Statistical Analysis Plan

NCT Number: NCT05137717

Title: A Phase 3, Open-Label, Single-Arm Study to Assess the Efficacy, Safety, and Pharmacokinetics of Maribavir for the Treatment of Cytomegalovirus (CMV) Infection in Japanese Recipients of a Hematopoietic Stem Cell Transplant (HSCT) or Solid Organ Transplant (SOT)

Study Number: TAK-620-3001

Document Version and Date: Version 3.0 / 26-Jul-2023

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STATISTICAL ANALYSIS PLAN

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Phase: 3

Version: 3.0

Date: 26-Jul-2023

Prepared by: [redacted]

Based on:

Protocol Version: Amendment 1.0

Protocol Date: 28-Oct-2021

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
1.0	16-Nov-2021	[Not Applicable]
2.0	23-May-2023	・Updated the wording throughout this document according to the protocol amendment of v1.0. ・Updated the ABBREVIATIONS list. ・Section 1.1.2 and 1.2.2.1: Updated secondary objectives and endpoints details as per protocol amendment 1. ・Section 5.0: Described PPS exclusion criteria to clarify the definition. ・Section 6.2.1: Updated analysis category because the classification dealing with an item in the treatment phase incorrectly dealt with an item in the overall study. ・Section 6.3, 6.4.2, 6.5, 6.6.1, 6.6.1.1, 6.6.2, 6.6.3, 6.6.4, 6.6.8: Added analysis by subject type because it was needed to evaluate the results. ・Section 6.3.1: Updated analysis variables by reviewing related studies and the data collected in this study. ・Section 6.4: Described the analysis set to clarify the analysis set used in the relevant sections. ・Section 6.4.1: Described the dictionary used for coding and the analysis set to be used in the listing for clarification. ・Section 6.4.2: Modified to add the missing analysis period and removed unnecessary descriptions found during the review layouts of analysis results. ・Section 6.4.3: Added reference to the definition of "on-treatment period" for clarification. ・Section 6.5.1.1: Maintained for clarity of description to show that the condition is the same as in the related studies. ・Section 6.5.1.2: Added listing and table of reasons for non-responders to be able to prepare the same type of analysis results as the related studies. ・Section 6.5.1.3: Added analysis (type 6-8) and clarified conditions for each analysis to be able to prepare the same type of analysis results as the related studies. ・Section 6.5.1.4: Clarified conditions for analysis to be able to prepare the same type of analysis results as the related studies. ・Section 6.5.2.2: Maintained for clarity of description. ・Section 6.5.2.3: Clarified conditions for analysis to be able to prepare the same type of analysis results as the related studies. ・Section 6.5.2.3: Corrected plot type to use an appropriate layout. ・Section 6.5.2.5: Changed analysis due to change of endpoint in protocol amendment 1. ・Section 6.5.3.1: Deleted unnecessary analysis found during the review layouts of analysis results.

Version	Approval Date	Primary Rationale for Revision
		・Section 6.5.3.2: Deleted section due to deletion of endpoint in protocol amendment 1. ・Section 6.5.4: Updated analysis subgroup to match Section 6.3.1 update. ・Section 6.6: Added the definition of "on-treatment period" for clarification. ・Section 6.6.1 and 6.6.1.1: Added and removed the required analysis types found during the review layouts of analysis results. ・Section 6.6.1.2: Added section to be able to analyze AEs that were specifically indicated in the protocol. ・Section 6.6.1.3: Added section for necessary analysis found during the review layouts of analysis results. ・Section 6.6.2: Clarified conditions for analysis and added "Potentially Clinically Significant (PCS) Laboratory Results" table needed in protocol. ・Section 6.6.3: Corrected an error. ・Section 6.6.6: Changed to refer to another section to be prepared separately as an AEs table. ・Section 6.6.7 and 6.6.8: Deleted unnecessary analyses found during the review layouts of analysis results. ・Section 6.7.1 and 6.7.2: Described contents of analysis. ・Section 9.2.6: Added for descriptions not appropriate to be included in section 9.2.3. ・Section 9.3: Added section to define renal disorder TEAEs and AESIs.
3.0	26-Jul-2023	Modification in the results of the consistency check between SAP and layout of TLFs. 1. Modification of analysis. ・Section 6.4.2: Changed the type of analysis table by time period. ・Section 6.6.6: Added analysis table using concentration data. ・Section 6.6.8: Modification of the compliance definition to match the study design and data structure. 2. Clarification of definitions and maintenance of terminology. ・Section 6.3.2: Modification of analysis item names. ・Section 6.4.2: Clarified that "blood" is included in "blood products". ・Section 6.5: Delete the definition of "rebound" not used for analysis. ・Section 6.5.2: Added the definition of "infection symptom control". ・Section 6.5.2.4: Deletion of duplicate description. ・Section 6.5.4: Modification to align with updates in Section 6.3.2 (deletion of an unnecessary subgroup). ・Section 6.6.2: Corrected the test items for CTCAE grading. ・Section 6.6.2, Section 6.6.3, Section 6.6.4: Corrected the definition of the denominator in the calculation of the percentage by visit.

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LIST OF IN-TEXT TABLES

ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
CI	confidence interval
C_{min}	minimum observed plasma concentration
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
GVHD	graft-versus-host disease
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplant
ICE	intercurrent event
ICF	informed consent form
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PCI	potentially clinically important
PCS	potentially clinically significant
PDs	Protocol deviations
PK	pharmacokinetics
PRO	patient-reported outcomes
PT	Preferred Term (MedDRA)
Q1	25^{th} percentile
Q3	75^{th} percentile
QTc	corrected QT interval
QTcF	QT Interval Corrected for Heart Rate using Fridericia's Formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
SOC	System Organ Class
SOT	solid organ transplant
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objectives

- To evaluate the efficacy of maribavir in CMV viremia clearance at the end of Study Week 8 (8 weeks after start of administration) in Japanese HSCT or SOT recipients with CMV infection.
- To assess the safety and tolerability of maribavir in Japanese transplant recipients with CMV infection.

1.1.2 Secondary Objectives

- To assess the maintenance of CMV viremia clearance and infection symptom control achieved at Study Week 8 (8 weeks after start of administration), through Study Week 12 (4 weeks post-treatment), Study Week 16 (8 weeks post-treatment), and Study Week 20 (12 weeks post-treatment).
- To evaluate the time to first confirmed CMV viremia clearance.
- To evaluate the recurrence of confirmed CMV viremia requiring treatment during the 12-week follow-up period in subjects who achieve confirmed viremia clearance at Week 8.
- To assess the time course of changes in plasma CMV viremia load from Baseline.
- To evaluate the recurrence of CMV viremia during study treatment and in the follow-up period after the subject is discontinued from study treatment.
- To assess the profile of mutations in the CMV genes conferring resistance to maribavir.
- To assess the CMV viremia clearance at cut-off value of 137 IU/mL at the end of Study Week 8
- To characterize the pharmacokinetics (PK) of maribavir.

1.1.3 [redacted]

- [redacted]

1.2 Endpoints

1.2.1 Primary Endpoints

- Efficacy endpoint: Confirmed clearance of plasma CMV DNA (CMV viremia clearance) at the end of Study Week 8.

- Safety and tolerability assessments: treatment-emergent SAEs, TEAEs (including instances of CMV disease), maribavir dose interruptions for AEs, maribavir dose discontinuations for AEs, number of subjects with clinically significant vital signs, number of subjects with abnormal physical examination findings, number of subjects with abnormal clinical laboratory evaluations, number of subjects with clinically significant ECG parameters, and concentration of immunosuppressant drug. New onset of acute or chronic GVHD, graft rejection, or graft loss will be reported and may be assessed as AE/SAE.

1.2.2 Secondary Endpoints

1.2.2.1 Efficacy Endpoints

- The maintenance of the confirmed CMV viremia clearance and infection symptom control achieved at Study Week 8 through Study Week 12 (4 weeks of post-treatment period), Study Week 16 (8 weeks of post-treatment/follow-up phase), and Study Week 20 (12 weeks post-treatment).
- The time to first confirmed viremia clearance at any time during the study.
- The recurrence of confirmed CMV viremia requiring treatment during the 12-week follow-up period in subjects with confirmed viremia clearance at Study Week 8.
- The time course of changes in plasma CMV viremia load from Baseline by study week.
- Recurrence of CMV viremia during study treatment and in the follow-up period after the subject is discontinued from study treatment.
- Assessment of the profile of mutations in the CMV genes conferring resistance to maribavir.
- Confirmed plasma CMV DNA at the end of Study Week 8 to be less than 137 IU/ mL.

1.2.2.2 Pharmacokinetic Endpoint

- Maribavir C_{min} (predose maribavir concentration)

1.2.3 [redacted]

- [redacted]

1.3 Estimands

Table 1 Estimand Framework

Estimand: Primary efficacy endpoint					
	Attributes				
Definition	**Treatment**	**Population**	**Variable (or Endpoint)**	**Strategy for Addressing Intercurrent Event**	**Population-Level Summary**
The primary estimand is the Confirmed clearance of plasma CMV DNA of TAK-620 at Study Week 8 in targeted patient population	During the treatment phase (Study Week 1 to Study Week 8), TAK-620 will be administered twice daily.	Japanese HSCT or SOT recipients with CMV infection	Confirmed clearance of plasma CMV DNA (confirmed CMV viremia clearance) at Study Week 8	The following intercurrent events (ICEs) are considered: 1. Taking alternative anti-CMV treatment before Study Week 8 regarded as ICE. 2. Study discontinuation without data to confirm viremia clearance at Study Week 8 regarded as ICE. For these two types of ICEs, apply the composite variable strategy and assume non-response. Handling of missing data is described in Section 6.5.1.1.	The proportion of subjects achieving the confirmed CMV viremia clearance at Study Week 8 and the corresponding 95% exact CI

2.0 STUDY DESIGN

This is a Phase 3, multicenter, open-label study to evaluate the efficacy, safety and tolerability, and PK of maribavir in Japanese HSCT or SOT recipients with CMV infection, including subjects with symptomatic CMV infection who are resistant or refractory to ganciclovir, valganciclovir, or foscarnet. The study will assess the efficacy of maribavir by measuring the plasma CMV DNA clearance at Study Week 8. To be eligible for the study, subjects must have a documented CMV infection with a screening value of >455 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by a central specialty laboratory quantitative polymerase chain reaction (qPCR) or comparable quantitative CMV DNA results. Results should be available prior to the first study treatment administration to confirm subject eligibility for the study. Both samples should be taken within 14 days prior to first dose of study treatment with the second sample obtained within 5 days prior to first dose of study treatment at Visit 2/Day 0.

As shown in Figure 1 of the Protocol, the study will have 3 phases: (1) 2-week screening phase; (2) 8-week treatment phase; and (3) 12-week follow-up phase. Subjects will be required to visit the site up to 18 times for up to a 22-week period.

- Screening Phase:

As presented in the Schedule of activities (SoA) (Table 1 of the Protocol), subjects will be screened from Day -14 to Day 0 to establish eligibility for study participation. If applicable, subjects who meet eligibility requirements will undergo washout of any prohibited medications, the length of which is specified in Table 6 of the Protocol.

- Study Treatment Phase:

Once all screening assessments following informed consent (and assent where applicable) are completed and eligibility is confirmed, the subject will receive maribavir 400 mg BID for 8 weeks starting at Visit 2/Day 0.

Assessments to be performed at weekly study visits during treatment include: CMV DNA quantification testing, evaluation of symptoms suggestive of CMV disease, underlying disease assessments, graft outcomes and GVHD assessments, resolution or improvement of tissue-invasive CMV disease (symptomatic subjects only), clinical laboratory testing (hematology and chemistry), and concomitant medications and AE review. Pharmacokinetic sample collection, physical examination, vital sign assessment, ECGs, immunosuppressive drug level monitoring, and urinalysis will be conducted at selected visits throughout the treatment phase.

Monitoring of concomitant immunosuppressant concentration levels (eg, tacrolimus, cyclosporine, and everolimus) will be conducted at designated study time points. Cytomegalovirus DNA genotyping will be performed on samples at Baseline and in cases of rebound, or lack of response to therapy.

Historical laboratory results for tests specified in the SoA (Table 1 of the Protocol) may be used for eligibility assessment (HIV or hepatitis test results) provided that these are obtained within the specified time period. The Screening and Visit 2/Day 0 visits can occur on the same day if laboratory results are available for the determination of eligibility.

All Visit 2/Day 0 procedures and screening laboratory results needed to confirm eligibility must be completed and documented prior to study treatment administration and all clinical laboratory results required for eligibility verification must be available prior to treatment administration, including 2 separate CMV DNA assessments. Initiation of study treatment (ie, first dose) will only occur after completion of all required Visit 2/Day 0 procedures and confirmation of eligibility. This will be done under the supervision of investigator site personnel. If the baseline sample analyzed by central specialty laboratory reports mutation, then the subject will continue receiving treatment but will be excluded from the Per Protocol Set for analysis.

All subjects will perform study-specific evaluations weekly during the 8-week study treatment phase (Table 1 of the Protocol).

Depending on the time of the first dose of study treatment on Visit 2/Day 0, a second dose should be administered on Visit 2/Day 0 provided that doses can be separated by a minimum of 8 hours; otherwise, only 1 dose should be administered on Visit 2/Day 0. Study treatment will

then be administered (preferably) every 12 hours (q12h). When q12h dosing is not feasible, the doses should be separated by a minimum of 8 hours.

For subjects that, in the investigator's judgment, have a lack of response or are unable to tolerate treatment and require discontinuation of study treatment, alternative anti-CMV treatment may be administered as deemed necessary. Subjects who discontinue study treatment prior to Study Week 8 will complete the end of treatment procedures described for Study Week 8 in the SoA. These subjects will follow a modified SoA through the remaining weekly visits of the study treatment phase and regular SoA through the 12-week follow-up phase.

All subjects who complete the study treatment phase through Visit 10/Study Week 8 will enter the 12-week follow-up phase.

- Follow-up Phase:

Study-specific evaluations including central specialty laboratory CMV testing and safety assessments will occur weekly for the first 4 weeks, then every 2 weeks for the final 8 weeks of the 12-Week Follow-up Phase. Refer to SoA 2 (Table 2 of the Protocol). See Section 7 of the Protocol for details regarding discontinuation and withdrawal.

If a subject is unable to travel to the site for the follow-up visits, AEs and SAEs collection may be completed by telephone follow-up call on the day of the scheduled visit. It is recommended that the end of study visit be completed at the site if the subject is able to travel.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not applicable.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

Post-transplant (SOT/HSCT) CMV infection is a rare condition and the number of patients expected to participate in this clinical trial in Japan is anticipated to be limited. For the start of domestic development of TAK-620, Takeda conducted a feasibility assessment for the planned clinical study. Specifically, a survey on the number of patients in university or large hospitals in Japan where HSCT or SOT are performed was carried out. The number of patients with asymptomatic CMV infection was estimated to be about 44 for HSCT and about 9 for SOT, for a total of about 53 patients. Assuming a dropout rate of 15%, approximately 44 patients with asymptomatic CMV infection/infection are expected to be enrolled. On the other hand, the

number of patients with refractory or resistant CMV infection is very small, and only a few patients (approximately 3) can be expected to be enrolled at the maximum.

From the standpoint of feasibility, approximately 44 asymptomatic patients and few resistant or refractory patients are expected to be enrolled in this study.

The target number of patients with asymptomatic CMV infection should be determined from the viewpoint of evaluating the similarities in outcome between the prospective study and the overseas Phase III study (Study SHP620-302) as well as the feasibility of the new study.

For the proportion of patients who achieved CMV clearance at Week 8 in the TAK-620 group in Study SHP620-302, since the results have not been available, we can assume 68%, which was used as the estimation for sample size justification in Study SHP620-302. Regarding the proportion of patients who achieved CMV clearance at Week 8 in this study, since it is the same target population and primary endpoint as Study SHP620-302, it is appropriate to assume 68% as Study SHP620-302.

In addition, we considered it appropriate to use -15% as a reference value for the difference in the point estimate between studies based on the noninferiority margin used in 2 noninferiority studies comparing valganciclovir and ganciclovir for CMV treatment (The study reported by Chawla et al. (2012) and VICTOR study (Asberg et al. 2007).

With a sample size of 44 in asymptomatic patients, if the true response rates for this study is the same as that of the Study SHP620-302, the probability of observing a response rate similar to that of the Study SHP620-302 is high, that is, over 95% the point estimate from this study will be above the point estimate of Study SHP620-302 minus 15%.

Of note, the similarity between SHP620-302 study and Japan study will be based on both the primary endpoint and secondary endpoints.

5.0 ANALYSIS SETS

- Enrolled Set: consists of all subjects who have signed an informed consent and have begun some study procedures.
- Full Analysis Set: consists of all subjects who have taken at least 1 dose of study treatment; the Full Analysis Set will be used for efficacy analyses.
- Per Protocol Set: consists of all subjects in Full Analysis Set who do not have major predefined protocol deviations that may affect the primary efficacy assessment.

  The major protocol deviations that lead to exclusion from the Per Protocol Set include but are not limited to the following:

  - Early discontinuation defined as discontinuation from study treatment within 72 hours of first dose of study assigned treatment
  - Violations of inclusion criteria #2-5 or 7
  - Violations of exclusion criteria #1, 2 or 8

- Received prohibited concomitant anti-CMV medications for more than one day while on treatment
  - Any of the following systemic anti-CMV therapies:
    - Ganciclovir
    - Valganciclovir
    - Foscarnet
    - CMV immune globulin
    - IVIG
    - Leflunomide
    - Artesunate
    - Letermovir
    - Use of other investigational anti-CMV agent such as CMV specific T-cell transfer (considered investigational)
- If the result of maribavir resistance mutation at baseline is positive after study treatment has been initiated for an assumed asymptomatic subject.

- Safety Set: consists of all subjects who have taken at least 1 dose of study treatment. The Safety set will be used for safety analyses.
- Pharmacokinetic Set: consists of all subjects in the Safety Set who have plasma samples drawn and tested for maribavir concentrations.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, interquartile ranges (Q1, Q3), minimum, maximum. Categorical and count variables will be summarized by the number and the percent of subjects in each category. The denominator for the percentages will be based on the number of subjects in the analysis set unless otherwise specified. Time-to-event endpoints will be summarized using Kaplan-Meier estimation and 95% exact confidence intervals (CIs) will be presented for the estimated 25%, 50%, and 75% times estimates.

6.1.1 Handling of Treatment Misallocations

Not applicable.

6.2 Disposition of Subjects

6.2.1 Disposition

A listing of all Screen Failures (i.e. subjects who were screened but not entered Study Treatment Phase) will be presented along with reasons for screen failure.

The number and percentage (calculated using the Enrolled Set as the denominator) of Screen Failures by reason will be presented.

The number of subjects included in each analysis set (i.e., Full Analysis Set, Per Protocol Set, Safety Set, and Pharmacokinetic Set) will be summarized. Percentages will be provided using the subject enrolled in the study treatment period as the denominator.

The number and percentage (calculated using the subject enrolled in the study treatment period as the denominator) of subjects in the following categories will be presented.

- Completed 8-week study treatment or discontinued study treatment early and by reason for early discontinuation of study treatment
- Completed the 8-week treatment phase (regardless of number of weeks of treatment) or did not complete the 8-week treatment phase
- Status of subjects who completed the 8-week treatment phase (entered follow-up phase, did not enter the follow-up phase)
- Final status (i.e. study completer vs discontinued early). Completed the study at the end of study, or discontinued from the study and by reason

In addition, the number of subjects enrolled, taken at least 1 dose of study treatment and completed will be tabulated by site for the subject enrolled in the study treatment period.

6.2.2 Protocol Deviations

Protocol deviations (PDs) will be recorded. Protocol deviations related to COVID-19 pandemic will be captured. The CRO/Sponsor will classify major/significant and minor/non-significant protocol deviations per the agreed study Deviations Rules Document. The study team will review the protocol deviations and their classification throughout the study.

Non-programable protocol deviations identified by medical monitoring will be incorporated into the datasets.

Confirmed major and minor protocol deviations will be documented in the Protocol Deviation tracker for the study.

Major/minor protocol deviations will be summarized for the Safety Set by category and site. Major/minor protocol deviations will be listed for the Safety Set. A summary and listing of PDs causing subjects to be excluded from the Per Protocol Set will be provided. A summary of the number and percentage of subjects with any COVID-19 pandemic related deviations, major and minor, will be produced using Safety Set.

6.3 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be determined using the screening visit or last observation on or prior to first dose of study treatment, whichever is later.

Descriptive summaries of demographic and baseline characteristics will be presented for the Full Analysis Set and Per Protocol Set.

The same analyses as for the Full Analysis Set will be performed by subject type ("Asymptomatic CMV infection" and "Resistant or Refractory CMV infection"(R/R)).

6.3.1 Demographics

The following demographic characteristics will be summarized: age, age group (<18, 18-44, 45-64, and ≥65 years old), sex, ethnicity, race, weight, height, and BMI.

Age will be calculated as following:

- Age (years): Integer value of ((date of Informed consent – date of birth) / 365.25)

BMI will be calculated as following:

- BMI (kg/m^2) = weight (kg)/ (height (m))^2

6.3.2 Baseline Characteristics

The following baseline characteristics including transplant history and CMV history will be summarized.

Baseline characteristics will be treated as categorical variables:

- Current transplant type (SOT/HSCT)
    - If SOT,
        - by organ type
    - If HSCT
        - Underlying condition for current transplantation
        - Is this recurrence of underlying disease
        - Type of transplant (autologous, allogeneic)
            - If allogenic haploidentical (yes/no)
            - If allogenic human leukocyte antigen (HLA), match type
        - Stem cell source for current HSCT
        - Current graft status at baseline
        - Type of preparative conditioning regimen
- History of transplants prior to the current transplant type (yes/no)

- Number of HSCT transplants prior to current transplant
- T-cell depletion modality
- Was a donor T-cell infusion given post-HSCT (yes/no)
- CMV serostatus (Donor positive/ recipient positive (D+/R+), Donor negative/ recipient positive (D-/R+), Donor positive/ recipient negative (D+/R-), Donor negative/ recipient negative (D-/R-)) overall and by transplant type (SOT, HSCT)
- Is current CMV infection the first episode post-transplant? (yes/no)
- Have history of CMV tissue invasive disease (yes/no) and by type
- Category of current CMV infection based on investigator's assessment (CMV Syndrome for SOT subjects only, tissue invasive disease, asymptomatic)
- Current CMV infection (Asymptomatic / Refractory or Resistant)
- Baseline CMV DNA category based on central laboratory results (high/intermediate/low)*
- Does subject have resistance mutation according to central laboratory result (yes/no)
- If yes, region (UL97, UL54, UL27)
- Acute GVHD status at baseline (presence/absence)
- Chronic GVHD status at baseline (presence/absence)
- Baseline total leukocyte (<2.7, ≥2.7 and <7, ≥7 10^9/L)

Baseline characteristics treated as continuous variable:

- The nucleated cell number transplanted in 10^6 for the current transplant
- Days from onset of current CMV infection to first dose of study treatment
- Days from the current transplant to the first dose of study treatment
- Days from the current transplant to onset of current CMV infection
- Baseline total leukocyte count
- Baseline CMV DNA levels from central laboratory

*Baseline CMV DNA concentration levels, based on plasma CMV DNA concentration as determined by the most recent central specialty laboratory qPCR results, are classified as follows:

- high viral load with CMV DNA ≥91000 IU/mL
- intermediate viral load ≥9100 and <91000 IU/mL
- low viral load CMV DNA <9100 IU/mL

6.4 Medical History and Concurrent Medical Conditions

All analyses for medical history and concurrent medical conditions will be conducted on the Safety Set, unless stated otherwise.

6.4.1 Medical History

The medical history will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) at the start of the study. The medical history will be summarized by system organ class (SOC) and preferred term (PT) for the Safety Set. Listing will be provided for the Enrolled Set.

6.4.2 Prior, Concomitant, and Post-Treatment Medications

World Health Organization (WHO) Drug Dictionary dated March 2021 or newer will be used for coding prior and concomitant medications, classified by Anatomical Therapeutic Chemical (ATC) class and preferred drug name.

Prior medication is defined as any medication (therapies) with the start date prior to the date of the first dose of study treatment.

Concomitant medication is defined as any medication with a start date prior to the date of the first dose of study treatment and continuing after the first dose of study treatment or with a start date and time after the study treatment initiation and before the end of the on-treatment period; the on-treatment period is defined in Section 9.2.3.

Post-treatment medication is defined as any medication with a start date during the on-treatment period and continuing into the follow-up period or with a start date after the end of the on-treatment period through the end of follow-up period.

Prior and concomitant medication usage will be summarized by the number and proportion of subjects by ATC Level III and preferred drug name using the Safety Set. Medications can be counted both as prior and concomitant medication. Multiple medication usage by a subject in the same category will be counted only once.

Additionally, "growth factor uses", "immunosuppression drug use", "other anti-CMV drugs" and "blood and blood products use" ("blood" is "whole blood" and "blood products" are otherwise) will be summarized using the Safety Set for the on-treatment period.

The same analyses as for the immunosuppression drug use will be performed by subject type ("Asymptomatic CMV infection" and "Resistant or Refractory CMV infection"(R/R)).

All prior, concomitant, and post-treatment medications will be provided in the by subject listings. Additionally, "immunosuppression drug use" and "blood and blood products use" will be provided in separate data listings.

6.4.3 Prior, Concomitant, and Post-Treatment Procedures

A concomitant procedure is any therapeutic and diagnostic intervention (e.g., surgery/biopsy) or diagnostic assessment (bacterial cultures, imaging such as X-ray, CT scans) performed between the dates of the first dose of the study treatment and the end of the follow-up phase, inclusive.

Prior procedure is defined as any procedure with a start date prior to the date of the first dose of study treatment.

Concomitant procedure during the on-treatment period is defined as any procedure with a start date prior to the date of the first dose of study treatment and continuing after the first dose of study treatment or with a start date and time after the study treatment initiation and before the end of the on-treatment period; the on-treatment period is defined in Section 9.2.6.

Post-treatment procedure is defined as any procedure with a start date during the on-treatment period and continuing into the follow-up period or with a start date after the end of the on-treatment period through the end of follow-up period.

All prior, concomitant, and post-treatment procedures will be provided in a by-subject listing.

6.5 Efficacy Analysis

All efficacy analyses will be conducted on the Full Analysis Set, unless stated otherwise.

For the primary endpoint, secondary endpoints and subgroup analyses, the same analyses as for the Full Analysis Set will be performed by subject type ("Asymptomatic CMV infection" and "Resistant or Refractory CMV infection"(R/R)).

All CIs will be 2-sided 95% exact CIs, unless stated otherwise.

Efficacy measurements assessed during the treatment phase and follow-up phase before non-study anti-CMV treatment initiation for more than one day, are included in the efficacy analysis to assess effect of the study treatments unless otherwise specified. Efficacy measurements after initiation of alternative non-study anti-CMV treatment for more than one day will be marked in data listings.

All definitions and specifications described below will apply to all subsections.

Unless otherwise specified, all efficacy analyses of CMV DNA concentration will be based on results from central laboratory.

Confirmed viremia clearance: defined as plasma CMV DNA concentration below the lower limit of quantification (<LLOQ, i.e., <34.5 IU/mL for primary efficacy endpoint, <137 IU/mL for secondary efficacy endpoint) when assessed by COBAS® 8800/COBAS® CMV Test at selected central specialty laboratory, in 2 consecutive post-baseline samples, separated by at least 5 days.

Confirmed recurrence of CMV viremia: defined as plasma CMV DNA concentration ≥LLOQ when assessed by COBAS® 8800/COBAS® CMV Test at selected central specialty laboratory in 2 consecutive plasma samples at least 5 days apart, after achieving confirmed viremia clearance.

6.5.1 Primary Endpoint Analysis

6.5.1.1 Derivation of Endpoints

This section describes the outcome classification for the primary analysis.

The primary efficacy endpoint (a binary response) for the study is confirmed clearance of plasma CMV DNA (confirmed CMV viremia clearance) at the end of Study Week 8.

For clearance of CMV viremia to be declared at the end of Study Week 8, the subject must have received exclusively study treatment through Study Week 8 (i.e., did not receive alternative non-study anti-CMV treatment through Study Week 8).

Confirmed CMV viremia clearance at the end of Study Week 8 (Visit10) is defined as plasma CMV DNA concentrations <LLOQ (i.e., <34.5 IU/mL), in 2 consecutive post-baseline samples separated by at least 5 days, regardless of whether study treatment was discontinued before the end of the stipulated 8 weeks of therapy. This is further described in Table 2 under different scenarios.

In order to be classified as a responder (confirmed clearance of plasma CMV DNA at the end of Study Week 8), subjects must meet all of the following criteria based on Study Day relative to the first dose of study treatment:

- Two negative CMV DNA readings in the vicinity of Study Week 8 (between Study Day 39 [lower limit of Week 6 Visit window] and Study Day 66 [upper limit of Week 9 Visit window] of which one must occur on Study Day 53 or later): an initial negative CMV DNA reading, named as the primary sample (Sample A), and a confirmatory negative CMV DNA reading, named as the confirmatory sample (Sample B) at least 5 days after Sample A is read.
- No positive CMV DNA reading between the primary and confirmatory samples, i.e. Sample A and B
- No alternative anti-CMV DNA treatment prior to the primary or confirmatory sample

These criteria will be assessed by an algorithm that initially chooses a potential confirmatory sample (sample B) within the scheduled Week 8 Visit window and then selecting the closest sample at least 5 days earlier within the Week 6, Week 7 or Week 8 scheduled visit windows as a potential primary sample (Sample A). If no sample meets the criteria for Sample A, then the sample initially chosen as sample B is reclassified as sample A (a potential primary sample) and the closest sample at least 5 days later within the Week 8 or Week 9 scheduled visit windows is chosen as a potential confirmatory sample (Sample B). If no sample meets the criteria for Sample B then the subject is classified as a non-responder.

If there is no sample within the Week 8 visit window and there is a sample within the Visit 7 window, then a potential primary sample (Sample A) will be chosen within the Week 7 visit window and the closest sample at least 5 days later within the Week 9 scheduled visit window is chosen as a potential confirmatory sample (Sample B). If no sample meets the criteria for Sample B then the subject is classified as a non-responder.

If there is no sample within the Week 7 or Week 8 visit windows and there is a sample within the Visit 6 window, then a potential primary sample (Sample A) will be chosen within the Week 6 visit window and the closest sample at least 5 days later within the Week 9 scheduled visit window is chosen as a potential confirmatory sample (Sample B). If no sample meets the criteria for Sample B then the subject is classified as a non-responder.

Details of the algorithm will be included in the analysis dataset specifications.

Table 2 illustrates the algorithm as above. Note that Table 2 is not exhaustive. The logic above should be used for derivation of the primary efficacy endpoint, not Table 2.

Table 2 Assessments of Virological Response at Study Week 8

Scenario	CMV DNA Weeks on Study					
	Week 6[a]	Week 7	Week 8	Week 9[b]	Response	Rationale
1	+ / -	-	-	+/-/NA	Yes	2 consecutive "-" at Week 7 and Week 8
2	+ / -	-	+	+/-/NA	No	Not 2 consecutive "-" at Week 7 and Week 8
3	+ / -	+	-	+/-/NA	No	Not 2 consecutive "-" at Week 7 and Week 8
4	+ / -	-	NA	-	Yes	2 consecutive "-" as shown by available data and both "-" at Week 7 and Week 9 for missing Week 8
5	-	NA	-	+/-/NA	Yes	2 consecutive "-" as shown by available data and both "-" at Week 6 and Week 8 for missing Week 7
6	-	NA	NA	-	Yes	2 consecutive "-" as shown by available data at Week 6 and Week 9 and both "-"

Table 2 Assessments of Virological Response at Study Week 8

Scenario	CMV DNA Weeks on Study					
	Week 6[a]	Week 7	Week 8	Week 9[b]	Response	Rationale

CMV: Cytomegalovirus

NA=not available for evaluation of study treatment effect; reason could be not assessable by lab, starting alternative anti-CMV, or withdrawal from study etc.

[a] Week 6 data, if available to evaluate the effect of study treatment, only to be used if Week 7 data are unavailable or missing

[b] Week 9 data, if available to evaluate the effect of study treatment, only to be used if Week 8 data are unavailable or missing

Notes: Scenarios in the table above are provided as examples and may not be all-inclusive of all possibilities.

Only CMV DNA data evaluable for assessment of effect of study treatment will be included (ie, prior to the start of alternative anti-CMV treatment if any).

"-" = CMV DNA concentration <LLOQ (<34.5 IU/mL)

"+" = CMV DNA concentration ≥LLOQ (ie, quantifiable)

Response = Confirmed clearance of plasma CMV DNA (CMV viremia clearance) = 2 consecutive post-baseline assessments of CMV DNA target <LLOQ, separated by at least 5 days.

Subjects who discontinue treatment prior to Study Week 8 after receiving exclusively study assigned treatment will be classified as a responder or non-responder based on CMV DNA data according to the algorithm above and not on the data at the end of treatment assessment.

6.5.1.2 Main Analytical Approach

The proportion of subjects achieving the confirmed CMV viremia clearance at Study Week 8 and the corresponding 95% exact CI will be calculated for the Full Analysis Set.

Reason for being non-responders will be listed and summarized. Non-response will be categorized as non-response based on observed CMV DNA data and non-response without sufficient observed CMV DNA data. To be classified as non-response based on observed data, subjects must have sufficient CMV DNA data to determine response or non-response based on observed data: non-response for these subjects will be based on having either the primary sample (Sample A) or confirmatory sample (Sample B) ≥LLOQ in the algorithm described in Section 6.5.1.1.

Non-response without sufficient observed data will be based on not having either the primary sample (Sample A) or confirmatory sample (Sample B) to apply the algorithm described in Section 6.5.1.1.

Non-response without sufficient observed data will be further sub-categorized as

(a) Alternative Anti-CMV treatment taken prior to having sufficient CMV DNA data to assess the primary endpoint

(b) Missing CMV DNA data will be subcategorized as due to early study discontinuation (broken down by reason) and remained on study with CMV DNA data not available.

6.5.1.3 Supportive Analysis

In Section 6.5.1.3 we propose some supportive analyses. Some subjects classified as non-responders due to missing data will be re-classified as responders or non-responders in some supportive analyses.

The following 8 types of supportive analyses will be performed for the primary efficacy endpoint. These analyses will be conducted using the Full Analysis Set unless specified otherwise.

Type	Analysis Type
1	Analysis using Per Protocol Set
2	Analysis using subset defined by baseline CMV DNA concentration
3	Analysis restricted to subjects not impacted by COVID-19 pandemic
4	Analysis restricted to subjects who received 8 weeks of study treatment
5	Analysis allowing for the use of non-study anti-CMV treatment
6	Analysis treating subjects with confirmed viremia clearance at the time of early treatment discontinuation as responders
7	Analysis treating subjects with confirmed viremia clearance at the time of alternative anti-CMV treatment initiation or early study discontinuation before Week 8 as responders
8	Analysis treating subjects with confirmed viremia clearance at the time of early treatment discontinuation for reasons other than adverse event or death as responders, while treating subjects with early treatment discontinuation due to adverse events or death as non-responders

1. Supportive Analysis 1: Analysis restricted to subjects in Per Protocol Set

   (a). Rationale

   An analysis of primary endpoint using subjects in Per Protocol Set is of clinical interest.

   (b). Derivation of Endpoint:

   The primary efficacy analysis will be performed in subjects in Per Protocol Set. This analysis will be conducted following the same methods as described in the primary analysis.

   (c). Analytical Approach

   Same as primary analysis (does not include summary of reasons for non-responder)

2. Supportive Analysis 2: Using Subset Defined by Baseline CMV DNA Concentration from Central Laboratory

   (a). Rationale

   An analysis of primary endpoint on a subset of subjects with baseline CMV DNA concentration levels from central lab in a restricted interval of clinical interest.

   (b). Derivation of Endpoint:

   The analysis of the primary efficacy endpoint will be repeated using the subset of the subjects whose baseline CMV DNA concentration based on the central lab assessment were within the range of ≥455 IU/mL and ≤91000 IU/mL

   The analysis of the primary efficacy endpoint will also be repeated using the subset of the subjects whose baseline CMV DNA concentration above LLOQ based on the central lab assessment.

   (c). Analytical Approach

   Same as primary analysis (does not include summary of reasons for non-responder)

3. Supportive Analysis 3: Analysis restricted to subjects not impacted by COVID-19 pandemic

   (a). Rationale

   An analysis of primary endpoint on a subset of subjects not affected by the COVID-19 pandemic is of clinical interest.

   (b). Derivation of Endpoint:

   The primary efficacy analysis will be performed in the subset of subjects who do not have missing CMV DNA data between Visit 6 and Visit 10 due to the COVID-19 pandemic and who have not discontinued the study prior to Week 8 due to the COVID-19 pandemic. This analysis is proposed to demonstrate that the results are consistent with the primary results when subjects with data impacted by the COVID-19 pandemic are removed. This analysis will be conducted following the same methods as described in the primary analysis.

   This analysis will be conducted only if there are ≥5% of subjects that have missing CMV DNA data between Visit 6 and Visit 10 due to the COVID-19 pandemic and who have not discontinued the study prior to Week 8 due to the COVID-19 pandemic

   (c). Analytical Approach

   Same as primary analysis (does not include summary of reasons for non-responder)

4. Supportive Analysis 4: Analysis restricted to subjects in Full Analysis Set who received 8 weeks of study treatment

   (a). Rationale

   An analysis of primary endpoint on a subset of subjects in Full Analysis Set who received 8 weeks of study treatment is of clinical interest.

   (b). Derivation of Endpoint:

   The primary efficacy analysis will be performed in the subset of subjects in Full Analysis Set who received 8 weeks of study treatment. This analysis is proposed to demonstrate that the results are consistent with the primary results when subjects receiving less than 8 weeks of study treatment are removed. This analysis will be conducted following the same methods as described in the primary analysis.

   (c). Analytical Approach

   Same as primary analysis (does not include summary of reasons for non-responder)

5. Supportive Analysis 5: Analysis allowing for the use of non-study anti-CMV treatment

   (a). Rationale

   An analysis of primary endpoint allowing the use of non-study anti-CMV treatment

   (b). Derivation of Endpoint:

   Response (defined as 2 consecutive post-baseline assessments of CMV DNA target <LLOQ, separated by at least 5 days) at end of Study Week 8 (see Table 2) regardless of the use of non-study anti-CMV treatment, will be assessed following the same method as described for the primary endpoint of response at Study Week 8.

   (c). Analytical Approach

   Same as primary analysis (does not include summary of reasons for non-responder)

6. Supportive Analysis 6: Analysis treating subjects with confirmed viremia clearance at the time of early treatment discontinuation as responders

   (a). Rationale

   In order to assess the on-treatment effect, an analysis will be performed that classifies subjects who discontinue treatment early with confirmed clearance at the time of treatment discontinuation as responders.

   Patients who discontinue treatment early and remain in the study with sufficient observed CMV DNA data to determine confirmed viremia status at Week 8 will have response status determined by whether confirmed viremia clearance is attained at end of treatment and the Week 8 CMV DNA data if available will be ignored in this analysis.

(b). Derivation of Endpoint:

Same as primary analysis for subjects who do not discontinue treatment early. Patients who discontinue treatment early will be classified as responders if both of the following are met

(i) Subject discontinues treatment prior to study Week 8 treatment without taking other anti-CMV medication prior to the visit of early discontinuation from the study and without a CMV DNA ≥ LLOQ within 5 days of early treatment discontinuation.

(ii) At the visit of early treatment discontinuation, CMV DNA data is <LLOQ, and the reading at the immediate prior scheduled visit Week is at least 5 days earlier than the reading at the end of treatment visit and is <LLOQ. (If the reading at the immediate prior scheduled visit week is <LLOQ but within 5 days of the reading at end of treatment visit then the reading at two visits prior may be used in its place). If at the visit of early treatment discontinuation CMV DNA data is <LLOQ, and there is no prior CMV reading at either of the two prior scheduled and the subject received at least 14 days of treatment then the first reading at least 5 days after treatment discontinuation through 10 days after treatment discontinuation and on or prior to the initiation of alternative anti-CMV treatment (if applicable) will be used as the second sample to establish confirmed viremia clearance at the time of early treatment discontinuation.

(c). Analytical Approach

Same as primary analysis (does not include summary of reasons for non-responder)

7. Supportive Analysis 7: Analysis treating subjects with confirmed viremia clearance at the time of alternative anti-CMV treatment initiation or early study discontinuation before Week 8 as responders

(a). Rationale

In order to verify that results of the primary analysis are not overly influenced by treating patients doing well at the time of initiation of alternative anti-CMV medication or early study discontinuation as non-responders, an analysis will be performed that classifies all subjects who receive alternative anti-CMV treatment or discontinue the study prior to week 8 with confirmed viremia clearance at the time of alternative anti-CMV treatment initiation or early study discontinuation as responders.

(b). Derivation of Endpoint:

Same as primary analysis, except that all subjects who receive alternative anti-CMV treatment or discontinue the study prior to week 8 with confirmed viremia clearance at the time of alternative anti-CMV treatment initiation or early study discontinuation are responders. In this analysis, for subjects who initiate alternative CMV treatment prior to Week 8, only samples taken on or prior to the date of the initiation of anti-CMV treatment can be used as primary and secondary samples to establish confirmed viremia clearance (See Section 6.5.1.1).

(c). Analytical Approach

Same as primary analysis (does not include summary of reasons for non-responder)

8. Supportive Analysis 8: Analysis treating subjects with confirmed viremia clearance at the time of early treatment discontinuation for reasons other than adverse event or death as responders, while treating subjects with early treatment discontinuation due to adverse events or death as non-responders

(a). Rationale

This analysis is performed to assess the on-treatment treatment effect while incorporating tolerability in the assessment.

(b). Derivation of Endpoint:

Same as supportive analysis 6, except that all subjects who discontinue treatment early due to adverse events or death are treated as non-responders, regardless of CMV viremia status at Week 8 in this sensitivity analysis.

(c). Analytical Approach

Same as primary analysis (does not include summary of reasons for non-responder)

6.5.1.4 Supplementary Analyses

In Section 6.5.1.4, we propose some supplementary analyses. Some subjects classified as non-responders due to missing data will be re-classified as responders or non-responders in some supplementary analyses.

The following 2 types of supplementary analyses will be performed for the primary efficacy endpoint. These analyses will be conducted using the Full Analysis Set unless specified otherwise.

Type	**Analysis Type**
1	Analysis assessing non-responder imputation for subjects who discontinue study early with confirmed clearance at the time of study discontinuation
2	Analysis using additional imputation by taking account of COVID-19 impact

1. Supplementary Analysis 1: Analysis to assess non-responder due to missing data for subjects who discontinue study early (during the treatment period) without alternative treatment and who have confirmed clearance at the time of study discontinuation

(a). Rationale

The primary analysis follows a derivation process for the responder status as specified in Section 6.5.1.1 in which some subjects are non-responders due to insufficient CMV DNA data to evaluate confirmed viremia clearance at Week 8. In order to assess potential

impact of the derivation, an analysis will be performed that classifies subjects classified as non-responders who discontinue study early (during the treatment phase) with confirmed clearance at the time of study discontinuation as responders if they were classified as non-responders due to missing data in the primary analysis.

(b). Derivation of Endpoint:

Same as primary analysis, except that subjects classified as non-responders due to missing data in the primary analysis will be classified as responders in this supplementary analysis if they meet all the following

(i). Subject discontinues study early (during treatment phase) without taking other anti-CMV medication prior to the visit of early discontinuation from the study.

(ii). At the visit of early study discontinuation, CMV DNA data is <LLOQ, and the reading at the immediate prior scheduled visit Week is at least 5 days earlier than the reading at the end of study visit and is <LLOQ. (If the reading at the immediate prior scheduled visit week is <LLOQ but within 5 days of the reading at end of study visit then the reading at two visits prior may be used in its place).

If data is available to definitively determine confirmed viremia clearance at Week 8 based on observed CMV DNA data (yes or no) then it will be used and the criteria for the primary analysis outlined in Section 6.5.1.1 will be followed. Subjects who discontinue the study early (during the treatment phase) and take alternative CMV treatment prior to discontinuation will be classified as non-responders. Subjects who discontinue the study early (during the treatment phase) without taking alternative CMV treatment prior to discontinuation will have response determined based on confirmed clearance at the visit of early discontinuation.

(c). Analytical Approach

Same as primary analysis

2. Supplementary Analysis 2: Taking Account of COVID-19 Impact

(a). Rationale

Subjects with missing data due to the COVID-19 pandemic are more likely to be classified as a non-responder due to missing data. An analysis allowing the use of Visit 5 data to replace missing Visit 7 and of Visit 10 data to replace missing Visit 8 for subjects with missing data due to the COVID-19 pandemic is proposed.

(b). Derivation of Endpoint:

To assess the impact of COVID-19 pandemic, the primary endpoint definition as outlined in the algorithm in Section 6.5.1.1 and illustrated in Table 2 will be followed except for subjects who are non-responders due to missing data with some of the missing data due to the COVID-19 pandemic will be assessed by a modified algorithm. Subjects who had missing CMV DNA level data to confirm response at Week 8 due to COVID-19 will be identified based on COVID-19 related missing assessment as recorded in the protocol

deviations and electronic case report form (eCRF). The modified algorithm will reduce the earliest allowed Study Day for Sample A from Study Day 39 to Study Day 32 and it will increase the latest allowed Study Day for Sample B from Study Day 67 to Study Day 73.

The specifics of the modified algorithm are described in the analysis dataset specifications.

Table 2 illustrates that subjects will not be classified as non-responders due to missing data even though there are some missed visits (2 or less) around Week 8 in the primary analysis of the primary endpoint. Similarly, Table 3 below illustrates that for patients with missing data due to the COVID-19 pandemic, 3 or more consecutive weeks of missed visits around Week 8 may occur without having the subject declared as a non-responder due to missing data. For such scenarios, available CMV DNA level at Week 5 and/or 10 data will be included in the modified algorithm.

Table 3 below illustrates the modified algorithm as above. Note that Table 3 is not exhaustive. The logic above should be used for derivation of the endpoint, not Table 3.

Table 3 Assessments of Virological Response at Study Week 8 in Subjects with missing data between Week 6 and Week 9 due to COVID-19 (Modified Algorithm of Table 2)

Scenario	CMV DNA Weeks on Study					
	Last of Week 5 and Week 6	Week 7	Week 8	First of Week 9 and Week 10	Response	Rationale
1	+ / -	-	-	+/-/NA	Yes	2 consecutive "-" at Week 7 and Week 8
2	+ / -	-	+	+/-/NA	No	Not 2 consecutive "-" at Week 7 and Week 8
3	+ / -	+	-	+/-/NA	No	Not 2 consecutive "-" at Week 7 and Week 8
4	+ / -	-	NA	-	Yes	2 consecutive "-" as shown by available data and both "-" at Week 7 and Week 9/10 for missing Week 8

Table 3 Assessments of Virological Response at Study Week 8 in Subjects with missing data between Week 6 and Week 9 due to COVID-19 (Modified Algorithm of Table 2)

Scenario	CMV DNA Weeks on Study					
	Last of Week 5 and Week 6	Week 7	Week 8	First of Week 9 and Week 10	Response	Rationale
5	-	NA	-	+/-/NA	Yes	2 consecutive "-" as shown by available data and both '-' at Week 5/6 and Week 8 for missing Week 7
6	-	NA	NA	-	Yes	2 consecutive "-" as shown by available data at Week 5/6 and Week 9/10 and both "-"

(c). Analytical Approach

Same as primary analysis

6.5.2 Secondary Endpoints Analysis

The analysis of secondary efficacy endpoints will be conducted using the Full Analysis Set unless otherwise specified.

For the following 2 secondary endpoints (a) and (b), the proportion of subjects reaching the endpoint and the corresponding 95% exact CIs will be calculated.

a) The maintenance of the confirmed CMV viremia clearance and infection symptom control achieved at Study Week 8 through Study Week 12 (4 weeks of post-treatment period), Study Week 16 (8 weeks of post-treatment/follow-up phase), and Study Week 20 (12 weeks post-treatment)

b) Confirmed-plasma CMV DNA at the end of Study Week 8 to be less than 137 IU/mL (CMV viremia clearance).

Details of derivations of virological response maintenance for (a) and (c) are contained in Section 9.2.4 of the Appendix.

For the following (c) secondary endpoints, the number and the proportion of subjects reaching the endpoints will be calculated.

c) The recurrence of confirmed CMV viremia during the 12-week follow-up period in subjects with confirmed viremia clearance at Study Week 8.

For treatment effect of clearance of CMV viremia and CMV infection symptom control to be declared at the end of Study Week 8, regardless of whether study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy, and maintenance of such effect through Week 20, the subject must have received exclusively a study-assigned treatment. CMV infection symptom control include:

- Resolution or improvement of tissue invasive disease or CMV syndrome for symptomatic subjects at baseline,
- no new symptoms for subjects asymptomatic at baseline.

The investigator will perform the initial diagnosis of tissue-invasive CMV disease or CMV syndrome for the symptomatic subjects at baseline and new occurrence of tissue invasive CMV disease or CMV syndrome for the asymptomatic subjects at baseline through the study and will continue with the assessment of the infection status (ie, no change, improvement, worsening, or resolution) at subsequent visits throughout the study.

6.5.2.1 The maintenance of the confirmed CMV viremia clearance and infection symptom control achieved at Study Week 8 through Study Week 12 (4 weeks of post-treatment period), Study Week 16 (8 weeks of post-treatment/follow-up phase), and Study Week 20 (12 weeks post-treatment)

For maintenance effect to be achieved at a time point, the subjects must have received exclusively study treatments up to that time point and have symptom control.

The response based on the maintenance of the effect of CMV viremia clearance, and CMV infection symptom control achieved at the end of Study Week 8 regardless of whether either study treatment was discontinued before the end of the stipulated 8 weeks of therapy, through Weeks 12, 16 and 20 will be determined as below:

- Identify subjects who achieved CMV viremia clearance, and CMV infection symptom control at Study Week 8 regardless of whether either study treatment was discontinued before the end of the stipulated 8 weeks of therapy;
- Subjects who maintain the effect achieved at Study Week 8 through Week 12 (16 or 20) will be classified as responder for Week 12 (16 or 20). If the effect is not maintained, subject will be classified as a non-responder.

The analysis of achievement of the confirmed CMV viremia clearance and CMV infection symptom control at Study Week 8, and maintenance through Week 12, 16, 20 will be conducted following the same method as described for the primary endpoint.

6.5.2.2 The time to first confirmed viremia clearance at any time during the study

Time to first confirmed viremia clearance is defined as time from the start date of first dose of study treatment to the date of confirmed viremia clearance (event), or the date of last CMV DNA assessment on study before the initiation of alternative anti-CMV treatment (censored). The date of confirmed viremia clearance is the first of two consecutive samples with plasma CMV DNA <LLOQ that meet the criteria of confirmed CMV viremia clearance. Patients who start alternative treatment prior to CMV viremia clearance will be censored at the day before the initiation of alternative treatment. Patients who never achieve viremia clearance and do not initiate alternative therapy will be censored at the last CMV assessment day on study.

Time to confirmed viremia clearance on study will be measured in days and is calculated as stop (event or censored) date minus date of dosing plus 1 day.

The time to confirmed viremia clearance any time on study will be summarized using Kaplan-Meier method, and will also be summarized descriptively (minimum, median, and maximum).

Additionally, time to confirmed viremia clearance within Week 8 will be summarized.

6.5.2.3 The recurrence of confirmed CMV viremia requiring treatment during the 12-week follow-up period in subjects with confirmed viremia clearance at Study Week 8

All CMV DNA measurements after achieving confirmed viremia clearance will be included in the assessment.

The following recurrence of CMV viremia will be provided.

- Of the number of subjects who achieved viremia clearance at Week 8, the number and percentage of subjects who had recurrence requiring alternative anti-CMV treatment afterwards

6.5.2.4 The time course of changes in plasma CMV viremia load from Baseline by study week

The CMV viral load, i.e., plasma CMV DNA concentration assessed by the central laboratory will be summarized and reported. The number (%) of subjects with plasma CMV DNA (Not Detected, detected <LLOQ, ≥LLOQ) by week on study after receiving study treatment and prior to non-study anti-CMV medication, will be provided.

Additionally, baseline and change from baseline in log10 plasma CMV DNA concentration from the central laboratory prior to receiving non-study anti-CMV therapy will be summarized descriptively. For analysis purpose, results reported as "Not detected" or "<LLOQ" will be imputed as half of the LLOQ value (i.e. 34.5/2=17.25) in the calculation. In addition, the viral load change over time will be presented using the plots by subject.

All CMV viral load data will be provided in data listing. CMV viral load data collected after the initiation of non-study anti-CMV treatment will be indicated in the data listing.

6.5.2.5 Recurrence of CMV viremia during study treatment and in the follow-up period after the subject is discontinued from study treatment

The recurrence of CMV viremia during study assigned treatment and in the follow-up period after the subject is discontinued from study treatment will be calculated as follows.

- Of the number of subjects who achieved the confirmed viremia clearance any time on study after receiving study treatment, the number and percentage of subjects who have recurrence in the following period will be summarized
  - During the first 8 weeks of treatment phase
  - During the 12 weeks of follow-up phase
  - At any time during the study
  - While on study assigned treatment
  - While off study assigned treatment.

6.5.2.6 Assessment of the profile of mutations in the CMV genes conferring resistance to maribavir

A subject will be categorized as having developed resistance to maribavir if the central lab genotyping results indicate treatment emergent resistance mutations. Analyses of resistance profile will be described separately.

6.5.2.7 Confirmed-plasma CMV DNA at the end of Study Week 8 to be less than 137 IU/mL (CMV viremia clearance)

Response as achieving the confirmed CMV viremia clearance at 137 IU/mL of plasma CMV DNA at the end of Study Week 8 will be assessed following the same method as described in the primary endpoint.

6.5.3 [redacted]

[redacted]

6.5.3.1 [redacted]

[redacted]

[redacted]

6.5.4 Subgroup Analyses

The following list of subgroup analyses will be performed for the primary efficacy endpoint. The proportion of responders and the corresponding 95% exact CI for each endpoint will be summarized. Subgroup analysis results will be summarized in a forest plot.

Subgroup:

- Transplant type (HSCT, SOT)
  - If SOT, by organ type
- Symptomatic CMV Infection (CMV syndrome (SOT) or CMV tissue invasive disease) (Yes/No)
- CMV DNA viral load (high/intermediate/low)
- Acute GVHD presence/absence at baseline
- Age group, adjacent groups may be collapsed to have adequate sample size
  - <18 years of age
  - ≥18 to <45 years of age
  - ≥45 to <65 years of age
  - ≥65 years of age
- Gender
- CMV serostatus (D+/R+, D-/R+, D-/R-, D+/R-)

6.6 Safety Analysis

The analysis of safety will be based on the "treatment-emergent" principle.

The safety analysis will be performed using the Safety Set, unless specified otherwise.

The safety analyses will include evaluation and procedures to meet the primary objective of assessing the safety and tolerability of maribavir. Safety evaluation will be made during the periods as illustrated in Figure 1 of the Protocol, i.e., Screening Phase, Treatment Phase, and Follow-up Phase.

Two observation periods are defined for safety analyses:

- The on-treatment period starts at the time of study treatment initiation through 7 days after the last dose of study treatment. For subjects who transfer from the study treatment to a non-study anti-CMV treatment, the on-treatment observation period starts at the time of the study treatment initiation through 7 days after the last dose of study treatment, or until the non-study anti-CMV treatment initiation, whichever is earlier.

- The overall-study observation period starts at the time of the start of the study treatment through the end of the study.

The safety endpoints for this study are as follows:

- Treatment-emergent AEs (TEAEs) and treatment-emergent SAEs (TESAEs), overall study AEs and overall study SAEs
- Clinical laboratory evaluations (including incidence of neutropenia defined as absolute neutrophil count (ANC) <500/mm^3 [0.5×10^9/L] or ANC <1,000/mm^3 [1.0×10^9/L] at any time during the study [on-treatment (defined as last dose date+7), and overall study period], and time to neutropenia development).

Safety assessments will also include vital sign measurements, physical examination, and ECG.

The last valid assessment obtained after baseline during the on-treatment period will be defined as the last value on treatment. The last valid assessment obtained after baseline during the overall-study period will be defined as the last value on study.

6.6.1 Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 dated March 2021 or later.

An AE (classified by system organ class and preferred term) that has a start date on or after the first dose of study treatment or if it has a start date before the date of first dose of study treatment but increases in severity after first dose of study treatment will be considered a TEAE. If more than one AE with the same preferred term is reported before the date of the first dose of study treatment, then the AE with the highest severity will be used as the benchmark for comparison to the AEs occurring after the start of study treatment under the preferred term.

AEs that occur from the time of informed consent form (ICF) signature to first dose will be collected but not evaluated in the safety analyses. They will be listed as pretreatment adverse events.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment or treatment emergent. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment. Handling of missing AE start/end dates, missing severity and missing relationship are detailed in Section 9.2.2.3, Section 9.2.2.4 and Section 9.2.2.5, respectively.

If more than one AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to study treatment.

TEAE summaries will be produced for the on-treatment period and overall-study period, respectively using the Safety Set. The primary focus of adverse event reporting will be the

TEAEs occurring during the on-treatment period. Summaries in terms of severity and relationship to study medication will also be provided.

The following summaries will be provided for TEAEs for the on-treatment period

- An overall summary of TEAEs, including the number and percentage of subjects with any TEAEs, any serious treatment-emergent adverse events (TESAEs), any severe TEAEs, TEAEs and TESAEs causing discontinuation of study medication, TEAEs and TESAEs leading to withdrawals from study and fatal AEs as well as the total number of events for each category
- Summary of TEAEs by system organ class (SOC) and preferred term (PT), including the number and percentage of subjects with a TEAE, as well as the total number of events
- Summary of frequently occurring in >= 10% TEAEs by PT in descending order
- Summary of TEAEs related to study treatments by SOC and PT
- Summary of frequently occurring TEAEs related to study treatments by PT in descending order
- Summary of TEAEs by maximum severity, SOC, and PT
- Summary of TEAEs related to study treatments by maximum severity, SOC, and PT
- Summary of TESAEs by SOC and PT
- Summary of TESAEs by maximum severity, SOC and PT
- Summary of TESAEs considered related to study treatments by SOC and PT
- Summary of TEAEs leading to study treatment discontinuation by SOC and PT
- Summary of TEAEs leading to study discontinuation by SOC and PT
- Summary of TEAEs related to study treatments leading to study treatment discontinuation by SOC and PT
- Summary of TEAEs related to study treatments leading to study discontinuation by SOC and PT
- Summary of TEAEs leading to death by SOC and PT
- Summary of TEAEs related to study treatments leading to death by SOC and PT

The following summaries will be provided for TEAEs for the overall period

- An overall summary of TEAEs, including the number and percentage of subjects with any TEAEs, any TESAEs, any severe TEAEs, TEAEs causing discontinuation of study medication, TEAEs leading to withdrawals from study and fatal AEs, related TESAEs leading to death as well as the total number of events for each category

- Summary of TEAEs by SOC and PT, including the number and percentage of subjects with a TEAE, as well as the total number of events
- Summary of TEAEs related to study treatments by SOC and PT
- Summary of TESAEs by SOC and PT
- Summary of TEAEs leading to death by SOC and PT
- Summary of related TESAEs by SOC and PT

All AEs will be presented in a listing. Additional data listings will be presented for SAEs, AEs causing discontinuation of study treatment or withdrawal from the study and fatal AEs.

The following analyses as for the Safety Set for the on-treatment period will be performed by subject type ("Asymptomatic CMV infection" and "Resistant or Refractory CMV infection"(R/R)).

- An overall summary of TEAEs, including the number and percentage of subjects with any TEAEs, any TESAEs, any severe TEAEs, TEAEs and TESAEs causing discontinuation of study medication, TEAEs and TESAEs leading to withdrawals from study and fatal AEs as well as the total number of events for each category
- Summary of TEAEs by SOC and PT, including the number and percentage of subjects with a TEAE, as well as the total number of events
- Summary of TEAEs related to study treatments by SOC and PT
- Summary of TESAEs by SOC and PT
- Summary of TESAEs considered related to study treatments by SOC and PT
- Summary of TEAEs by maximum severity, SOC, and PT
- Summary of TEAEs leading to study treatment discontinuation by SOC and PT
- Summary of TEAEs related to study treatments leading to study treatment discontinuation by SOC and PT

6.6.1.1 Renal Disorder TEAEs

The following summaries of sponsor-defined renal disorder TEAEs will be provided using the Safety Set for the on-treatment period, including the number and percentage of subjects as well as the total number of events:

- Summary of renal disorder TEAEs by SOC and PT, including the number and percentage of subjects with a renal disorder TEAE, as well as the total number of events
- Summary of renal disorder TEAEs related to study treatments by SOC and PT
- Summary of renal disorder TEAEs by maximum severity, SOC, and PT
- Summary of renal disorder TEAEs related to study treatment by PT and maximum severity

- Summary of serious renal disorder TEAEs by maximum severity, SOC, and PT
- Summary of serious renal disorder TEAEs related to study treatment by PT and maximum severity

The following analyses as for the Safety Set for the on-treatment period will be performed by subject type ("Asymptomatic CMV infection" and "Resistant or Refractory CMV infection"(R/R)).

- Summary of renal disorder TEAEs by SOC and PT, including the number and percentage of subjects with a renal disorder TEAE, as well as the total number of events
- Summary of renal disorder TEAEs related to study treatments by SOC and PT

The list of renal disorder TEAEs is provided in respective tables in Appendix 9.3.

6.6.1.2 Adverse Events of Special Interest

The following summaries of adverse event of special interest (AESI) will be provided using the Safety Set for the on-treatment period and the overall study, including the number and percentage of subjects as well as the total number of events:

- Summary of AESIs by category of AESI and PT, including the number and percentage of subjects with a TEAE, as well as the total number of events
- Summary of AESIs related to study treatments by category of AESI and PT

  Class of AESIs:

  - Taste disturbance
  - Immunosuppressant drug level increased
  - Gastrointestinal disorders
  - Neutropenia
  - Tissue-invasive CMV disease
  - Graft-versus-host Disease
  - Graft rejection

  The list of AESIs is provided in respective tables in Appendix 9.3.

  The above analyses as for the Safety Set for the on-treatment period will be performed by subject type ("Asymptomatic CMV infection" and "Resistant or Refractory CMV infection"(R/R)).

6.6.1.3 Subgroup Analysis for Adverse Events

The following list of subgroup analyses will be performed for the Safety Set.

Subgroup:

- Transplant type (HSCT, SOT)
- Age group, adjacent groups may be collapsed to have adequate sample size
  - <18 years of age
  - ≥18 to <45 years of age
  - ≥45 to <65 years of age
  - ≥65 years of age
- Gender

The following summaries of TEAEs will be provided for the on-treatment period for the subgroups:

- Summary of TEAEs by SOC and PT
- Summary of TEAESI by SOC and PT
- Summary of TESAEs by SOC and PT

6.6.2 Clinical Laboratory Data

The clinical laboratory assessments are described in Section 8.2.3.4 of the study protocol at the time points specified in Table 1 and Table 2 of protocol. The L/H ratio (low-density lipoprotein/ high-density lipoprotein ratio) will be calculated as following:

- L/H ratio = low-density lipoprotein (mg/dL) / high-density lipoprotein results (mg/dL)

Clinical laboratory tests will be performed at a central laboratory for all specified time points during the study including baseline. Local laboratory results can be used for eligibility and their results must be available prior to baseline. Analysis of clinical laboratory variables for hematology, chemistry and urinalysis will be based on results from central laboratories, unless otherwise specified. Central laboratory data will be summarized by descriptive statistics and presented in a data listing. Local laboratory results will be provided in separate data listings. Laboratory data during the follow-up period after initiation of non-study anti-CMV treatment will be flagged in data listings and excluded from summaries and plots.

Laboratory data summaries for all parameters with a continuous distribution will be presented throughout study by visit, change from baseline throughout the study by visit, at end of treatment, change from baseline to end of treatment, at end of study and change from baseline to end of study. Change from baseline by visit, change from baseline to end of treatment, change from baseline to the end of study will also be presented in boxplots.

Additional laboratory summaries for selected parameters to assess bone marrow effects and renal toxicity will include summaries of values and change from baseline by visit throughout study with corresponding box plots. In these analysis data after treatment discontinuation will be summarized by weeks since treatment discontinuation.

To evaluate bone marrow effects:

- Hemoglobin
- Leukocytes
- Lymphocytes
- Neutrophils
- Platelets
- Reticulocytes

The following hematology and chemistry laboratory results will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 or higher.

- Hematology: White blood cell and differential counts (WBC), Hemoglobin, Platelet count, International normalized ratio
- Chemistry: Serum sodium, potassium, Bicarbonate/carbon dioxide, Glucose, Creatinine, Calcium, Magnesium, Albumin, Direct bilirubin, ALT, AST, gamma-glutamyl transferase, Alkaline phosphatase, Total cholesterol, Triglycerides

Shift tables showing the shift in NCI CTCAE toxicity grades from baseline to maximum grade post-baseline for the on-treatment period and the overall-study period will be provided reflecting the toxicity trend in the course of treatment.

Additionally, the number and percentage of subjects with shifts in laboratory results from lower grade to maximum grade of either 3 or 4 post-baseline for the on-treatment period and the overall-study period will be provided. Specifically for ANC, the number and percentage of subjects with shifts in laboratory results from lower grade to a maximum grade of 3 (ANC $<1000/mm^3$ [0.5×10^9/L]), to a maximum grade of 4 (ANC $<500/mm^3$ [1.0×10^9/L]) in addition to a maximum grade of either 3 or 4 post-baseline for the on-treatment period (last dose date +7) and the overall-study period will be provided. For creatinine, a shift analysis from a lower grade to maximum grade of 2, 3 or 4 post baseline will be performed.

Furthermore, the time to maximum grade for those subjects who have experienced shifts in laboratory results including ANC, Hgb, platelet, WBC, ALC and creatinine from lower grade to maximum grade of 3 or 4 post-baseline will be evaluated. The time to the first episode of shift from lower grade at baseline to either grade of 3 or 4 post-baseline for the on-treatment period and the overall-study period will be summarized using descriptive statistics. For creatinine, an analysis of time from a lower grade to a maximum grade of 2, 3 or 4 post-baseline will be provided.

Clinical laboratory test values are potentially clinically significant (PCS) if they meet either the low or high PCS criteria listed in Table 4. The number and percentage of subjects with post-baseline PCS values will be tabulated by visit. The percentages will be calculated relative to the number of subjects with available non-PCS baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with assessment value at each visit. A supportive listing of subjects with post-baseline PCS values will be provided including the subject number, baseline, and post-baseline values.

Table 4 Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	Classification	Criteria: SI Units (Conventional Units)
Hematology		
Hemoglobin	High	>200 g/L (20g/dL)
	Low and Decrease	<100 g/L (10g/dL) AND Decrease of ≥ 20 g/L (2.0 g/dL) from baseline value
Hematocrit	High	>1.3 × ULN
	Low and Decrease	≤0.6 × LLN AND Decrease of ≥6.0% from baseline value
RBC	High	$>7.5 \times 10^{12}$/L
	Low	$<3.0 \times 10^{12}$/L
Platelets (thrombocytes)	High	>1.5 × ULN OR $>500 \times 10^9$/L (500×10^3/μL)
	Low	<0.6 × LLN OR $<100 \times 10^9$/L (100×10^3/μL)
WBC	High	>2 × ULN OR $>16.0 \times 10^9$/L (16×10^3/μL)
	Low	<0.5 × LLN OR $<3.0 \times 10^9$/L (3×10^3/μL)
Neutrophils	High	$>6.2 \times 10^9$/L (6.2×10^3/μL) OR > 70 %
	Low	$<1.5 \times 10^9$/L (1.5×10^3/μL) OR < 40%
Lymphocytes	High	$>4.0 \times 10^9$/L (4.0×10^3/μL) OR > 44 %
	Low	$<0.8 \times 10^9$/L (0.8×10^3/μL) OR < 22 %
Monocytes	High	$>1.1 \times 10^9$/L (1.1×10^3/μL) OR >11 %
	Low	<4 %
Eosinophils	High	$>0.5 \times 10^9$/L (0.5×10^3/μL) OR > 10.0%
	Low	NA
Basophils	High	$>0.2 \times 10^9$/L (0.2×10^3/μL) OR > 2%
	Low	NA

Table 4 Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	Classification	Criteria: SI Units (Conventional Units)
Biochemistry		
Sodium	High	>5 mmol/L (5 mEq/L) above ULN
	Low	>5 mmol/L (5 mEq/L) below LLN
Potassium	High and Increase	Above ULN AND Increase of > 0.5 mmol/L (0.5 mEq/L) from baseline value
	Low and Decrease	Below LLN AND Decrease of >0.5 mmol/L (0.5 mEq/L) from baseline value
Glucose (fasting)	High	≥6.7 mmol/L
	Low	≤4.2 mmol/L
BUN	High	>1.5 × ULN

The above PCS analyses as for the Safety Set will be performed by subject type ("Asymptomatic CMV infection" and "Resistant or Refractory CMV infection"(R/R)).

6.6.3 Vital Signs

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, pulse rate, temperature, body weight and respiration rate) and their changes from baseline at each post-baseline visit, the on-treatment period and the overall-study period will be provided.

Vital sign values will be considered potentially clinically important (PCI) if they meet both the observed value criteria and the change from baseline criteria listed in Table 5. The number and percentage of subjects with PCI post-baseline values will be tabulated. The percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with assessment value at each visit. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, site, baseline, and post-baseline PCI values.

Table 5 Criteria for Potentially Clinically Important Vital Signs

Vital Sign Parameter	Criteria	
	Observed Value	Change from Baseline
Systolic blood pressure (mmHg)	<90	
	≥140	
	≥160	
Diastolic blood pressure (mmHg)	<60	
	≥90	
	≥100	

Table 5 Criteria for Potentially Clinically Important Vital Signs

Vital Sign Parameter	Criteria	
	Observed Value	Change from Baseline
Pulse rate (beats per minute)	≤50	
	≥100	
	≥120	
Weight (kg)	-	Increase of ≥7%
	-	Decrease of ≥7%
Temperature (°C)	<35.0	
	>39.0	

The above PCI analysis as for the Safety Set will be performed by subject type ("Asymptomatic CMV infection" and "Resistant or Refractory CMV infection"(R/R)).

All vital signs data will be listed for the Safety Set.

6.6.4 Electrocardiogram (ECG)

A 12-lead ECG will be performed at Visit 2/Week 0, Visit 10/Week 8 (end of treatment visit), Visit 18/Week 20 (the on-treatment period and the overall-study period will be provided), and at any additional time during the study, if clinically indicated. ECG data will include heart rate, RR duration, PR duration, QT duration, and QRS duration. The corrected QT interval (QTc) will be calculated using the Fridericia's formula. The investigator will be responsible for providing the interpretation for all ECGs in terms of clinical significance to the subject. Summary of investigator's interpretation of the ECG results will be provided.

In addition, ECG variable values will be considered potentially clinically significant (PCS) if they meet or exceed the upper limit values listed in Table 6. The number and percentage of subjects with post-baseline PCS values will be tabulated by visit. The percentages will be calculated relative to the number of subjects with available non-PCS baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with assessment value at each visit. A listing of all subjects with post-baseline PCS values will be provided including the subject number, site, baseline, and post-baseline PCS values.

Table 6 Criteria for Potentially Clinically Significant ECG Values

ECG Parameter	Criteria
	Observed Value
Heart Rate (bpm)	≤50
	≥100
QRS Interval (msec)	≥200
QRS Duration (msec)	≥120

Table 6 Criteria for Potentially Clinically Significant ECG Values

ECG Parameter	Criteria
	Observed Value
QT Interval Corrected for Heart Rate using Fridericia's Formula (QTcF) (msec)	≥450 and <480
	≥480 and <500
	≥500
QTcF (msec) change from baseline	≥30 and <60
	≥60
PR interval (msec)	>200

bpm: beat per minute; msec: millisecond

The above PCS analysis as for the Safety Set will be performed by subject type ("Asymptomatic CMV infection" and "Resistant or Refractory CMV infection"(R/R)).

All ECG data will be presented in a by-subject listing.

6.6.5 Other Safety Data

Physical examinations will be performed at timepoints specified in the Schedule of Events in the study protocol (Table 1 and Table 2) according to standard practices at the investigational site. Abnormalities identified at the screening visit (Visit 1) will be documented in the subject's source documents and on the medical history CRF. Changes after the screening visit (Visit 1) will be captured as AEs on the AE CRF page, as deemed clinically relevant by the investigator.

Physical examinations performed will be provided in a data listing.

The number and percentage of subjects receiving hemopoietic growth factors, blood, blood products at least once and by type during the on-treatment period and overall-study period for the study treatment will be provided.

All blood and blood products transfusions will be provided in a data listing. A data listing including the hemopoietic growth factors will be provided.

6.6.6 Immunosuppressant Drug Concentration Level

The analysis of immunosuppressant drug concentration level increased will be summarized for the Safety Set. The number of patients with an increased drug concentration level of at least one immunosuppressant drug will be summarized as well as the number of patients with increased drug concentrations in each of the following: cyclosporine, tacrolimus and everolimus.

6.6.7 Extent of Exposure and Compliance

Exposure to study treatment will be summarized in terms of exposure duration and number of doses for the Safety Set. Study treatment administration will be recorded on the DOSING ORAL eCRF. The dose adjustment and dose interruption for study treatments will be collected on the eCRF. Available data collected on eCRF will be used in assessing the treatment exposure.

- Exposure duration will be calculated as the number of days from the date of first dose of study treatment to the date of the last dose of study treatment plus 1.
- Actual exposure days to study treatment will be calculated as the number of days on which at least 1 dose of study treatment was taken.

The measures of exposure will be summarized using descriptive statistics and will be reported.

All drug exposure and compliance information, study treatment administrations will be presented chronologically by subject in data listings.

6.6.8 Measurement of Treatment Compliance

The treatment compliance is defined as the number of actual exposure days divided by the exposure duration days multiplied by 100.

The dosing compliance is defined as the total number of doses taken divided by the expected number of doses multiplied by 100. The total number of doses is calculated as total number of dispensed tablets - total number of returned tablets. The expected number of doses is calculated as the 4 tablets (morning and evening) multiplied by the actual exposure days.

Treatment compliance and dosing compliance will be summarized using descriptive statistics for the Safety Set.

Dose interruptions due to adverse events is allowed.

The following summaries for dose interruption will be provided:

- Dose interruption:
  - The number and percentage of subjects with at least one interruption, total number of interruption, and reason of interruption.

The above analyses as for the Safety Set will be performed by subject type ("Asymptomatic CMV infection" and "Resistant or Refractory CMV infection"(R/R)).

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

All summaries and analyses of the pharmacokinetic data will be based on the Pharmacokinetic Set. Individual maribavir concentrations will be listed. Maribavir C_{min} (predose maribavir concentration) will be summarized using descriptive statistics (n, mean, standard deviation (SD),

median, minimum, maximum, coefficient of variation, geometric mean, and geometric coefficient of variation) by Visit.

Additional analysis may be conducted and will be described in a separate pharmacokinetic data analysis plan if applicable.

6.7.1.1 Drug Concentration

Predose at Week 1, Week 4 and Week 8 and between 2 to 4 hour postdose at Week 1 and Week 8 will be collected.

Additional PK plasma samples will be collected from the subjects with biopsy-proven gastrointestinal graft-versus-host disease (GI GVHD) with diarrhea (>300 mL/day), biopsy-proven GI GVHD with nausea and vomiting, documented acute GVHD of liver (Stage II, total bilirubin >3 mg/dL or biopsy-proven) with diarrhea (>500 mL/day), or biopsy-proven acute GVHD of the skin with diarrhea (>500 mL/day).

PK samples will be analyzed for the determination of plasma maribavir concentrations. Any pre-dose or post-dose PK samples that were collected post dosing or prior to dosing, respectively, will be included in the PK concentration listings, but will be excluded from PK concentration summaries. Only pre-dose C_{min} will be summarized.

6.7.1.2 Handling Below Lower Limit of Quantitation Values

The following procedures will be used for plasma concentrations below the lower limit of quantification (LLOQ):

- Samples that are below LLOQ are treated as zero in the calculation of descriptive statistics (e.g. mean, SD, etc.) for the plasma concentrations at individual time points except for geometric mean. Concentrations that are LLOQ will be excluded from the computation of geometric mean.
- Mean concentrations are reported as zero if all values are below LLOQ, and no descriptive statistics are reported. If the calculated mean (±SD) concentration is less than the LLOQ, the value will be reported as calculated. The mean values derived using these conventions will be used to create the mean plasma concentration versus time plots.
- Missing data will not be imputed.

6.7.1.3 Analysis of Pharmacokinetic Endpoints

Maribavir concentrations will be listed by subject, visit, planned sampling time, and actual sampling time after last dosing. Planned pre-dose PK sample which were collected at post-dose time will be included in the listing with flag and exclude from descriptive statistics. Additionally, a by-subject listing of maribavir concentrations in subjects with GI GVHD will be generated. A by-subject listing of week 8 viremia response and recurrence of CMV viremia at any time due to low Maribavir concentrations during the treatment phase will be generated for subjects with C_{min} (predose maribavir concentration) below LLOQ at one or more PK visits.

Maribavir C_{min} will be summarized by visit using descriptive statistics (number of observations, mean, SD, coefficient of variation, median, maximum, minimum and geometric mean, and geometric coefficient of variation) using Pharmacokinetic Set. Planned pre-dose PK samples which were collected at post-dose time will not be used in C_{min} summary.

Average C_{min} will be calculated for each subject using pre-dose maribavir concentration values at Week 1, Week 4, and Week 8 and a listing will be provided. C_{min} values that were below the LLOQ were imputed with ½ LLOQ.

Box plot of average C_{min} by confirmed CMV viremia clearance response at Week 8 for all subjects will be provided.

6.7.2 Pharmacodynamic Analysis

Not applicable.

6.7.3 Biomarker Analysis

Not applicable.

6.8 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

6.8.1 PRO Analysis

Not applicable.

6.8.2 Health Care Utilization Analysis

Not applicable.

6.9 Other Analyses

Not applicable.

6.10 Interim Analyses

Not applicable.

6.11 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

No Data Monitoring Committee or Internal Review Committee is planned.

7.0 REFERENCES

Asberg, A., Humar, A., Rollag, H., Jardine, A. G., Mouas, H., Pescovitz, M. D., et al. 2007. Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant,* 7(9), 2106-13.

Chawla, J. S., Ghobadi, A., Mosley, J., 3rd, Verkruyse, L., Trinkaus, K., Abboud, C. N., et al. 2012. Oral valganciclovir versus ganciclovir as delayed pre-emptive therapy for patients after allogeneic hematopoietic stem cell transplant: a pilot trial (04-0274) and review of the literature. *Transpl Infect Dis,* 14(3), 259-67.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

See "REVISION HISTORY".

9.2 Data Handling Conventions

9.2.1 Repeated or Unscheduled Assessments of Safety Parameters

It is possible that repeat or unscheduled assessments are made for some safety variables (e.g., clinical laboratories, vital signs, and ECGs, etc.).

If a subject has repeated assessments before the start of study treatment, then the results from the most recent assessment prior to the start of study treatment will be used as baseline. If the end of study assessments is repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating descriptive statistics.

However, all post-baseline assessments will be used for PCS value determination and all assessments will be presented in the data listings.

9.2.2 Handling of Missing, Unused, and Spurious Data

9.2.2.1 Missing Date of Investigational Product

When the date of the last dose of study treatment is missing for a subject in the safety set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when study treatment was returned will be used in the calculation of treatment duration.

9.2.2.2 Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

For prior or concomitant medications, or procedure, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

9.2.2.2.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same, but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same, but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

9.2.2.2.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same, but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the last dose of investigational product or if both years are the same, but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

9.2.2.3 Missing Date Information for Adverse Events

For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study treatment administration, e.g. AE start year and month are the same as the year and month of the first dose of investigational product, then the AE will be classified as treatment-emergent.

To facilitate categorization of AEs as treatment emergent, imputation of dates can be used. For AEs, the default is to only impute incomplete (i.e., partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

AE with incomplete start date will be imputed following the same rule as described above for incomplete start date for the concomitant medications.

AE with incomplete stop date will be imputed following the same rule as described above for incomplete stop date for the concomitant medications.

9.2.2.4 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

9.2.2.5 Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to investigational product will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

9.2.2.6 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable. The appropriately determined coded value will be used in the statistical analysis. Coding of Special Character Values for Clinical Laboratory Variables are described in Table 7. However, the actual values as reported in the database will be presented in data listings.

Table 7 Examples for Coding of Special Character Values for Clinical Laboratory Variables

Clinical Laboratory	Possible Results (in SI units)	Coded Value for Analysis
Chemistry: ALT	<5	0
Chemistry: AST	<5	0
Chemistry: Total Bilirubin	<2	0
Urinalysis: Glucose	≥55	Positive
	≤0	Negative
Urinalysis: pH	≥8.0	8.0

9.2.3 Definition of Visit Windows

For the purpose of analysis, the week on study (Study Week 0 through Study Week 20) for all data on treatment phase and follow-up phase will be determined based on the analysis visits. Visit windows are described in Table 8. If two measurements end up in one week, the measurement closest to the scheduled visit study start will be used for the summary by week. Assessments done on or before the first study treatment administration are considered baseline.

Table 8 Definition of Visit Windows

Analysis Visit	FROM	TO
Week 0	-x	0
Week 1	1	9
Week 2	10	16
Week 3	17	23

Table 8 Definition of Visit Windows

Analysis Visit	FROM	TO
Week 4	24	30
Week 5	31	38
Week 6	39	45
Week 7	46	52
Week 8	53	59
Week 9	60	66
Week 10	67	73
Week 11	74	80
Week 12	81	90
Week 14	91	104
Week 16	105	118
Week 18	119	132
Week 20	133	146

For the purpose of analysis, the week on study (Study Week 0 through Study Week 20) for all efficacy measurements on treatment phase and follow-up phase will be determined based on the analysis visits. If two measurements end up in one week, the measurement closest to the scheduled visit study start will be used for the summary by week. The earlier measurement will be classified as unscheduled. Measurements after day 146 will be classified as unscheduled. Assessments done on or before the first study treatment administration are considered baseline.

9.2.4 Derivation of Maintenance for Secondary Endpoints

Patients must be free of CMV symptoms throughout a period in order classify as response maintenance.

For secondary outcomes (a) and (c) of Section 6.5.2, to determine the virological response maintenance at Week 12, all the following conditions need to be satisfied:

1. Viremia clearance achieved at Week 8
2. No two consecutive positives before Week 12
3. Evidence of maintenance around Week 12, meaning one of the following must be true:
   a. Week 12 is negative, or
   b. If Week 12 is missing, but Week 14 (or unscheduled visit after Week 12) is negative, or

c. If Week 12 is positive, both Week 11 (or unscheduled visit prior to week 12) and Week 14 (or unscheduled visit after Week 12) must be negative

4. No alternative anti-CMV therapy through Week 12

Additionally, to determine the virological response maintenance at Week 16, all the following conditions need to be satisfied:

1. Viremia clearance achieved at Week 8
2. Virological response maintenance at Week 12; this clarifies the amount of missingness permitted
3. No two consecutive positives before Week 16
4. Evidence of maintenance around Week 16, meaning one of the following must be true:
   a. Week 16 is negative, or
   b. If Week 16 is missing, but Week 18 (or unscheduled visit after Week 16) is negative, or
   c. If Week 16 is positive, both Week 14 (or unscheduled visit prior to week 16) and Week 18 (or unscheduled visit after Week 16) must be negative
5. No alternative anti-CMV therapy through Week 16

Moreover, to determine the virological response maintenance at Week 20, all the following conditions need to be satisfied:

1. Viremia clearance achieved at Week 8
2. Virological response maintenance at Week 16; this clarifies the amount of missingness permitted
3. No two consecutive positives before Week 20
4. Week 20 is negative
5. No alternative anti-CMV therapy through Week 20

9.2.5 Definition of Baseline

The baseline value for efficacy variables is defined as the last available value before or on the first dose date of study treatment on Visit 2/Week 0/Day 0.

Baseline safety analyses is defined as the last value for the assessment prior to taking the first dose of study treatment.

9.2.6 Definition of Treatment Period

Three observation periods are defined for safety analyses:

- The on-treatment period starts at the time of study treatment initiation through 7 days after the last dose of study treatment. For subjects who transfer from the study treatment to a non-study anti-CMV treatment, the on-treatment observation period starts at the time of the study treatment initiation through 7 days after the last dose of study treatment, or until the non-study anti-CMV treatment initiation, whichever is earlier.
- The follow-up period starts one day after the end of the on-treatment period through the end of the study.
- The overall-study observation period starts at the time of the start of the study treatment through the end of the study.

9.3 Definition of renal disorder TEAEs and AESIs

Definition information for Renal Disorder TEAEs and AESIs in MedDRA ver.26.0 is provided in Section 9.3.1 and Section 9.3.2.

9.3.1 Definition of Renal Disorder TEAEs

Table 9.1 Renal disorder

HLT_CODE	HLT_NAME	HLT_KANJI
10038443	Renal failure and impairment	腎不全および腎機能障害
10010180	Renal failure complications	腎不全合併症
10038454	Renal function analyses	腎機能検査
PT_CODE	Preferred Term_NAME	PT_KANJI
10037032	Proteinuria	蛋白尿

9.3.2 Definition of AESIs

Table 9.2 Taste disturbance

PT_CODE	PT_NAME	PT_KANJI
10001480	Ageusia	味覚消失
10013911	Dysgeusia	味覚不全
10020989	Hypogeusia	味覚減退
10082490	Taste disorder	味覚障害

Table 9.3 Immunosuppressant drug level increased

PT_CODE	PT_NAME	PT_KANJI
10062015	Immunosuppressant drug level increased	免疫抑制剤濃度増加

Table 9.4 Gastrointestinal disorders

PT_CODE	PT_NAME	PT_KANJI
10012735	Diarrhoea	下痢
10028813	Nausea	悪心
10047700	Vomiting	嘔吐

Table 9.5 Neutropenia

PT_CODE	PT_NAME	PT_KANJI
10001507	Agranulocytosis	無顆粒球症
10016288	Febrile neutropenia	発熱性好中球減少症
10029354	Neutropenia	好中球減少症
10029366	Neutrophil count decreased	好中球数減少

Table 9.6 Tissue-invasive CMV disease

PT_CODE	PT_NAME	PT_KANJI
10048843	Cytomegalovirus chorioretinitis	サイトメガロウイルス性脈絡網膜炎
10048983	Cytomegalovirus colitis	サイトメガロウイルス性大腸炎
10049074	Cytomegalovirus enteritis	サイトメガロウイルス性小腸炎
10049015	Cytomegalovirus enterocolitis	サイトメガロウイルス性腸炎
10049016	Cytomegalovirus gastritis	サイトメガロウイルス性胃炎
10051349	Cytomegalovirus gastroenteritis	サイトメガロウイルス性胃腸炎
10052817	Cytomegalovirus gastrointestinal infection	サイトメガロウイルス性消化管感染
10011830	Cytomegalovirus hepatitis	サイトメガロウイルス肝炎
10049018	Cytomegalovirus oesophagitis	サイトメガロウイルス性食道炎
10014586	Encephalitis cytomegalovirus	サイトメガロウイルス性脳炎

Table 9.6 Tissue-invasive CMV disease

PT_CODE	PT_NAME	PT_KANJI
10035676	Pneumonia cytomegaloviral	サイトメガロウイルス性肺炎
10065036	Cytomegalovirus mucocutaneous ulcer	サイトメガロウイルス性皮膚粘膜潰瘍
10056262	Cytomegalovirus syndrome	サイトメガロウイルス症候群

Table 9.7 Graft-versus-host Disease

PT_CODE	PT_NAME	PT_KANJI
10066260	Acute graft versus host disease	急性移植片対宿主病
10066264	Acute graft versus host disease in intestine	急性腸管移植片対宿主病
10066263	Acute graft versus host disease in liver	急性肝移植片対宿主病
10066262	Acute graft versus host disease in skin	急性皮膚移植片対宿主病
10083513	Acute graft versus host disease oral	急性口腔移植片対宿主病
10066261	Chronic graft versus host disease	慢性移植片対宿主病
10083757	Chronic graft versus host disease in eye	慢性眼移植片対宿主病
10072158	Chronic graft versus host disease in intestine	慢性腸管移植片対宿主病
10072160	Chronic graft versus host disease in liver	慢性肝移植片対宿主病
10072159	Chronic graft versus host disease in skin	慢性皮膚移植片対宿主病
10083514	Chronic graft versus host disease oral	慢性口腔移植片対宿主病
10018651	Graft versus host disease	移植片対宿主病
10075160	Graft versus host disease in gastrointestinal tract	消化管移植片対宿主病
10067742	Graft versus host disease in lung	肺移植片対宿主病
10064675	Graft versus host disease in skin	皮膚移植片対宿主病
10064676	Graft versus host disease in liver	肝移植片対宿主病

Table 9.8 Graft rejection

PT_CODE	PT_NAME	PT_KANJI
10023439	Kidney transplant rejection	腎移植拒絶反応
10051604	Lung transplant rejection	肺移植拒絶反応
10060872	Transplant failure	移植不全
10044439	Transplant rejection	移植拒絶反応

9.4 Analysis Software

All statistical analyses will be performed using SAS, Version 9.4 or higher.