's standard of care.				X	X	X	X
Blood sample for central CMV PCR analysis	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

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.

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

APPENDIX B: CLINCIAL LABORATORY ANALYTES

Liver Function Tests and Enzymes:

Albumin

Alkaline phosphatase

Alanine aminotransferase

Aspartate aminotransferase

Direct bilirubin

γ-glutamyl transpeptidase

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 = $141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black] where: Scr 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 Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.
5. Central laboratory would calculate glomerular filtration rate.