STATISTICAL ANALYSIS PLAN

NCT Number: NCT02927067

Study Title: A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients

Study Number: SHP620-302

SAP version and Date:

Version 2.0: 27 April 2022

STATISTICAL ANALYSIS PLAN

Study Number: SHP620-302

Study Title: A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients

Phase: 3

Version: 2.0

Date: 27-APR-2022

Prepared by: [redacted]

Based on:

Protocol Version: Amendment 9 (Version 10.0)

Protocol Date: 15 September 2021

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Draft 0.1	31-Mar-2020	First stable version
1.0	23 Jul 2021	Transfer to new SAP template and update based on protocol amendment 8
2.0	27 Apr 2022	Incorporate FDA comment on SAP, clarify and add analysis details planning for final report.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ATC	anatomical therapeutic chemical
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration versus time curve
$AUC_{(0\text{-}tau)}$	area under the plasma concentration versus time curve over the 12-hour dosing interval at steady state
β-HCG	beta-human chorionic gonadotropin
BID	twice daily
bpm	beats per minute
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CI	confidence interval
CL/F	apparent oral clearance
CMH	Cochran-Mantel-Haenszel
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CrCl	creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
DNA	deoxyribonucleic acid
eCRF	electronic case report form
eDiary	electronic Diary
ECG	electrocardiogram
[redacted]	[redacted]
FU	follow-up
GGT	gamma−glutamyltransferase
GI	gastrointestinal
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HLA	human leukocyte antigen
[redacted]	[redacted]
HSCT	hematopoietic stem cell transplant

INR	international normalized ratio
IRT	interactive response technology
ITT	intention-to-treat
LLOQ	lower limit of quantification
NCI	National Cancer Institute
NI	noninferiority
MedDRA	Medical Dictionary for Regulatory Activities
OC	observed cases
PCS	potentially clinically significant
PD	Pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per-protocol
PT	preferred term
Q1	25th Percentile
Q3	75th Percentile
QTc	corrected QT interval
QTcF	QT Interval Corrected for Heart Rate using Fridericia's Formula
RAP	resistance analysis plan
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SMQ	Standardized MedDRA® Query
SOC	system organ class
SOT	solid organ transplant
TEAE	treatment-emergent adverse event
T_{max}	time when maximum concentration is observed
V_z/F	apparent volume of distribution
WHO	World Health Organization

1. OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

The primary objective of the study is to compare the efficacy of maribavir to valganciclovir in CMV viremia clearance at the end of Study Week 8 in asymptomatic CMV infection in HSCT recipients.

1.1.2 Secondary Objectives

The key secondary objective of this study is to compare the efficacy of maribavir and valganciclovir on maintenance of CMV viremia clearance, achieved at the end of Study Week 8 through Study Week 16 (8 weeks of post-treatment/follow-up phase).

The other secondary objectives of this study are:

- To compare the efficacy of maribavir to valganciclovir in CMV viremia clearance after completion of 8 weeks of treatment for asymptomatic CMV infection in HSCT recipients.
- To compare the efficacy of maribavir and valganciclovir on maintenance of CMV viremia clearance, achieved after completion of 8 weeks of treatment, through Study Weeks 12 (4 weeks of post-treatment period), 16 (8 weeks of post-treatment/follow-up phase), and 20 (12 weeks post-treatment).
- To assess the maintenance of CMV viremia clearance, achieved at the end of Study Week 8, through Weeks 12 (4 weeks of post-treatment period), and 20 (12 weeks post-treatment).
- To evaluate the incidence of recurrence of confirmed CMV viremia in the 2 study treatment arms during the first 8 weeks of the study, during the 12-weeks of the follow-up study phase, and at any time during the study.
- To evaluate the incidence of recurrence of confirmed CMV viremia in the 2 study treatment arms when subjects are on treatment and off treatment.
- To evaluate the incidence of treatment-emergent grade 3 or 4 neutropenia (defined as ANC<1000/mm^3 or ANC<500/mm^3) while on treatment.
- To assess the safety and tolerability of maribavir compared to valganciclovir.
- To characterize the PK of maribavir.

1.1.3 Exploratory Objectives

[redacted]

1.2 Endpoints

1.2.1 Primary Endpoint

The primary efficacy endpoint of this study is confirmed clearance of plasma CMV DNA (CMV viremia clearance) at the end of Study Week 8. The detail of definition is in Section 6.5.1.1.

1.2.2 Secondary Endpoints

1.2.2.1 Key Secondary Endpoint

The key secondary efficacy endpoint is defined as the maintenance of confirmed CMV viremia clearance and symptom control achieved at the end of Study Week 8 through Week 16. The detail of definition is in Section 6.5.2.1.

1.2.2.2 Other Secondary Endpoints

The other secondary endpoints of this study specified in Section 6.5.3 are:

- The achievement of the confirmed CMV viremia clearance after 8 weeks of receiving study-assigned treatment.
- The maintenance of the confirmed CMV viremia clearance after completion of 8 weeks of receiving study-assigned treatment, through Study Weeks 12 (4 weeks post-treatment period), 16 (8 weeks of post-treatment/follow-up phase), and 20 (12 weeks post-treatment).
- The maintenance of the CMV viremia clearance achieved at the end of Study Week 8 through Study Weeks 12, and 20, regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. For maintenance effect to be achieved at a time point, the subjects must have received exclusively study-assigned treatments up to that time point and also must have symptom control.
- The recurrence of CMV viremia during the first 8 weeks of the study, in the follow-up period of 12 weeks, and at any time during the 20 weeks of the study, regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy.

- The recurrence of confirmed CMV viremia in the 2 study treatment arms when subjects are on treatment and off treatment.
- The incidence of grade 3 or 4 neutropenia (defined as ANC <1,000/mm^3 [1.0 x 10^9/L]) or ANC <500/mm^3 [0.5 x 10^9/L], respectively).

1.2.3 Exploratory Endpoints

[redacted]

1.2.4 Safety Endpoints

- Treatment-emergent AEs and treatment-emergent SAEs, overall study AEs and overall study SAEs.
- Clinical laboratory evaluations (including incidence of neutropenia defined as ANC <500/mm^3 [0.5 x10^9/L] or ANC <1,000/mm^3 [1.0 x 10^9/L] at any time during the study [on treatment and overall study period] and time to neutropenia development), and study treatment dose adjustments due to AEs.
- Safety assessments will also include vital sign measurements, physical examination, and ECG.

1.2.5 Pharmacokinetic Endpoints

Pharmacokinetic samples will be obtained for all subjects as in the Schedule of Assessment 1 (Table 1, SHP620-302 protocol), but analyzed for only those subjects who are taking maribavir.

- Maribavir C_{min} (pre-dose maribavir concentration).

For adolescent subjects who provided intensive PK samples at Visit 3/Week 1:

- $AUC_{(0\text{-}tau)}$: area under the concentration time curve over the 12-hour dosing interval at steady state.
- C_{max}: maximum concentration.
- T_{max}: time when maximum concentration is observed
- CL/F: apparent oral clearance.
- V_z/F: apparent volume of distribution.

In a separate analysis and report, maribavir concentration data (pre-dose and post-dose) will be analyzed by population PK analysis approac [redacted]

1.2.6 [redacted]

- [redacted]
- [redacted]

1.2.7 [redacted]

- [redacted]

1.3 Estimand(s)

The primary and key secondary estimands that are to support regulatory decisions are described in Table 1.

Table 1 List of Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Primary	The primary estimand of this study is the effect of SHP620 compared to valganciclovir in treatment of CMV infection at the end of Study Week 8.	HSCT recipients with first episode of asymptomatic CMV infection	Proportion of responders, defined as subjects with confirmed viremia clearance at Study Week 8 and no alternative anti-CMV treatment	The following intercurrent events are considered: 1. If a subject takes alternative anti-CMV treatment before Study Week 8, assume non-response 2. If a subject drops out of study before Study Week 8 without data to confirm viremia clearance at Study Week 8, assume non-response	Difference in proportion of responders at Study Week 8 between SHP620 and valganciclovir treatment groups
Key Secondary	The key secondary estimand is the maintenance effect of SHP620 compared to valganciclovir in treatment of CMV infection achieved at the end of Study Week 8 through Study Week 16	HSCT recipients with first episode of asymptomatic CMV infection	Proportion of responders, defined as subjects who achieved confirmed viremia clearance and CMV infection symptom control at Study Week 8 and maintain through Study Week 16 and no alternative anti-CMV treatment	The following intercurrent events are considered: 1. If a subject takes alternative anti-CMV treatment before Study Week 16, assume non-response 2. If a subject drops out of study before Study Week 16 without data to confirm the maintenance of viremia clearance and CMV infection symptom control at Study Week 16, assume non-response	Difference in proportion of responders for the key secondary endpoint between SHP620 and valganciclovir treatment groups

2. STUDY DESIGN

2.1 Study Design and Flow Chart

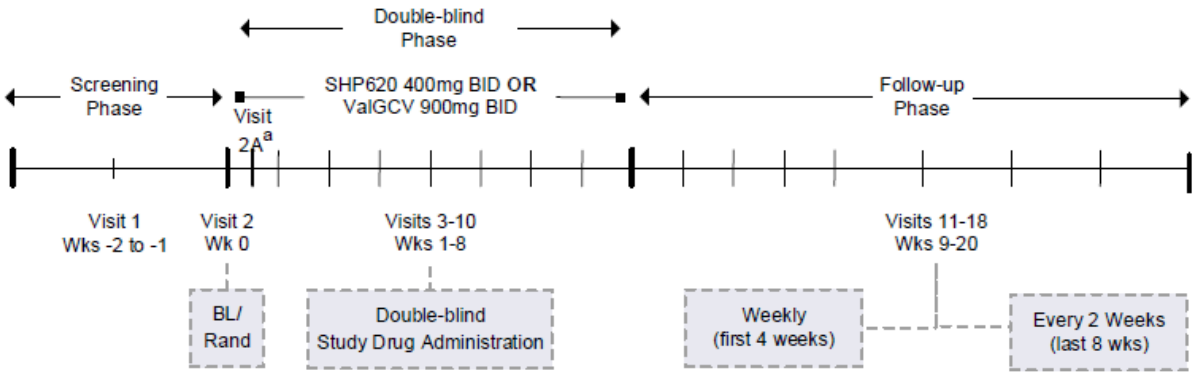
This is a multicenter, randomized, double-blind, double-dummy, active-controlled study of maribavir compared to valganciclovir for the treatment of asymptomatic CMV infection in HSCT recipients. "Asymptomatic subjects" at baseline will be defined as HSCT recipients who do not have tissue invasive CMV disease as determined by the investigator according to the criteria specified by Ljungman et al (2016). The study will assess the efficacy of maribavir by measuring the plasma CMV DNA clearance. To be eligible for the study, subjects must have a documented asymptomatic CMV infection with a screening value of CMV DNA ≥1365 IU/mL to ≤273000 IU/mL in whole blood or ≥455 IU/mL to ≤91000 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory quantitative polymerase chain reaction (qPCR) or comparable quantitative CMV DNA results. Results for CMV and, in subjects with very low viral load, evaluations for high-risk CMV infection (study protocol Section 7.1.1) should be available before the subject is randomized to verify subject eligibility for the study. Both samples should be taken within 14 days prior to randomization with the second sample obtained within 5 days before randomization. The same laboratory and sample type should be used for these assessments. Subjects must not have CMV tissue invasive disease (symptomatic CMV infection), must not have a CMV infection that is known to be genotypically resistant to anti-CMV drugs and must meet the remaining specified eligibility criteria. Subjects treated with ganciclovir, valganciclovir, foscarnet or letemovivir for the current CMV infection should not be treated with these anti-CMV agents for longer than 72 hours prior to enrolling in the study.

All eligible subjects will be stratified based on last pre-baseline whole blood or plasma CMV DNA concentration (high viral load with CMV DNA ≥27300 IU/mL in whole blood or ≥9100 IU/mL in plasma, low viral load with CMV DNA ≥2730 IU/mL to <27300 IU/mL in whole blood or ≥910 IU/mL to <9100 IU/mL in plasma, and in subjects with high-risk infection, very low viral load with CMV DNA <2730 IU/mL in whole blood or <910 IU/mL in plasma) as determined by the local or central specialty laboratory qPCR. Subjects will also be stratified based on acute GVHD status (presence or absence at baseline). Subjects in each stratum will then be randomized in a 1:1 allocation ratio to receive double-blind maribavir 400 mg BID or valganciclovir 900 mg BID, 450 mg BID, or 450 mg QD, based on subject's CrCl at eligibility, for 8 weeks. Valganciclovir dose may be adjusted during the study for renal function impairment or neutropenia.

An independent Data Monitoring Committee (DMC) will be established to assess the data at specified periodic intervals for safety and to ensure the validity and scientific merit of the trial. Detailed plans for the DMC's purpose and responsibilities will be described in the DMC charter and this statistical analysis plan.

As shown in the study schematic in Figure 1 (Study Design Flow Chart) below, the study will have 3 phases: (1) Up to a 2-week screening phase; (2) 8-week double-blind study 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.

Figure 1 Study Design Flow Chart



BID: twice daily; BL: baseline; Rand: randomized; wks: weeks
a Visit 2A is required only for subjects receiving tacrolimus, cyclosporine, everolimus, or sirolimus at baseline.

2.2 Blinding

This is a double-blind, double-dummy, active controlled study. The blind will be accomplished by use of identical looking placebo formulations of maribavir and valganciclovir. The subject will receive maribavir and placebo (identical to valganciclovir) tablets if randomized to the maribavir treatment arm, or valganciclovir and placebo (identical to maribavir) if randomized to the comparator arm (valganciclovir).

The investigators, subjects and their families, or any member of the study team, either at the study site or with the Sponsor, will remain blinded to the treatment assignments until the routine un-blinding occurs after completion of the last subject's last visit and data base lock.

Bioanalysis of PK samples will be conducted by un-blinded staff from the bioanalysis laboratory/CRO. If needed, an interim population PK analysis of maribavir PK data obtained from the subjects receiving maribavir may be performed by an independent un-blinded team/CRO outside of the blinded study team.

3. STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

The following four hypotheses for the primary and key secondary endpoints are to be tested.

- Primary endpoint
  - Null hypothesis H11 (Non-inferiority assessment)
  - Null hypothesis H12 (Superiority assessment)
- Key Secondary endpoint
  - Null hypothesis H21 (Non-inferiority assessment)
  - Null hypothesis H22 (Superiority assessment)

3.1.1 Non-inferiority for the Primary Endpoint

The non-inferiority (NI) margin of the primary efficacy endpoint is 7%. A 7% NI margin was chosen based on the following considerations:

- It preserves at least 85% of the effect size assumed for the valganciclovir treatment group
- It is less than half of 15%, a common NI margin in antiviral trials
- Discussions with clinical experts confirmed it as a conservative choice.

The null hypothesis and alternative hypothesis for the non-inferiority analysis of the primary endpoint (H11) are:

$$H11_{0:}\ P1_T - P1_C \leq -0.07$$

vs

$$H11_{1:}\ P1_T - P1_C > -0.07$$

$P1_T$: proportion of responders in maribavir treatment group who achieve confirmed viremia clearance at the end of Study Week 8

$P1_C$: proportion of responders in valganciclovir group who achieve confirmed viremia clearance at the end of Study Week 8

The difference in the proportion of responders (i.e., subjects with confirmed CMV viremia clearance 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) will be calculated for each treatment group after adjusting for baseline viral load and acute GVHD at baseline.

3.1.2 Superiority for the Primary Endpoint

The null hypothesis and alternative hypothesis for the superiority analysis of the primary endpoint (H12) are:

$$H12_{0:}\ P1_T - P1_C = 0$$

vs

$$H12_{1:}\ P1_T - P1_C \neq 0$$

$P1_T$: proportion of responders in maribavir treatment group who achieve confirmed viremia clearance at the end of Study Week 8

$P1_C$: proportion of responders in valganciclovir group who achieve confirmed viremia clearance at the end of Study Week 8

3.1.3 Non-inferiority for the Key Secondary Endpoint

The key secondary efficacy endpoint will use the same 7% NI margin as the primary endpoint for the same reasons.

The null hypothesis and alternative hypothesis for the non-inferiority analysis of the key secondary endpoint (H21) are:

$$H21_{0:}\ P2_T - P2_C \leq -0.07$$

vs

$$H21_{1:}\ P2_T - P2_C > -0.07$$

$P2_T$: proportion of responders in maribavir treatment group who achieve confirmed viremia clearance and CMV infection symptom control at the end of Study Week 8 and maintain the effect through Study Week 16.

$P2_C$: proportion of responders in valganciclovir group who achieve confirmed viremia clearance and CMV infection symptom control at the end of Study Week 8 and maintain the effect through Study Week 16.

3.1.4 Superiority for the Key Secondary Endpoint

The null hypothesis and alternative hypothesis for the superiority analysis of the key secondary endpoint (H22) are:

$$H22_{0:}\ P2_T - P2_C = 0$$

vs

$$H22_{1:}\ P2_T - P2_C \neq 0$$

$P2_T$: proportion of responders in maribavir treatment group who achieve confirmed viremia clearance and CMV infection symptom control at the end of Study Week 8 and maintain the effect through Study Week 16.

$P2_C$: proportion of responders in valganciclovir group who achieve confirmed viremia clearance and CMV infection symptom control at the end of Study Week 8 and maintain the effect through Study Week 16.

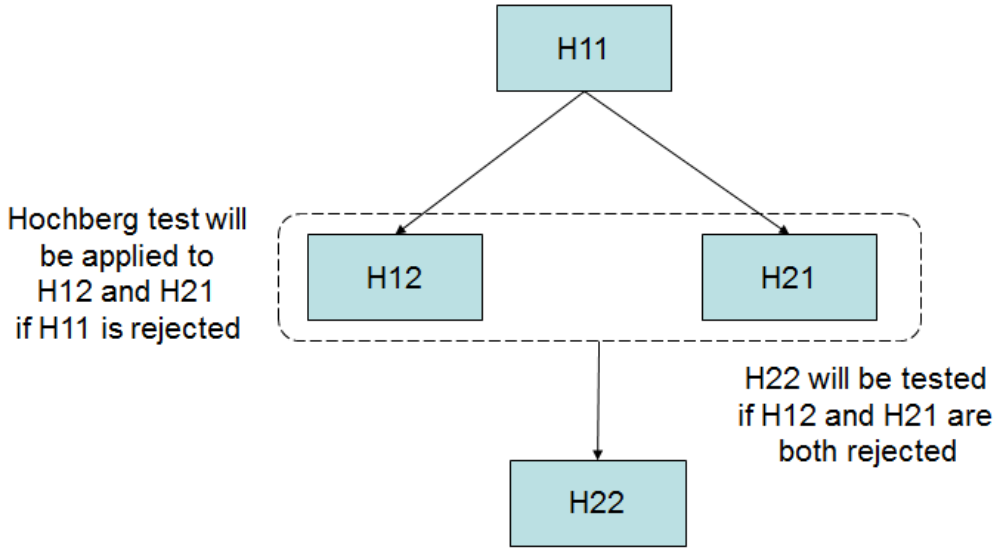
3.2 Statistical Decision Rules

The difference in proportion of responders (i.e., subjects who achieve confirmed viremia clearance and CMV infection symptom control at end of Study Week 8 and maintain the effect through Study Week 16) between treatment groups will be obtained using Cochran-Mantel-Haenszel (CMH) weighted average across all strata, with baseline plasma CMV DNA concentration (high, low, very low) and acute GVHD (present, absent) as two stratification factors. The difference in the proportion of responders will be calculated for each treatment group after adjusting for baseline CMV DNA concentration and acute GVHD at baseline. The 95% confidence intervals (CI) of the weighted average of difference across strata will be provided using the normal approximation. If the lower limit of the 95% CI is greater than -7%, non-inferiority of maribavir to vanganciclovir will be declared and it will be concluded that maribavir is as efficacious as valganciclovir. If non-inferiority of maribavir to vanganciclovir is declared then the superiority of maribavir to vanganciclovir will be tested as part of the procedure described in Section 3.3. If the lower limit of the 95% CI is greater than 0, it will be concluded that maribavir is more efficacious than valganciclovir.

The primary analysis for both NI and superiority testing will be performed in the Modified Randomized Set. Both NI and superiority analyses will also be performed in the per protocol (PP Set) as supportive.

3.3 Multiplicity Adjustment

The hypotheses testing will be adjusted for multiple comparisons using the gatekeeping testing procedure as specified below to control the family-wise Type 1 error rate at 2-sided α=5% level. The testing will be done in the order of primary efficacy endpoint NI testing (H11) first, the primary efficacy endpoint superiority testing (H12) and the key secondary efficacy endpoint NI testing (H21) second, and lastly the key secondary efficacy endpoint superiority testing (H22).



- First, the NI hypothesis of the primary efficacy endpoint (H11) will be tested based on the 2-sided 95% CI of the adjusted difference in proportion of subjects who have CMV viremia clearance at Study Week 8 stratified by baseline CMV DNA level and presence/absence of acute GVHD at baseline. If the lower limit of the 95% CI is above - 7%, NI of the primary efficacy endpoint is considered established, i.e. H11 is rejected.
- If and only after the NI of the primary efficacy endpoint is established, i.e. H11 is rejected, the superiority hypothesis of the primary efficacy endpoint (H12) and the NI hypothesis of the key secondary endpoint of maintenance of response through Study Week 16 (H21) will be tested in parallel. Hochberg procedure will be used to control family-wise Type 1 error rate at α=5% level.
- If and only if the superiority of the primary efficacy endpoint and NI of key secondary efficacy endpoint are established, i.e. H12 and H21 are both rejected, the superiority hypothesis of the key secondary efficacy endpoint (H22) will be tested based at the two-sided 0.05 level.

4. SAMPLE-SIZE DETERMINATION

For sample size calculation, to be conservative, it is assumed that 68% and 60% subjects will achieve confirmed CMV viremia clearance for the primary efficacy endpoint, in the maribavir and valganciclovir groups, respectively. Using the normal approximation method, a 2-sided 95% confidence interval (CI) of the difference in the proportions of subjects with the confirmed CMV viremia clearance will be calculated. If the lower limit of the CI is greater than -7%, the noninferiority will be assumed. The sample size is estimated based on a 2-group test of equivalence in proportions by using nQuery Advisor 7.0. Based on the above assumptions, 494 eligible subjects (247 per treatment group) will result in a >90% power to declare noninferiority of maribavir to valganciclovir for the primary efficacy endpoint. Considering 10% dropout subjects, not included in the Per Protocol (PP) Set, 550 subjects (275 subjects per treatment arm) will be enrolled and randomized.

5. ANALYSIS SETS

- The Enrolled Set will consist of all subjects who have signed an informed consent and have begun some study procedures.
- The Randomized Set will consist of all subjects in the Enrolled Set for whom a randomization number has been assigned.
- The Modified Randomized Set will consist of all subjects in the Randomized Set who have taken at least 1 dose of assigned study treatment.
- The Safety Set will consist of all subjects who have taken at least 1 dose of study treatment.
- The Per-protocol (PP) Set consists of all subjects in the Randomized Set who do not have relevant major protocol deviations that may affect the primary efficacy assessment.

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

  - Taking wrong study treatment or receiving no study treatment
  - Early discontinuation defined as discontinuation from study treatment within 72 hours of first dose of study assigned treatment
  - Violations of inclusion criteria 2-6 or 8
  - Violations of exclusion criteria 1-6 or 12
  - Received prohibited concomitant anti-CMV medications for more than one day while on treatment

- The pharmacokinetic (PK) Set will consist of all subjects in the Safety Set *who received maribavir treatment and* had plasma samples drawn and tested for maribavir concentrations.
- The adolescent PK set will consist of all subjects of ≥16 to <18 years of age in the safety set who received maribavir treatment and had plasma samples drawn and tested for maribavir concentrations.
- The supportive PK Set will consist of all subjects in PK Set who are also in the PP Set.

The Modified Randomized Set and PP Sets will be used for efficacy analyses. If there is more than 10% difference in the number of subjects between the Modified Randomized Set and Randomized Set, then the analysis for the primary and key secondary endpoints will be performed for the Randomized Set. The Safety Set will be used for safety analyses. Pharmacokinetic data will be analyzed using the PK Set as well as supportive PK set. If there is more than 10% difference in the number of subjects between the PK Set and supportive PK Set then pharmacokinetic data will be analyzed using the supportive PK Set as well.

6. 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. 95% confidence intervals for the estimated 25%, 50%, and 75% times will be presented.

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

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

Unless otherwise specified, time part will be excluded from the baseline calculation when comparing the dates

6.1.1 Handling of Treatment Misallocations

For summary or analysis of safety set, the actual treatment is used, otherwise, the randomized treatment is used. The efficacy analysis will be based on the randomized treatment unless otherwise specified.

6.2 Disposition of Subjects

6.2.1 Disposition

A listing of all Screen Failures (i.e. subjects who were screened but not randomized) will be presented along with reasons for screen failure and details of any AEs.

The number of subjects included in each analysis set (i.e., Enrolled Set, Randomized Set, Modified Randomized Set, Safety Set, PP Set, Pharmacokinetic Set, and adolescent PK Set) will be summarized by treatment group and for the overall population. Percentages will be provided (except for the Enrolled Set) using the Randomized Set as the denominator.

The number and percentage (calculated using the Randomized Set as denominator) of subjects in the following categories will be presented by treatment group and overall.

- Completed 8-week study-assigned treatment or discontinued study treatment early and by reason for early discontinuation of study treatment early
- Completed the 8-week treatment phase (regardless of number of weeks of treatment) or discontinued from the study during the 8-week treatment phase, and by reason if discontinued treatment early during the 8-week treatment-phase early.

- Final status (i.e. study completer vs discontinued early). Completed the study at the end of study, and by reason if discontinued from the study discontinuation

In addition, the number of subjects enrolled and randomized , will be tabulated by region, country and site. The number of subjects completed for the Modified Randomized Set will be tabulated by region, country and site .

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.

For any criteria for protocol deviations that can be completely implemented by a computer program, the detailed algorithm will be agreed upon. Details of such algorithms will be included in the derived dataset specifications and finalized before treatment unblinding. 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.

The number of subjects and number of events with major/minor protocol deviations will be summarized for the Randomized Set by category and site for each treatment group overall and by time. Major/minor protocol deviations will be listed for the Randomized Set. A summary of the number and percentage of subjects with any COVID-19 related deviations, major and minor, will be produced using Randomized Set.

6.3 Demographic and Other Baseline Characteristics

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the on-treatment summary statistics in the efficacy and safety sections (refer to Section 6.5 and Section 6.6).

6.3.1 Demographics

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

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group and overall for the Randomized Set, the Modified Randomized Set and PP Set.

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.

6.3.2 Baseline Characteristics

The following baseline characteristics including HSCT history and CMV history will be summarized. The following baseline characteristics will be treated as categorical variables:

- HSCT history
    - Number of HSCT transplants prior to current transplant
    - Underlying disease for current transplantation
    - Is this recurrence of underlying disease
    - Type of transplant (autologous, allogeneic)
        - If allogenic haploidentical (yes/no)
        - If allogenic HLA, match type
    - Stem cell source for current HSCT
    - Current graft status at baseline
    - Type of preparative conditioning regimen
    - T-cell depletion modality
    - Was a donor T-cell infusion given post-HSCT
- CMV serostatus
- CMV DNA category (high, low, very low) used in randomization from IRT
- CMV DNA category (high, low, very low) based on baseline central laboratory results
- Does subject have resistance mutation according to central laboratory result (yes/no)
    - If yes, region (UL97, UL54, UL27)
- Is net immunosuppression reduced prior to start of study treatment, specifically due to current CMV infection (yes/no)
    - If yes, strategies used
- Use of T-cell depletion agent
- Acute GVHD status at baseline (presence/absence)
- Chronic GVHD status at baseline (presence/absence)
- History of CMV prophylaxis
- CD69+CD4+ cells from immune function assay (<0.5%, ≤0.5% and <2%, ≥2%)
- CD69+CD8+ T cells from immune function assay (<0.5%, ≤0.5% and <2%, ≥2%)
- Baseline leukocyte (<2.7, ≤2.7 and <7, ≥7 $10^{\wedge 9}$/L)
- Hepatic impaired subjects (no impairment, impairment and by grade)
- Renal impaired subjects (no, mild, moderate, severe)
- Karnofsky score

Baseline characteristics treated as continuous variable:

- The nucleated cell number transplanted in 10^6 for the current transplant
- The number of CD34+ transplanted in 10^6 for the current transplant
- Days from onset of current CMV infection to first dose of study assigned treatment
- Days from the current transplant to the first dose of study assigned treatment
- Baseline CMV DNA levels from central laboratory
- Most recent screening CMV DNA levels from local laboratory for eligibility
- Baseline leukocyte count

6.4 Medication History and Concomitant Medications

6.4.1 Medical History

The medical history will be summarized by system organ class (SOC) and preferred term (PT) for each treatment group for the Safety Set.

6.4.2 Prior, Concomitant, and Post-Treatment Medications

World Health Organization (WHO) Drug Dictionary dated March 2019 or in effect at the time 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/procedures) 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 in each treatment group receiving each medication by ATC Level III and preferred term by treatment group 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 factors product uses will be summarized for baseline, on-treatment period, off-treatment period and overall post-baseline study period. Immunosuppression drug use will be summarized for baseline, during treatment phase, after treatment phase, on-treatment period, off-treatment period and overall post baseline study period. Anti-CMV drugs use will be

summarized for during treatment phase, after treatment phase, on-treatment period, off-treatment period and overall post-baseline study period. Blood products use will be summarized for the on-treatment period and overall study period.

All prior, concomitant, and post-treatment medication will be provided by subject in the listings. Additionally, immunosuppression regimen and treatment with blood derived products or blood transfusions 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.

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 PP Set and the Modified Randomized Set, unless stated otherwise.

All efficacy analyses will be conducted according to the treatment assigned.

All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise. Control of Type I error is discussed in Section 3.3 in detail.

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 assigned treatments unless otherwise specified. Efficacy measurements after initiation of alternative 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., <137 IU/mL) when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test at a central specialty laboratory, in 2 consecutive post-baseline samples, separated by at least 5 days.

Recurrence of CMV viremia: defined as plasma CMV DNA concentration ≥LLOQ when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in 2 consecutive plasma samples at least 5 days apart, after achieving confirmed viremia clearance.

Rebound of CMV viremia: defined as increase in viral DNA load for >1 $\log_{10}$ above nadir without any prior clearance of viremia.

6.5.1 Primary Endpoint(s) Analysis

6.5.1.1 Derivation of Endpoint(s)

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-assigned treatments through Study Week 8 (i.e., did not receive alternative 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., <137 IU/mL), when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test at a central specialty laboratory, in 2 consecutive post-baseline samples separated by at least 5 days, regardless of whether study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. This is further described in Table 2 (Table 12 in the study protocol) 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 drug:

- 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

This criteria will be assessed by an algorithm that initially chooses a potential confirmatory sample (sample B) within the scheduled Week 8 Visit window (if there is more than one sample within the Visit 8 window choose the one closet to Day 56; if there are two samples an equal number of days from Day 56 choose the later sample) 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 but on or before the start of alternative CMV treatment 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 but on or before the start of alternative CMV treatment 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 but on or before the start of alternative CMV treatment 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, as copied from Section 9.8.1 of the protocol, 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 "-"

CMV: Cytomegalovirus

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

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

[b] Week 9 data, if available to evaluate the effect of study drug, 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.

"-" = CMV DNA concentration <LLOQ (<137 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. This follows the virology first hierarchy, that the confirmed viremia clearance at the end of Week 8 based on CMV DNA data are assessed first.

6.5.1.2 Main Analytical Approach

The difference in proportion of responders between maribavir and valganciclovir treatment groups will be obtained using Cochran-Mantel-Haenszel (CMH) weighted average across all strata, with baseline plasma CMV DNA concentration (high, low, very low) and baseline acute GVHD (present, absent) as two stratification factors. The 95% confidence intervals (CI) of the weighted average of difference across strata will be provided using the normal approximation. If the minimum expected number of subjects in a response category in a treatment group within a level of one of the stratification factors is less than 5, then the adjacent groups will be collapsed into one stratum level.

The CMH weighted 95% CI is adjusted across the strata and this will form the basis of NI and superiority testing. As supportive data, an unadjusted 95% confidence interval based on combining the strata will be reported based on the normal approximation to the binomial distribution. Homogeneity across strata will be tested using Breslow-Day test. If the test is significant at the alpha=0.05 level, stratum-specific differences in proportions will be reported.

If the lower limit of the 95% CI is greater than -7%, it will be concluded that maribavir is as efficacious as valganciclovir. If the lower limit of the 95% CI is greater than 0, it will be concluded that maribavir is more efficacious than valganciclovir.

For the NI analysis for primary endpoint defined in Section 3.1.1, the method is specified in Section 3.2. For the superiority for the primary endpoint defined in Section 3.1.2, the method is specified in Section 3.2. The multiplicity adjustment method is described in Section 3.3.

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 including Randomized but not dosed

(c) 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.

Additionally, a snapshot approach will be utilized to summarize the primary efficacy results and reason for non-response. The snapshot algorithm is described in detail in Appendix A of the CDER (2015) guidance on developing antiretroviral drugs for treatment of Human Immunodeficiency Virus-1 Infection (see reference section in this SAP). In the snapshot analysis, non-responders will be characterized as non-response due to virologic failure including subjects who failed to achieve viremia clearance at Week 8 or at time of alternative treatment or early discontinuation for reason other than AE or death, non-response due to drug/ study discontinuation, and non-response due to other reasons.

6.5.1.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

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

The following 12 types of sensitivity and supplementary analyses will be performed for the primary efficacy endpoint. These analyses will be conducted using the PP Set and the Modified Randomized Set unless specified otherwise.

Type	Analysis Type
1	Analysis addressing sparse strata
2	Analysis using stratification level from randomization
3	Analysis assessing non-responder due to missing data for subjects who discontinue study early with confirmed clearance at the time of study discontinuation
4	Analysis using subset defined by baseline CMV DNA concentration
5	Analysis taking account of COVID impact
6	Analysis excluding subjects affected by the COVID 19 pandemic
7	Analysis restricted to subjects who received 8 weeks of study assigned treatment
8	Analysis allowing for the use of non-study anti-CMV treatment
9	Analysis treating subjects with confirmed viremia clearance at the time of early treatment discontinuation as responders
10	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

Type	Analysis Type
11	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

The following table summarizes key aspects of the sensitivity analyses.

Attributes of Sensitivity Analyses

No	Preserve Responders [a]	Preserve Non-Responders [b]	Adjustments based on				Subset Analysis	Model/ Strata adjustment
			Early Study Disc.	Early Treatment Disc.	Alternative Anti-CMV Use	Covid19		
1	Y	Y	N	N	N	N	N	y
2	Y	Y	N	N	N	N	N	Y
3	Y	N	Y	N	N	N	N	N
4	Y	Y	N	N	N	N	Y	N
5	Y	N	Y*	N	N	Y	N	N
6	Y	Y	N	N	N	Y	Y	N
7	Y	Y	N	N	N	N	Y	N
8	Y	N	N	N	Y	N	N	N
9	N	N	N	Y	N	N	N	N
10	Y	N	Y	N	Y	N	N	N
11	N	N	N	Y	N	N	N	N

[a] All responders in the primary analysis are responders in the sensitivity analysis
[b] All non-responders in the primary analysis are non-responders in the sensitivity analysis
*Only if due to Covid 19

1. Sensitivity Analysis 1: Analysis to Address Sparse Strata

(a) Rationale

Methods that are less affected by sparse strata then the CMH test and Breslow Day test will be performed after pooling strata in the strata in the same manner as the primary analysis.

(b) Derivation of Endpoint:

Same as primary analysis

(c) Analytical Approach

In this analysis, confidence intervals for the difference in the proportion of responders in the treatment groups will be based on the stratified Wilson's score test instead of the CMH test and Zelen's exact test will be conducted for equal odds ratio across strata as an alternative to the

Breslow-Day test. This analysis will be based on the same pooling of strata as the primary analysis.

The adjusted difference and stratified Newcombe 95% confidence intervals for the difference in the proportion of responders in the treatment groups based on the stratified Wilson's score test will be presented. As supportive data, an unadjusted 95% Newcombe confidence interval for the difference in proportion of responders in the treatment groups based on combining the strata will be presented. A test for homogeneity of odds ratios across strata using Zelen's test will be performed. If Zelen's test is significant at alpha=0.05 level, stratum-specific difference in proportion with Newcombe confidence intervals will also be reported in addition to the adjusted difference and 95% CI in proportion of responders based on the stratified Wilson score test.

2. Sensitivity Analysis 2: Use of CMV VL Stratification Level from Randomization

(a) Rationale

The baseline CMV viral load (VL) from the central laboratory is used to determine CMV viral level (high, low, very low) strata in the primary analysis. However, the randomization stratification was based on the screening CMV VL mostly from local laboratory. An analysis will be performed to reflect the actual randomization. This sensitivity analysis is stipulated in the study protocol.

(b) Derivation of Endpoint:

Same as primary analysis

(c) Analytical Approach

The analysis of the primary efficacy endpoint will be repeated using the stratification level used in randomization. For example, the CMV DNA level used in the randomization will be used in the analysis rather than the baseline CMV DNA level determined based on the central laboratory results. This is to evaluate the impact of treatment effect on primary analysis due to the difference in stratum assignment used in randomization for CMV DNA level and the same based on central laboratory results.

3. Sensitivity Analysis 3: 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 sensitivity 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 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 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 study early (during the treatment phase) and take alternative CMV treatment prior to discontinuation will be classified as non-responders. Subjects who discontinue 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.

4. Sensitivity Analysis 4: 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.

5. Sensitivity Analysis 5: Taking Account of COVID 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 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 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 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
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. Sensitivity Analysis 6: 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 sensitivity 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 or who have discontinued the study prior to Week 8 due to the COVID 19 pandemic

(c) Analytical Approach

Same as primary analysis.

7. Sensitivity Analysis 7: Analysis restricted to subjects who received 8 weeks of study assigned treatment

(a) Rationale

An analysis of primary endpoint on a subset of subjects who received 8 weeks of study assigned treatment is of clinical interest.

(b) Derivation of Endpoint:

The primary efficacy analysis will be performed in the subset of subjects who received 8 weeks of study assigned 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 assigned 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.

8. Sensitivity Analysis 8: 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 conducted following the same method as described for the primary endpoint of response at Study Week 8.

(c) Analytical Approach

Same as primary analysis.

9. Sensitivity Analysis 9: 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 will be ignored in this sensitivity 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 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 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 visits then the first reading at least 5 days after treatment discontinuation through 10 days after treatment discontinuation l 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. Additionally reasons for responders will be presented which include details of responders in this analysis who were non-responders in the primary analysis.

A snapshot approach will be performed to classify responders and non-responders in this analysis.

10. Sensitivity Analysis 10: Analysis treating 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

    (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..

11. Sensitivity Analysis 11: Analysis treating subjects with confirmed viremia clearance at the time of early treatment discontinuation for reasons other than an 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 sensitivity analysis 9, 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.

6.5.2 Secondary Endpoints Analysis

6.5.2.1 Key Secondary Endpoint Analysis

The key secondary efficacy endpoint is defined in Section 1.2.2.1.

The key secondary endpoint of this study is a binary response (yes/no) with following criteria:

- Achievement of clearance of viremia at the end of Study Week 8 (virologic response) and no clinical findings of CMV tissue invasive disease at the end of Study Week 8 (CMV infection symptom control), followed by maintenance of this treatment effect for an additional 8 weeks off treatment period (i.e., Follow-up Week 16).

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 either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy, and maintenance of such effect through Week 16, the subject must have received exclusively a study-assigned treatment (no alternative anti-CMV treatment) and maintained symptom control from week 8 through week 16.

CMV infection symptom control includes:

- no new clinical findings of CMV tissue invasive disease

The investigator will assess subjects for new occurrence of CMV tissue invasive disease through the study and will continue with the assessment of the infection status (i.e., no change, improvement, worsening, or resolution) at subsequent visits throughout the study. CMV pneumonia, CMV hepatitis, CMV nephritis, CMV GI CMV myocarditis, CMV pancreatitis, CMV retinitis, and other CMV symptoms will be assessed by the investigator at each visit. For the subject to have CMV infection symptom control at Study Week 8 there can be no clinical findings of CMV pneumonia, CMV hepatitis, CMV nephritis, CMV GI disease, CMV myocarditis, CMV pancreatitis ,CMV retinitis, and other CMV disease as assessed by the investigator at Study Week 8.

Criteria for defining the key secondary efficacy endpoint are:

First being a responder for the primary endpoint at the end of Study Week 8, irrespective of study treatment duration, based on CMV viremia clearance and assessment of the tissue invasive CMV disease status (i.e., no clinical findings of CMV disease at Week 8)

AND

Maintenance of this treatment effect (both CMV viremia clearance and CMV symptom control) through Study Week 16. Maintenance of CMV viremia clearance through Week 16 is determined by the absence of 2 consecutive "+" viral measurements (>LLOQ) through Week 16 (see Table 4).

A subject who fails to achieve response for the primary efficacy endpoint will be a non-responder for the key secondary efficacy endpoint. It is noted that plasma CMV DNA assessment done after the start of alternative anti-CMV treatment are not evaluable for the responder assessment toward the study assigned treatment.

Assessment of the key secondary endpoint will be based an algorithm based on Study Day using the following concepts.

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 around Week 12 (See Section 9.2.4 for details)
3. No two consecutive positives between Week 8 and Week 16

4. Evidence of maintenance around Week 16 (i.e., no confirmed recurrence 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 (through Week 18 for scenario 4c)

For the subject to have CMV infection symptom control through Study Week 16 there can be no clinical findings of CMV pneumonia, CMV hepatitis, CMV nephritis, CMV GI CMV myocarditis, CMV pancreatitis ,CMV retinitis, and other CMV disease clinical findings as assessed by the investigator from Week 8 through Study Week 16.

Table 4, as copied from Section 9.8.2 of the protocol, illustrates the algorithm as above. Note that Table 4 is not exhaustive. The logic above should be used for derivation of the key secondary endpoint, not Table 4.

Table 4 Assessments of Responders for Key Secondary Endpoint

Response* at Study Week 8	CMV DNA Assessment Week							Key secondary endpoint responder[2]	Rationale	Row
	9	10	11	12	14	16	18[1]			
Yes	+/-	+/-	+/-	+/-	+/-	+/-	+/-/NA	No	Any 2 consecutive "+" in FU by week 16	1
Yes	+/-	+/-	+/-	+/-	+/-	-	+/-/NA	Yes	Week 16 is "-" and no 2 consecutive "+" during FU	2
Yes	+/-	+/-	+/-	+/-	+/-	+	+/-/NA	No	Week 16 is "+" and week 18 is "+" or NA, criteria of 2 consecutive "+" is met	3
Yes	+/-	+/-	+/-	+/-	+/-	+	-	Yes	Week 16 is "+", and 2 consecutive "+" criteria is not met based on week 18 data	4
Yes	+/-	+/-	+	-	-	NA	-	Yes	Week 16 is missing, 2 consecutive "+" criteria is not met based on week 14 and 18 data	5
Yes	+/-	+/-	+	-	-	NA	+/NA	No	Week 16 is missing, 2 consecutive "+" criteria may be met based on available week 18 data	6
Yes	+/-/NA	+/-/NA	+/-/NA	+/-/NA	NA	NA	+/-/NA	No	Lack of data to show maintaining effect through week 16	7
No								No		8

*Both virological response and symptomatic CMV infection control
CMV: Cytomegalovirus; FU: Follow-up; NA=not available for evaluation of study drug effect; reason could be starting alternative anti-CMV treatment, withdrawal from study etc.
[1]Week 18 data, if available for evaluation of study drug effect, will be utilized to impute Week 16 data when Week 16 data is unavailable or missing.
[2] Must also meet the criterion of CMV infection symptom control to be a responder.
"-" = CMV DNA concentration <LLOQ (<137 IU/mL)
"+" = CMV DNA concentration ≥LLOQ (i.e., quantifiable)
Notes: Scenarios in the table above are provided as examples and may not be all-inclusive of all possibilities. Only CMV viremia data prior to receiving non-study CMV treatment or rescue treatment will be included in the assessment.

6.5.2.2 Main Analytical Approach

The proportion of responders (i.e., subjects who achieve confirmed clearance of viremia at the end of Study Week 8 (virologic response) and no clinical findings of CMV tissue invasive disease at the end of Study Week 8 (CMV infection symptom control), followed by maintenance of this treatment effect for an additional 8 weeks off treatment (i.e., Follow-up Week 16) after adjusting for baseline viral load and acute GVHD at baseline will be calculated for each treatment group. The difference in proportion of responders between treatment groups will be obtained using the same method as described for the primary efficacy endpoint. The NI analysis for the key secondary endpoint is specified in Section 3.2.

Upon meeting the criteria for superiority testing specified in Section 3.1.4 and subject to the multiplicity adjustment method described in Section 3.3, the superiority hypothesis (H22) of the key secondary efficacy endpoint will be tested in the way of Section 3.2.

6.5.2.3 Sensitivity and Supplementary Analyses of the Key Secondary Endpoint

The following sensitivity analyses will be conducted using the PP Set and the Modified Randomized Set unless otherwise specified:

1. Sensitivity Analysis 1: Analysis to Address Sparse Strata

In this analysis confidence intervals for the difference in the proportion of responders in the treatment groups will be based on Wilson's score test instead of the CMH test and Zelen's exact test will be conducted for equal odds ratio across strata as an alternative to the Breslow-Day test. This analysis will be based on the same pooling of strata as the primary analysis.

The adjusted difference and stratified Newcombe 95% confidence intervals for the difference in the proportion of responders in the treatment groups based on Wilson's score test will be presented. As supportive data, an unadjusted 95% Newcombe confidence interval for the difference in proportion of responders in the treatment groups based on combining the strata will be presented. A test for homogeneity of odds ratios across strata using Zelen's test. If Zelen's test is significant at α=0.05 level, stratum-specific difference in proportion with Newcombe confidence intervals will also be reported in addition to the adjusted difference and 95% CI in proportion of responders based on the Wilson score test.

2. Sensitivity Analysis 2: Use of Stratification Level from Randomization

The analysis of the key secondary efficacy endpoint will be repeated using the stratification level used in randomization. For example, the CMV DNA level used in the randomization will be used in the analysis rather than the CMV DNA level based on the baseline central laboratory results.

3. Sensitivity Analysis 3: Using Subset Defined by Baseline CMV DNA Concentration

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

The analysis of the key secondary 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.

4. Sensitivity Analysis 4: Removing the Requirement of Symptom Control

An analysis of the key secondary endpoint will be performed where a less stringent definition of response is used. In this analysis subjects are not required to be free of any symptoms of CMV infection (i.e., no requirement of symptom control) through Week 16. In this analysis subjects will be classified as a responder as long as CMV viremia clearance confirmed at Week 8 is maintained through Week 16.

5. Sensitivity Analysis 5: Analysis Restricted to Patients Not Impacted by COVID-19

The analysis of the key secondary outcome will be performed in the subset of subjects with do not have missing CMV DNA data between Visit 6 and Visit 16 due to the COVID 19 pandemic and who have not discontinued the study prior to Week 16 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.

6. Sensitivity Analysis 6: Analysis Restricted to Patients Who Receive 8 Weeks of Study Assigned Treatment

The analysis of the key secondary efficacy endpoint will be conducted in the subset of subjects who received 8 weeks of study assigned treatment following the same method as described above for the key secondary endpoint.

7. Sensitivity Analysis 7: Analysis allowing for the use of non-study anti-CMV treatment

An alternative definition of response at Study Week 16 will include subjects who achieved confirmed CMV viremia clearance and CMV infection symptom control at Study Week 8 and maintained this effect through Study Week 16, regardless of the use of non-study anti-CMV treatment. The proportion of alternative response will be analyzed following the same method as described above for the key secondary 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 and symptom control through study Week 8 which is maintained through Study Week 16 regardless of the use of non-study anti-CMV treatment, will be conducted following the same method as described for the key secondary endpoint.

6.5.3 Other Secondary Endpoints Analysis

The analysis of other secondary efficacy endpoints will be conducted using the Modified Randomized Set and PP Set unless otherwise specified. Other secondary efficacy endpoints will be summarized by treatment group, and, if indicated, analyzed statistically with a significance level of α=0.05 (2-sided), without adjustment for multiple comparisons.

For the following 3 secondary endpoints (a), (b) and (c), the proportion of subjects reaching the endpoint and the corresponding 95% CIs will be calculated for each treatment group separately.

The difference in each respective proportion between treatment groups and the associated 95% CI will be calculated using the same approach as the primary efficacy endpoint, and will be assessed using CMH test with acute GVHD and baseline CMV DNA concentration as 2 stratification factors.

a) The achievement of the confirmed CMV viremia clearance after 8 weeks of receiving study-assigned treatment

b) The maintenance of the confirmed CMV viremia clearance after completion of 8 weeks of receiving study-assigned treatment, through Study Weeks 12, 16, and 20

c) The maintenance of the CMV viremia clearance achieved and symptom control at the end of Study Week 8 through Study Weeks 12, and 20, regardless of whether either of the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy

Details of derivations of virological response maintenance for (b) and (c) are contained in Section 9.2.5 of the Appendix.

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

d) The recurrence of CMV viremia (See Section 6.5 for definition) during the first 8 weeks of the study, in the 12-week follow-up period, and at any time during the 20 weeks of the study, regardless of whether study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy

e) The recurrence of confirmed CMV viremia in the 2 study treatment arms when subjects are on treatment and off treatment

f) For the incidence of grade 3 or 4 neutropenia, defined as ANC <1,000/mm^3 [1.0 x 10^9/L] or ANC <500/mm^3 [0.5 x 10^9/L] respectively while on treatment, which will be analyzed using Safety Set

6.5.3.1 Achievement of confirmed CMV viremia after 8 weeks of receiving study assigned treatment

A subject is counted as a responder (a binary response) at Week 8 if meeting the following criteria, or non-responder if not meeting any of the following criteria:

- The achievement of the confirmed CMV viremia clearance at Week 8
- and received 8 weeks of study-assigned treatment

The analysis of response at Study Week 8 after receiving 8 weeks of study-assigned treatment will be conducted following the same method as described for the primary endpoint.

6.5.3.2 The maintenance of CMV viremia clearance after completion of 8 weeks of receiving study-assigned treatment, through Study Weeks 12, 16, and 20

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

A subject is counted as a responder (a binary response) at Week 8, 12, 16, 20 if meeting the following criteria, or non-responder if not meeting any of the following criteria:

- The achievement of the confirmed CMV viremia clearance at Week 8, and maintained through Week 12, 16, 20
- and received 8 weeks of study-assigned treatment

The analysis of response at Study Week 8, 12, 16, and 20 after receiving 8 weeks of study-assigned treatment will be conducted following the same method as described for the primary endpoint.

6.5.3.3 The maintenance of CMV viremia clearance and symptom control achieved at the end of study Week 8 through Study Weeks 12 and 20, regardless of whether either study assigned treatment was discontinued before the stipulated 8 weeks of therapy

For maintenance effect to be achieved at a time point, the subjects must have received exclusively study-assigned 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-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy, through Weeks 12 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-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy; this is similar to the first step in identifying responder for the key secondary efficacy endpoint
- Subjects who maintain the effect achieved at Study Week 8 through Week 12 (or 20) will be classified as responder for Week 12 (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, 20 will be conducted following the same method as described for the primary endpoint.

6.5.3.4 The recurrence of CMV viremia during the first 8 weeks of the study, in the follow-up period of 12 weeks, and at any time during the 20 weeks of the study, regardless of whether either study-assigned treatment was discontinued before the stipulated 8 weeks of therapy

The recurrence of CMV viremia is defined as plasma CMV DNA concentration ≥LLOQ when assessed by the central laboratory COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in 2 consecutive plasma samples at least 5 days apart, after achieving confirmed viremia clearance.

All CMV DNA measurements after achieving confirmed viremia clearance regardless of rescue or alternative treatment will be included in the assessment.

The recurrence of CMV viremia during the first 8 weeks of the study, in the follow-up period of 12 weeks, and at any time during the 20 weeks of the study, regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy will be provided.

- Of the number of subjects who achieved viremia clearance anytime on study after receiving study assigned treatment, the number and percentage who have recurrence in the following periods will be summarized
    - During the first 8 weeks of study, and in the 12 weeks of follow-up
    - Any time on study

6.5.3.5 The recurrence of confirmed CMV viremia in the 2 study treatment arms when subjects are on treatment and off treatment

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

- Of the number of subjects who achieved the confirmed viremia clearance any time on study after receiving study-assigned treatment, the number and percentage of subjects who have recurrence in the following period will be summarized
    - While on study-assigned treatment - breakthrough
    - While off study-assigned treatment

6.5.3.6 The incidence of grade 3 or 4 neutropenia (defined as ANC<10000/mm^3 or ANC<500/mm^3) while on treatment

For the incidence of grade 3 or 4 neutropenia, defined as ANC <1,000/mm^3 [1.0 x 10^9/L] or ANC <500/mm^3 [0.5 x 10^9/L] respectively, the frequency and time to events analysis will be analyzed using Safety Set. The number and proportion of subjects with neutropenia (shifts in ANC from lower grade to grade 3 or 4, as well as grade 4 post-baseline) while receiving study treatment, and the corresponding 95% CI will be calculated for each treatment group.

Time to first occurrence of grade 3 or 4 neutropenia while receiving study treatment will be defined as days from date of first dose to the date of first ANC shifts to grade 3 or 4 post-baseline and will be calculated as [(lab sample date - date of first dose) +1]. The time to first neutropenia while receiving study treatment will be summarized using Kaplan Meier

method. Subjects who have not experienced the event (grade 3 or 4 neutropenia) will be censored at the last date of clinical laboratory assessment at the end of treatment period.

6.5.4 Analyses of Exploratory Endpoints

[redacted]

6.5.4.1 [redacted]

[redacted]

6.5.4.2 [redacted]

[redacted]

6.5.4.3 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.5.4.4 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.5.4.5 [redacted]

[redacted]

6.5.4.6 [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

6.5.4.7 [redacted]

[redacted]

[redacted]

6.5.4.8 [redacted]

[redacted]

6.5.4.9 [redacted]

[redacted]

[redacted]

6.5.4.10 [redacted]

6.5.4.11 [redacted]

6.5.5 Subgroup Analyses

The following list of subgroup analyses will be performed for the primary efficacy endpoint and the key secondary efficacy endpoint. The proportion of responders and the corresponding 95% CI for each endpoint will be summarized by treatment group. The difference in proportion of responders between treatment groups and the 95% confidence limits of the difference will be calculated using methods similar to the primary efficacy analysis, stratifying for any factors used in the primary analysis that remains applicable. Subgroup analysis results will be summarized in a forest plot.

- CMV DNA viral load (high, low, very low)
- Acute GVHD presence/absence at baseline
- Age group, adjacent groups may be collapsed to have adequate sample size

- ≥16 to <18 years of age (adolescents)
- ≥18 to <45 years of age
- ≥45 to <65 years of age
- ≥65 years of age

- Enrolling regions (North America, Europe and Asia)
- Gender
- Use of T-cell depletion agent
- CMV serostatus (D+/R+, D-/R+ vs. D-/R-, D+/R-)
- History of CMV prophylaxis

6.6 Safety Analysis

The analysis of safety will be based on the "treatment-emergent" principle and for the study assigned treatment.

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

The safety analyses will include evaluation and procedures to meet the secondary objective of assessing the safety and tolerability of maribavir. Safety evaluation will be made during the periods as illustrated in Figure 1, 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 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 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 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 and overall study period], and time to neutropenia development), and study treatment dose adjustment due to AEs.

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

Safety endpoints will be summarized descriptively for the on-treatment period and overall-study period. Baseline assessments will be the last assessment before the first dose of study treatment. For each safety variable, the last value collected before the first dose of study treatment will be used as baseline for all analyses of that safety variable. 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 MedDRA Version 23 dated March 2020.

An AE (classified by preferred term) that started after the first dose of study assigned treatment or if started before the date of first dose of study assigned treatment, but increases in severity after first dose of study assigned 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 assigned 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 assigned 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.

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 investigational product.

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 AEs, any serious adverse events (SAEs), any severe AEs, AEs causing discontinuation of study medication, AEs leading to withdrawals from study, fatal AEs and AEs of special interest (AESI) 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 in each treatment group
- Summary of frequently occurring (in ≥5% in either treatment group) TEAEs by PT in descending order for maribavir treatment group
- 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 for maribavir treatment group
- Summary of TEAEs by maximum severity, SOC, and PT
- Summary of TEAEs related to study treatments by maximum severity, SOC, and PT
- Summary of treatment emergent SAEs by SOC and PT
- Summary of treatment emergent SAEs by maximum severity, SOC and PT
- Summary of treatment emergent SAEs considered related to study drugs by SOC and PT
- Summary of TEAEs leading to study treatment discontinuation or withdrawal from study by SOC and PT
- Summary of TEAEs related to study treatments leading to study treatment discontinuation or withdrawal from study 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 AEs, any serious adverse events (SAEs), any severe AEs, AEs causing discontinuation of study medication, AEs leading to withdrawals from study, fatal AEs and AEs of special interest (AESI) as well as the total number of events for each category
- Summary of treatment emergent SAEs by SOC and PT
- Summary of TEAEs leading to death by SOC and PT
- Summary of related treatment emergent SAEs by SOC and PT
- Summary of related TEAEs leading to death by SOC and PT

Additionally, exposure adjusted analyses of adverse events based on rates per 100 patient years exposure will include the following.

- An overall summary of TEAEs, including the number and percentage of subjects with any AEs, any serious adverse events (SAEs), any severe AEs, AEs causing discontinuation of study medication, AEs leading to withdrawals from study, fatal AEs and AEs of special interest (AESI) as well as the total number of events for each category

- Summary of treatment emergent SAEs by SOC and PT
- Summary of related treatment emergent SAEs by SOC and PT

For the exposure adjusted analysis of adverse events, rates per total length of treatment exposure will be displayed in which the total number of patients with at least one event of interest divided by the total years of patient year exposure in each treatment group.

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, fatal AEs and AESIs.

6.6.1.1 Renal Disorder TEAEs

The following summaries of sponsor-defined renal disorder TEAEs will be provided for each treatment group using the Safety Set for the on-treatment period:

- Summary of renal disorder TEAEs by preferred term and maximum severity
- Summary of renal disorder TEAEs related to study treatment by preferred term and maximum severity
- Summary of serious renal disorder TEAEs by preferred term and maximum severity
- Summary of serious renal disorder TEAEs related to study treatment by preferred term and maximum severity

The above summaries of renal disorder TEAEs will be repeated for the following subgroups:

- Renal impaired subjects (no, mild, moderate/severe).

6.6.2 Adverse Events of Special Interest

The following events of special interest will be closely monitored and reported throughout the study, regardless of relationship to study medication.

Two kinds of AESIs based on different severity grading are listed as follows (see Section 8.1.4 of study protocol for more details):

- **Adverse Events of Special Interest (severity grading based on CTCAE Version 4.03)**
  - Tissue invasive CMV
  - Relapse or progression of the underlying disease (disease for which transplant was performed)
  - Taste disturbance (dysgeusia)
  - Nausea, Vomiting, Diarrhea
  - Neutropenia
- **Adverse Events of Special Interest (grading based on standard severity categorization to mild, moderate, and severe)**
  - Immunosuppressant drug concentration level increased:

- Invasive fungal or bacterial infections
- Graft-versus-host-disease: CRF break it into two categories
  - Acute Graft-versus-host-disease
  - Chronic Graft-versus-host-disease

AESI as reported by Investigator and reviewed using the list of MedDRA search terms defined by Sponsor medical lead will be analyzed according to the above grouping, primary SOCs and PTs for the on-treatment period.

The following summaries will be provided for AESI including renal events for the on-treatment period:

- Summary of TEAE of special interest by SOC and PT
- Summary of TEAE of special interest related to study treatment by SOC and PT
- Summary of TEAE of special interest by PT in descending order of frequency for maribavir treatment group
- Summary of TEAE of special interest related to study treatments by PT in descending order of frequency for maribavir treatment group
- Summary of TEAE of special interest by maximum severity, SOC, and PT
- Summary of TEAE of special interest related to study treatments by maximum severity, SOC, and PT
- Summary of serious TEAE of special interest by SOC, and PT
- Summary of serious TEAE of special interest related to study treatments by SOC, and PT

Additionally, exposure adjusted analyses of AESI based on rates per patient years exposure will include the following

- Summary of TEAE of special interest by SOC and PT
- Summary of serious TEAE of special interest by SOC and PT

6.6.2.1 Time to Resolution for Dysgeusia and Similar Terms While on Treatment and When Off Treatment

For subjects who had reported AEs as dysgeusia and similar terms after receiving maribavir as study assigned treatment, the following durations will be calculated and summarized using Kaplan-Meier method and 95% confidence intervals for the estimated 25%, 50%, and 75% times will be presented.

Duration of AEs as dysgeusia and similar terms while on maribavir treatment will be calculated as event stop date – event start date + 1. The event start date is the start of the first reported event from the AEs as dysgeusia and similar terms while on maribavir treatment.

For subjects who had only one reported AE as dysgeusia and similar terms, the event stop date is the resolution date of the event or censored at the last dose of maribavir treatment, whichever is earlier.

For subjects who had more than one reported AE as dysgeusia and similar terms, the event stop date is the resolution date of the last reported event or censored at the last dose date of maribivir treatment, whichever is earlier.

Time to resolution of AE as dysgeusia and similar terms when off maribavir treatment will be calculated for all subjects with ongoing event at time of last dose of maribavir treatment as the event stop date – last dose date +1. For subjects who had one reported AE as dysgeusia and similar terms ongoing at time of last dose of maribavir treatment, the event stop date is the event resolution date in the off-treatment follow-up period or censored at the last study follow-up date, whichever is earlier. For subjects who had more than one reported AE as dysgeusia and similar terms ongoing at time of last dose of maribavir treatment, the event stop date is the last event resolution date in the off-treatment follow-up period or censored at the last study follow-up date.

6.6.2.2 Time to Resolution of Neutropenia While on Treatment and When Off Treatment

An analysis of time to resolution of neutropenia based on grouped adverse event terms will be performed.

Time to resolution of Grade 3/4 neutropenia and time to resolution of Grade 2/3/4 neutropenia and neutropenia of any grade will be analyzed in a similar manner to the endpoint time to resolution of dysgeusia and similar terms.

6.6.2.3 Immunosuppressant Drug Concentration Level Increased

The number and percent of subjects with immunosuppressant drug levels increased will be presented for each treatment group. 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: tacrolimus, sirolimus, everolimus and cyclosporine.

6.6.3 Subgroup Analysis of TEAE and AESIs

Subgroup analysis of TEAE and AESI will be prepared for the following subgroups.

- Race (white, black or African American, Asian, Others)
- Gender (male, female)
- Age group
  - ≥12 to <18 years of age (adolescents)
  - ≥18 to <45 years of age
  - ≥45 to <65 years of age
  - ≥65 years of age
- Enrolling regions (North America, Europe and Asia)
- Renal impaired subjects (yes. No) and (none, mild, moderate/severe)

- Hepatic impaired subjects (yes, no)

The following summaries of TEAEs and AESIs will be provided for the on-treatment period by treatment groups for the subgroups.

- Summary of TEAE by preferred term in descending order of frequency for maribavir treatment group for all the above subgroups.
- Summary of treatment-emergent SAEs by SOC and preferred term for all above subgroups excluding Race and Hepatic impaired subjects
- Summary of TEAEs of special interest by AESI class, preferred term in descending order of frequency for maribavir treatment group for all above subgroup excluding Race and Hepatic impaired subjects

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, fatal AEs and AESIs.

6.6.4 Clinical Laboratory Data

The clinical laboratory assessments are described in Section 7.2.3.5 of the study protocol at the time points specified in Table 1 and Table 2. 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 randomization. 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 a separate data listings. Laboratory data during the follow-up period after initiation of 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 for each treatment 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

To evaluate renal toxicity:

- Creatinine
- Urea nitrogen
    - Furthermore, the summary and box plots for creatinine and urea nitrogen at baseline and last on treatment will be repeated by renal impairment (none, mild, moderate/severe) at baseline

A summary of clinically significant (yes/no) laboratory (hematology, chemistry, and urinalysis) results as determined by the study investigator by treatment group for the on-treatment period and the overall study period.

The following hematology and chemistry laboratory results will be graded according to the NCI-CTCAE version 4.03 or higher.

- Hematology: ANC, Hgb, platelet, WBC, ALC
- Chemistry: Serum sodium, potassium, glucose, creatinine, calcium, phosphorus, magnesium, uric acid, creatinine phosphokinase, total bilirubin, ALT, AST, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total cholesterol, triglycerides

Shift tables showing the shift in NCI CTC 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 by treatment group.

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 by treatment group. 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 [1.0×109/L]) in addition to a maximum grade of either 3 or 4 post-baseline for the on-treatment period and the overall-study period by treatment group will be provided. (See also Section 6.5.3.6). 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 by treatment group. For creatinine an analysis of time from a lower grade to a maximum grade of 2, 3 or 4 post-baseline will be presented.

6.6.5 Vital Signs

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, pulse rate, temperature and body weight) and their changes from baseline at each post-baseline visit and at

the end of study will be presented by treatment group. Baseline will be defined as the last assessment before the first dose of study treatment.

Vital sign values will be considered potentially clinically important (PCI) if they meet the observed value criteria or the change from baseline criteria listed in Table 5. The number and percentage of subjects with PCI post-baseline values will be tabulated by study period and treatment group.. 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 Significant 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	
Pulse rate (beats per minute)	≤50	
	≥100	
	≥120	
Weight (kg)	-	Increase of ≥7%
	-	Decrease of ≥7%
Temperature (°C)	<35.0	
	>39.0	

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

6.6.6 Electrocardiogram (ECG)

A 12-lead ECG will be performed at Visit 2/Day 0, Visit 10/Week 8 (end of treatment visit), Visit 18/Week 20 (end of study visit), and at any additional time during the study, if clinically indicated. ECG data will include heart rate, RR duration, PR duration, QT duration, 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 treatment group for the on-treatment period and the overall study period. 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 at least 1 PCS post-baseline ECG value. 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
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

6.6.7 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.

6.6.8 Extent of Exposure

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 drug administration eCRF and eDiary. The dose adjustment and dose interruption for study drugs will be collected on the eCRF. Available data collected on eCRF and eDiary will be used in assessing the treatment exposure. It is noted that eDiary malfunction due to issues such as device or internet connection has been reported during the study resulting in some data loss.

- Exposure duration will be calculated as the number of days from the date of first dose of study drug to the date of the last dose of study treatment plus 1.
- Actual exposure days to study drug will be calculated as the number of days on which at least 1 dose of study drug was taken. Given the known eDiary issue, the actual exposure days will be calculated in the following two ways to assess the impact of the eDiary issue:
    1. Determine the number of days on which at least 1 dose of study drug was taken based on available eDiary data
    2. Determine the number of days on which at least 1 dose of study drug was taken based on available eDiary data; for subjects with no eDiary record, the exposure duration on

which at least 1 dose of study drug was taken will be based on exposure duration minus the number of days with dose withheld as recorded on the eCRF

- Total number of doses taken will be calculated as the cumulative number of doses taken as recorded on the eDiary.

The measures of exposure (exposure duration, actual exposure days) will be summarized using descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) and will be reported by treatment group.

The number and percent of subjects with dose change, type of change, and reason for change as recorded on the eCRF will be provided. Study treatment dose adjustment, specifically valganciclovir dose adjustment, and interruptions for neutropenia or renal function impairment or other AE, and maribavir dose interruptions for any AE, will be summarized. The assessment of missing eDiary entry in comparison to dose withheld as recorded in eCRF will be provided in a data listing by subject.

All drug exposure and compliance information, study drug administrations including dose change, type of change, and reason of change as recorded on eCRF and dose administration as recorded in eDiary will be presented chronologically by subject in data listings.

6.6.9 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 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 (n, mean, standard deviation, minimum, median, and maximum) by treatment group for the Safety Set. Treatment compliance will also be performed excluding subjects who missed at least 50% of doses during at least one weekly visit. The proportion of patients with at least 80% treatment compliance ,who took study treatment at least 80% of planned study treatment days (adjusting for dose interruptions according to the protocol) prior study treatment discontinuation (either at Week 8 or early treatment discontinuation) will be summarized by treatment group.

Dose adjustment and interruptions of Valganciclovir is allowed based on ANC and Creatinine Clearance as outlined in Table 7 of the study protocol as well as for adverse events. Only one dose of maribavir is used in the study. In order to maintain the blinding sham dose adjustments are performed in the maribavir group. Dose interruptions due to adverse events is allowed for both valganciclovir and maribavir.

The following summaries for dose adjustment and dose interruption will be provided:

- Dose adjustment:
    - The number and percentage of subjects with dose change at least once, and number of times

  - The number and percentage of subjects with dose adjustment (increased, decreased, frequency change) at least once, and number of times
  - The number of subjects with dose change, the number of subjects who have dose adjustment due to intolerance at least once, and number of times
- Dose interruption:
  - The number and percentage of subjects with at least one interruption, total number of interruption, and reason of interruption.

6.7 Pharmacokinetic and Pharmacodynamic Analyses

6.7.1 Pharmacokinetic Analysis

All summaries and analyses of the PK data will be based on the PK Set and adolescent PK Set as applicable. Analyses of the PK data may be performed using the supportive PK set if there is more than 10% difference in the number of subjects between the PK Set and Supportive PK Set.

For logistic reasons, PK data collected in Chinese subjects may be available at a later time than other countries. A separate data package (tables, figures, and listings) may be generated for Chinese PK data once available.

6.7.1.1 Drug Concentration

In adult subjects of at least 18 years old, who received maribavir treatment, sparse blood samples at pre-dose (C_{min}) and 2 to 4 hour post-dose administration at Week 1, Week 4, and Week 8 will be collected. For subjects ≥16 to <18 years of age, an intensive PK sampling (pre-dose, 1, 2, 3, 4,6, 8, and 12 hours post-dose) will be performed at Week 1 and sparse PK sampling similar to adults (≥18 years) will be performed at Week 4 (pre-dose only) and Week 8 (pre-dose and 2 to 4 hour post-dose). Unscheduled sparse PK samples will also be collected upon the diagnosis of GI GVHD during treatment phase. 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 dataset and PK concentration listings, but will be excluded from estimating PK parameters and PK concentration summaries.

It is noted that eDiary has malfunctioned during the study resulting in some loss of dosing date and time data. Some of the plasma maribavir concentrations are impacted because of the lack of actual time relative to dosing. It is noted that remediation by having the dosing date and time recorded at the site when drawing the PK samples has been implemented when the issue was confirmed. To evaluate the impact due to the eDiary malfunction, two sets of plasma maribavir concentrations will be constructed. The primary plasma maribavir concentration dataset will include all plasma maribavir concentrations, where impacted plasma maribavir concentrations will have the actual time imputed with nominal time according to the sparse sampling or intensive sampling schedule (primary concentration dataset) due to missing dosing date and time after eDiary malfunction. The impacted maribavir concentrations will be evaluated individually to confirm the appropriateness of this method, where a previous dosing pattern and/or the central tendency of actual time data distribution may be examined. A secondary plasma maribavir

concentrations dataset will include the subset of plasma maribavir concentrations where actual time are confirmed with the available dosing data (secondary concentration dataset).

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 summary statistics (e.g. mean, SD, etc.) for the plasma concentrations at individual time points. In boxplots for which median, Q1 and Q3 are presented, samples that are below LLOQ are treated as 1/2 LLOQ.
- 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.
- For calculation of area under the plasma concentration curve (AUC), below LLOQ values are set equal to zero in the dataset loaded into WinNonlin for pharmacokinetic analysis. WinNonlin uses the zero values that occur before the first time point with a concentration greater than LLOQ, but WinNonlin excludes the zero values from the AUC calculation for all later time points.
- Missing concentration 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 for all subjects including adolescent subjects. Planned pre-dose PK sample which were collected at post-dose time will be included in the listing with flag and excluded from summary statistics. Additionally, a by-subject listing of maribavir concentrations in subjects with confirmed GVHD will be generated. A by-subject listing of week 8 viremia response and recurrence during the treatment phase will be generated for subjects with pre-dose maribavir concentration below LLOQ at one or more PK visits. Maribavir concentrations will be summarized by visit and nominal time using descriptive statistics (number of observations [n], mean, SD, coefficient of variation (%CV), geometric mean, %CV of the geometric mean, median, maximum, minimum) using the PK Set (primary concentration dataset). Nominal time of 0 hour will be assigned for pre-morning dose samples, and for the 2 to 4 hours post morning dose sample, a nominal time based on the central tendency of actual time data distribution will be used. This summary will be repeated using the adolescent PK Set. If there are less than (≤) 3 observations in the adolescent PK set, only n, minimum, and maximum will be presented. This summary will also be repeated using the secondary concentration dataset as well as the Supportive PK Set as a sensitivity analysis to assess the impact of both eDiary malfunction and protocol deviations.

A scatter plot of all reportable maribavir concentration vs. actual sampling time will be generated using the primary concentration dataset and the secondary concentration dataset by using the PK

Set. This will be repeated using the adolescent PK Set. If there are less than 3 observations in the adolescent PK set, only n, minimum, and maximum will be presented.

C_{min} will be listed and summarized by visit using the PK Set. Planned pre-dose PK samples which were collected at post-dose time will not be used in C_{min} estimations.

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. This will be repeated separately using the adolescent PK Set if it has ≥3 subjects. For each adolescent subject, $AUC_{(0\text{-}tau)}$, C_{max}, T_{max}, CL/F, and V_z/F at week 1 will be listed. Summary (number of observations, mean, SD, coefficient of variation, median, maximum, minimum, geometric mean, and coefficient of variation of geometric mean) will be provided. If there are less than (<) 3 observations, only n, minimum, and maximum will be presented for the PK parameters. Box plot of average C_{min} by confirmed CMV viremia clearance response at Week 8 for all subjects will be provided.

6.7.1.4 Population PK and PK/PD Analysis

In a separate analysis and report, maribavir concentrations will be analyzed by population pharmacokinetic modeling (PopPK) using nonlinear mixed effect model approach with NONMEM v7 or above. Impact of subject demographics (e.g. age, gender, race and body weight) and other risk factors (e.g. hepatic impairment, renal impairment, concurrent medications, subject population) on model parameters will be evaluated. Post hoc maribavir PK parameters such as AUC, C_{max}, and C_{min} will be generated and summarized by identified covariates and subject demographics and characteristics of interest. This analysis may be conducted by combining maribavir PK data from other Phase 1, Phase 2 and Phase 3 studies.

[redacted]

If needed, an interim population PK analysis of maribavir PK data obtained from the study subjects will be performed. Interim population PK analysis will be performed by an independent unblinded team or CRO who will have no involvement in the conduct of the study. Results from this analysis will not be shared with any members of the study team until after database lock. Rules governing this process are detailed in the sponsor's (or designee's) standard operating procedures.

6.8 [redacted]

6.8.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.8.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.9 [redacted]

[redacted]

6.10 Interim Analyses

No formal interim analysis for efficacy will be performed.

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

An independent data monitoring committee (DMC) is established to act in an expert, advisory capacity for periodic assessment of the data to monitor participant safety and to ensure the validity and scientific merit of the trial.

7. REFERENCES

Ljungman P, Boeckh M, Hirsch HH, Josephson F, Lundgren J, Nichols G, Pikis A, Razonable RR, Miller V, Griffiths PD, 2016. Clinical Infectious Diseases, 64, 87–91

[redacted]

8. CHANGES TO PROTOCOL PLANNED ANALYSES

This statistical analysis plan is developed based on the analyses specified in the DATA MANAGEMENT AND STATISTICAL METHODS section of protocol amendment 8.

[redacted] A sensitivity analysis of the primary efficacy endpoint using multivariate regression in the protocol was removed from the SAP.

[redacted]

- [redacted]
- [redacted]

9. APPENDIX

9.1 Study Schedule

The study schedule tables refer to the SHP620-302 protocol:

Table 1: Schedule of Assessment 1: Screening Phase and Study Treatment Phase

Table 2: Schedule of Assessment 2: Follow-up Phase

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 assigned treatment, then the results from the most recent assessment prior to the start of study assigned treatment will be used as baseline. If end of study assessments are 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 assigned 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 assigned 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 treatment 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 drug 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 used 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 double-blind 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. However, the actual values as reported in the database will be presented in data listings. Some illustrative examples are provided below. Table A1 is not comprehensive.

Table A1 Examples for Coding of Special Character Values for Clinical Laboratory Variables

Clinical Laboratory Test	Possible Results (in SI units)	Coded Value for Analysis
Chemistry: ALT	<5	0
Chemistry: AST	<5	0
Chemistry: Total Bilirubin	<1.6	0
Urinalysis: Glucose	≥55	Positive
	≤0	Negative
Urinalysis: pH	≥9.0	9.0

9.2.3 Definition of Visit Windows

For the purpose of providing analyses by study visit, visit windows will be assigned based on the study day (i.e., the number of days from the first dose of study drug). Thus the grouping of data by study visit is accomplished based on the calendar date of the assessment at which the data are obtained rather than the nominal study visit for which the assessment was conducted. Visit windows for various variables are defined in the tables in this section based on schedules assessments.

Note: Study Day visit windows for data analysis purposes are not the same as protocol specified visit windows for the purpose of scheduling clinical assessments of subjects; in general the data analysis visit window corresponding to a specific study visit is larger than the clinical assessment visit window. References in this document to "visit window".

Baseline or treatment onset is defined as the last measurement on or prior to the first dose date of study-assigned treatment during the study. For the purpose of visit windowing study day is determined as the date of the assessment minus the date of the first dose for treated patients and the date of the assessment minus randomization date for randomized patients who were not dosed with study drug.

For the purpose of analysis of visit summaries, 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 the window below. If two or more measurements end up in one week with some taken on or before the start of alternative anti-CMKV treatment, the last measurement taken on or prior to the start date of alternative anti-CMV treatment within the window will be used for the summary by week. If all measurements within a window occur after the initiation of alternative anti-CMV treatment the last visit within the window will be chosen for the analysis visit. Flags for measurements taken after the start of alternative anti-CMV treatment will be created and readings after the start of alternative anti-CMV treatment will not be used in analyses when appropriate. Assessments done on or before the first study treatment administration are considered baseline.

The following table describes the windowing for assessments that are scheduled to be collected at baseline, weekly for Week 1 through Week 12, Week 14, Week 16, Week 18 and Week 20 (CMV DNA test, [redacted] Note that this visit windowing is not used to obtain the primary and confirmatory samples for the primary efficacy outcome (Section 6.5.1.1).

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

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 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 period starts at the time of the start of the study treatment through the end of the study.

Safety endpoints will be summarized descriptively for the on-treatment period and overall-study period. Baseline assessments will be the last assessment before the first dose of study treatment. For each safety variable, the last value collected before the first dose of study treatment will be used as baseline for all analyses of that safety variable. 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.

The following table describes the windowing during the treatment phase for hematology, and chemistry that are scheduled to be collected at baseline, weekly for Day 4, Week 1 through Week 8, Week 10, Week 12, Week 16 and Week 20.

Analysis Visit	FROM	TO
Week 0	**-x**	**0**
Day 4	**1**	**5**
Week 1	**6**	**9**
Week 2	**10**	**16**
Week 3	**17**	**23**
Week 4	**24**	**30**
Week 5	**31**	**38**
Week 6	**39**	**45**
Week 7	**46**	**52**
Week 8	**53**	**63**
Week 10	**64**	**77**
Week 12	**78**	**90**
Week 16	**91**	**104**
Week 20	**133**	**146**

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 (b) and (c) of Section 6.5.3, 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 Baseline for Efficacy and Safety Endpoints

Baseline or treatment onset is defined as the last measurement on or prior to the first dose date of study-assigned treatment during the study (Visit 2/Day 0).

9.3 Analysis Software

Statistical analyses will be performed using Version 9.2 (or newer) of SAS® on a suitably qualified environment.

Pharmacokinetic analysis will use WinNonlin Phoenix version 6.3 or higher (Pharsight Corporation, Mountain View, California, USA).

Statistical analyses will be performed using Version 9.2 (or newer) of SAS® on a suitably qualified environment.

Pharmacokinetic analysis will use WinNonlin Phoenix version 8.0 or higher (Pharsight Corporation, Mountain View, California, USA).

9.4 Changes from the Previous Version of the SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
Section 3.2	The NI analysis testing will be performed on the per protocol set (PP Set), superiority analysis will be performed on the Modified Randomized Set.	The primary analysis for both NI and superiority testing will be performed in the Modified Randomized Set. Both NI and superiority analyses will also be performed in the per protocol (PP Set) as supportive	Address regulatory feedback
Section 6.5.1.2		A descriptive analysis and listing of reasons for non-response for the primary outcome was added.	Address regulatory feedback
Section 6.5.1		Sensitivity analysis 9 for the primary endpoint added: analysis treating subjects with confirmed viremia clearance at the time of early treatment discontinuation as responders	Address regulatory feedback
Section 6.5.1		Sensitivity analysis 10 for the primary endpoint added: analysis treating 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.	Address regulatory feedback
Section 6.5.1		Sensitivity analysis 12 for the primary endpoint added; 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	Address regulatory feedback

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
		discontinuation due to adverse events or death as non-responders	
[redacted]			
Section 6.5.3.6		Analysis of time to neutropenia of any grade removed.	Because many patients have neutropenia at study entry it was decided that the analysis of time to Grade 3 neutropenia and the analysis of time Grade 3 or 4 neutropenia is sufficient.
[redacted]			
Section 6.6.1		Exposure adjusted AE analysis added	The information will be valuable in assessing the safety of study treatment
Section 6.6.2		Exposure adjusted AESI analysis added	The information will be valuable in assessing the safety of study treatment