STATISTICAL ANALYSIS PLAN

NCT Number: NCT02931539

Study Title: A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Treatment Compared to Investigator-assigned Treatment in Transplant Recipients with Cytomegalovirus (CMV) Infections that are Refractory or Resistant to Treatment with Ganciclovir, Valganciclovir, Foscarnet, or Cidofovir

Study Number: SHP620-303

SAP Version and Date:

Version 4.0 (Amendment 3): 28 Sep 2020

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Drug:	SHP620
Sponsor:	Shire ViroPharma, Incorporated 300 Shire Way, Lexington, MA 02421 USA
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Version No:	Document History Description of Update	Author(s)	Effective Date
1.0	Final Version	[redacted]	30 May 2018
2.0	Amendment 1, update for protocol amendment 5	[redacted]	18 July 2018
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4.0	Amendment 3, update to include analysis clarifications, additions, and COVID-19 related sensitivity analysis	[redacted]	28 Sep 2020

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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
β-HCG	beta-human chorionic gonadotropin
BID	twice daily
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus
CRA	clinical research associate
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
EAC	Endpoint Adjudication Committee
eCRF	electronic case report form
eDiary	electronic Diary
ECG	Electrocardiogram
[redacted]	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration
GGT	gamma−glutamyltransferase
GI	Gastrointestinal
GVHD	graft-versus-host disease
HLA	human leukocyte antigen
[redacted]	[redacted]
HSCT	Hematopoietic stem cell transplant
ITT	Intention-to-treat
IAT	investigator-assigned anti-CMV treatment
IRT	interactive response technology

IV	Intravenous
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
OC	observed cases
PCS	potentially clinically significant
PD	pharmacodynamic
PK	pharmacokinetic(s)
PP	Per-protocol
QoL	quality of life
qPCR	quantitative polymerase chain reaction
QTc	corrected QT interval
QTcF	QT Interval Corrected for Heart Rate using Fridericia's Formula
RAP	Resistance Analysis Plan
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOT	solid organ transplant
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety, [redacted] and pharmacokinetic (PK)/pharmacodynamic (PD) data as described in the most recent protocol amendment 6 dated 7 December 2018. [redacted] will be prepared separately. Population PK analysis plan and Resistance Analysis plan will also be prepared separately. Specifications for tables, figures, and listings will be provided in a separate document.

2. STUDY DESIGN

2.1 General Study Design

This is a multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of maribavir treatment compared to investigator-assigned anti-cytomegalovirus (CMV) treatment in hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients with CMV infections that are refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir, including CMV infections with confirmed resistance to 1 or more anti-CMV agents. 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 CMV infection in whole blood or plasma, with a screening value of ≥2730 IU/mL in whole blood or ≥910 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 test. Results 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 and will be used for the stratification level for the randomization. The same laboratory must be used for these assessments. The CMV infection must be refractory to 1 or more of the anti-CMV agents (ganciclovir, valganciclovir, foscarnet, or cidofovir) and the subjects must meet the remaining specified eligibility criteria.

"***Refractory***" will be defined as:

Documented failure to achieve >1 $\log_{10}$ (common logarithm to base 10) decrease in CMV DNA level in whole blood or plasma after 14 days or longer treatment period with IV ganciclovir, oral valganciclovir, IV foscarnet, or IV cidofovir. This definition applies to the current CMV infection and the most recently administered anti-CMV agent.

"***Resistant***" will be defined as:

Documented failure to achieve >1 $\log_{10}$ (common logarithm to base 10) decrease in CMV DNA level in whole blood or plasma after of 14 days or longer treatment period with IV ganciclovir, oral valganciclovir, IV foscarnet, or IV cidofovir. This definition applies to the current CMV infection and the most recently administered anti-CMV agent.

AND

Documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir, valganciclovir, foscarnet, and/or cidofovir.

Results from the same laboratory and the same sample type (whole blood or plasma) are to be used to determine the refractoriness. Note: Failure to respond to these agent(s) due to intolerance will not be considered 'refractoriness.'

The documentation of resistance during screening will be based on the local specialty laboratory genotyping assay results. Plasma samples obtained at baseline for CMV DNA genotyping will be used for the final determination of mutations in the UL97, UL27, and UL54 genes known to confer resistance to anti-CMV agents; this assessment will be based on the results from the central specialty laboratory and utilized for analysis.

The subjects randomized to the maribavir treatment arm will discontinue the anti-CMV therapy they were currently on at the time of enrollment. For subjects randomized to the investigator assigned treatment arm, the investigator will determine at the time of randomization/treatment initiation whether the subject will change the therapy they were currently on at the time of enrollment, or will remain on the same therapy (single or dual anti-CMV agent therapy) after randomization (per Inclusion Criterion 5). If the treatment was continued or started as 2 anti-CMV agents, withdrawal of 1 agent, while continuing the second one will be possible. After randomization, changes to the investigator treatment of choice could include a change in dose and/or dosing regimen, but will not include an addition of or switch to another anti-CMV agent. Addition of or switch to another anti-CMV agent will be declared as a failure for the purpose of study analysis. Note that changes between intravenous (IV) ganciclovir and oral valganciclovir are allowed. Combination therapy with cidofovir and foscarnet is prohibited.

All eligible subjects will be stratified by transplant type (HSCT or SOT) and screening whole blood or plasma CMV DNA concentration (high viral load with CMV DNA ≥273000 IU/mL in whole blood or ≥91000 IU/mL in plasma, intermediate viral load ≥27300 and <273000 IU/mL in whole blood or ≥9100 and <91000 IU/mL in plasma, and low viral load <27300 and ≥2730 IU/mL in whole blood or CMV DNA <9100 and ≥910 IU/mL in plasma as determined by the most recent local or central specialty laboratory qPCR results, available at the time of randomization) as 2 stratification factors and then randomized in a 2:1 allocation ratio to receive maribavir 400 mg twice daily (BID) or investigator-assigned anti-CMV treatment for 8 weeks.

A cohort of subjects will have tissue-invasive CMV disease or CMV syndrome at baseline, as determined by the investigator (also referred as "***symptomatic subjects"***). Therefore, this study will also assess improvement or resolution of tissue-invasive CMV disease or CMV syndrome at the end of the 8-week study treatment phase and during the follow-up phase for subjects with the symptomatic infection present at baseline.

"**A*symptomatic subjects***" will be defined as: Eligible enrolled subjects who do not have tissue-invasive CMV disease or CMV syndrome at baseline, as diagnosed by the investigator.

The investigator will perform the initial diagnosis of tissue invasive CMV disease or CMV syndrome for the symptomatic subjects at baseline and new occurrence of tissue invasive CMV disease or CMV syndrome for the asymptomatic subjects at baseline through the study, and will continue with the assessment of the status (ie, no change, improvement, worsening, or resolution) at subsequent visits through the study. All investigator-assessed cases of tissue invasive CMV disease and CMV syndrome will be reviewed and adjudicated by an independent Endpoint Adjudication Committee (EAC) both for the confirmation of the diagnosis of baseline and new symptomatic CMV infection and for the outcome (ie, no change, improvement, worsening, or resolution).

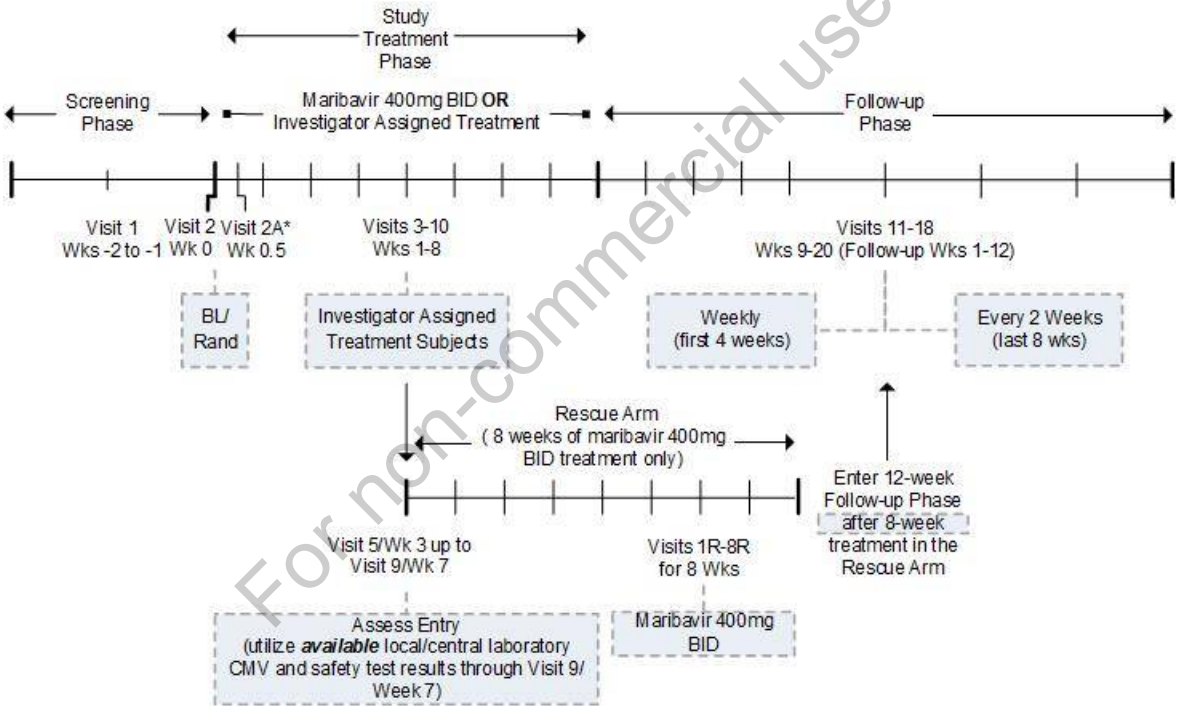
An independent data monitoring committee (DMC) will be established to act in an expert, advisory capacity for periodic assessment of the data to monitor participant safety and to ensure the validity and scientific merit of the trial.

As shown in the study schematic in the Study Design Flow Chart (Figure 1), the study will have 3 phases: (1) Up to a 2-week screening phase; (2) 8-week study treatment phase; and (3) 12-week follow-up phase. Subjects will be required to visit the site up to 19 times for up to a 22-week period. Subjects entering the maribavir rescue arm may participate in the study for a longer duration, depending on the time of the transition from the investigator-assigned study treatment to maribavir, with a maximal time of 29 weeks.

Approximately 140 sites in North America, Europe, and Asia Pacific will participate.

Additional details can be found in Section 3 of the Protocol.

Figure 1 Study Design Flow Chart



BID=twice daily; BL=baseline; R=rescue; Rand=randomized; wks=weeks

*Visit 2A/AR is only required for subjects taking tacrolimus, cyclosporine, everolimus, or sirolimus at Visit 2/2R.

Note: Eligibility to enter maribavir rescue arm will be assessed starting at Visit 5/Week 3 up to Visit 9/Week 7

2.2 Randomization

All eligible subjects will be stratified by 2 stratification factors:

- Transplant type (HSCT or SOT)

and

- CMV DNA concentration levels, based on whole blood or plasma CMV DNA concentration as determined by the most recent local or central specialty laboratory qPCR results, available at the time of randomization:
  - high viral load with CMV DNA ≥273000 IU/mL in whole blood or ≥91000 IU/mL in plasma,
  - intermediate viral load ≥27300 and <273000 IU/mL in whole blood or ≥9100 and <91000 IU/mL in plasma,
  - and low viral load <27300 and ≥2730 IU/mL in whole blood or CMV DNA <9100 and ≥910 IU/mL in plasma).

Following stratification, subjects will be randomized in a 2:1 allocation ratio to receive open-label maribavir 400 mg BID or investigator-assigned anti-CMV treatment for 8 weeks. The actual treatment given to individual subjects is determined by a randomization schedule automatically centrally assigned by the interactive response technology (IRT). The randomization number represents a unique number corresponding to study treatment allocated to the subject, once eligibility has been determined. Once a randomization number/unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a randomization number/unique identifier is allocated incorrectly, the clinical research associate (CRA)/study monitor must be notified as soon as the error is discovered.

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible subject is randomized, b) a subject is randomized based on an incorrect stratum, c) a subject is randomized twice.

   OR
2. A subject is given a study drug not allocated by the protocol-defined randomization, such as a) a subject randomized to investigator-assigned anti-CMV treatment (IAT) received maribavir or vice versa, or b) a nonrandomized subject is treated with study drug reserved for randomized subjects.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report.

2.3 Blinding

This is an open-label study. The investigator(s) and the subjects are unblinded to the treatment assignment.

2.4 Schedule of Assessments

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

Phase	Screening Phase	Study Treatment Phase[u]									
Study Visit / Rescue Arm Visit	**1/NA**	**2/2R**	**2A/2AR[w]**	**3/3R**	**4/4R**	**5/5R**	**6/6R**	**7/7R**	**8/8R**	**9/9R**	**10/10R (End of Treatment)**
Study Week[a]/Rescue Arm Week	**-2 to 0**	**0/0R**	**0.5/ 0.5R**	**1/1R**	**2/2R**	**3/3R**	**4/4R**	**5/5R**	**6/6R**	**7/7R**	**8/8R**
Study Day /Rescue Arm Day	**-14 to 0**	**0c/0R**	**4/4R**	**7/7R**	**14/14R**	**21/21R**	**28/28R**	**35/35R**	**42/42R**	**49/49R**	**56/56R**
Informed consent[b]	X										
Inclusion/exclusion criteria[c]	X	X									
Randomization		X									
Physical examination (including weight)[d]		X					X				X
Height	X										
Weight	X				X				X		
Vital signs	X	X			X		X		X		X
Medical history	X	X[e]									
Prior medications, therapies, and procedures	X	X[v]									
12-lead ECG[f]		X									X
Hematology/Chemistry[g]	X	X	X		X		X		X		X
Urinalysis[g]		X			X		X		X		X
Pregnancy test[g,h]	X	X					X				X
HIV status[i]	X										
HBV and HCV tests[j]		X[j,v]									
CMV DNA test[k]	X	X		X	X	X	X	X	X	X	X
Symptomatic CMV infection assessment[l]		X		X	X	X	X	X	X	X	X
[redacted]		X									X

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Phase	Screening Phase	Study Treatment Phase[u]									
Study Visit / Rescue Arm Visit	**1/NA**	**2/2R**	**2A/2AR[w]**	**3/3R**	**4/4R**	**5/5R**	**6/6R**	**7/7R**	**8/8R**	**9/9R**	**10/10R (End of Treatment)**
Study Week[a]/Rescue Arm Week	**-2 to 0**	**0/0R**	**0.5/ 0.5R**	**1/1R**	**2/2R**	**3/3R**	**4/4R**	**5/5R**	**6/6R**	**7/7R**	**8/8R**
Study Day /Rescue Arm Day	**-14 to 0**	**0c/0R**	**4/4R**	**7/7R**	**14/14R**	**21/21R**	**28/28R**	**35/35R**	**42/42R**	**49/49R**	**56/56R**
[redacted]											
Immunosuppressant drug concentration levels		X[n]	X[n]	X[n]							X
PK samples[o]				X[o]			X[o]				X
Rescue Arm Eligibility[p]						X[p]	X	X	X	X	
Interactive Response Technology[q]	X	X		X	X	X	X	X	X	X	X
Study treatment dispensed[r]		X		X	X	X	X	X	X	X	
Study diary[s]		X	X	X	X	X	X	X	X	X	X
Invasive bacterial, viral and fungal infection/transplant relevant infections assessment		X		X	X	X	X	X	X	X	X
Transplant status		X		X	X	X	X	X	X	X	X
GVHD assessment (for HSCT subjects only)		X		X	X	X	X	X	X	X	X
Liver function assessment by Child-Pugh classification		X[v]									
Comorbidity status evaluation		X					X				X
[redacted]		X					X				X
[redacted]		X			X		X		X		X
[redacted]		X		X	X	X	X	X	X	X	X

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

Phase	Screening Phase	Study Treatment Phase[u]									
Study Visit / Rescue Arm Visit	**1/NA**	**2/2R**	**2A/2AR[w]**	**3/3R**	**4/4R**	**5/5R**	**6/6R**	**7/7R**	**8/8R**	**9/9R**	**10/10R (End of Treatment)**
Study Week[a]/Rescue Arm Week	**-2 to 0**	**0/0R**	**0.5/ 0.5R**	**1/1R**	**2/2R**	**3/3R**	**4/4R**	**5/5R**	**6/6R**	**7/7R**	**8/8R**
Study Day /Rescue Arm Day	**-14 to 0**	**0c/0R**	**4/4R**	**7/7R**	**14/14R**	**21/21R**	**28/28R**	**35/35R**	**42/42R**	**49/49R**	**56/56R**
Concomitant medications, therapies, and procedures[t]		X	X	X	X	X	X	X	X	X	X
AE/SAE monitoring		X	X	X	X	X	X	X	X	X	X

AE=adverse event; CMV=cytomegalovirus; ECG=electrocardiogram; [redacted] GVHD=graft-versus-host disease; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HSCT=hematopoietic stem cell transplant; hx=history; IRT=interactive response technology; PK=pharmacokinetic; R=rescue; SAE=serious adverse event; [redacted]

Note: Subjects in the investigator-assigned anti-CMV treatment arm who discontinue study treatment phase to enter the maribavir rescue arm will follow the study procedures in the Schedule of Assessment 1 for the study treatment phase, beginning with Study Week 0 (visits denoted as "R"), and will exit after 8 weeks of maribavir 400 mg BID treatment to enter the follow-up phase. For subjects entering the maribavir rescue arm on the day of their end-of-treatment visit, duplicate procedures do not need to be repeated.

[a] Permissible assessment windows: Study Visit 2A/2AR (Day 4) ±1 day; Study Visit 3/3R (Day 7) +2 days; Study Weeks 2-4 ±2 days; Study Weeks 5-8 ±3 days.

[b] Informed consent must be obtained before any study-specific procedures are performed. All screening procedures will be completed within 14 days prior to initiation of study treatment, with the exception of: 1) screening clinical laboratory tests (hematology, chemistry, pregnancy), which must be performed within 7 days prior to initiation of study treatment; either central or local laboratory results for hematology/chemistry/pregnancy testing can be used for qualification, and 2) documentation of CMV infection in whole blood or plasma, with a screening value of ≥2730 IU/mL in whole blood or ≥910 IU/mL in plasma 2 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 should be available before the subject is randomized to verify subject eligibility for the study. Both samples should be taken within 14 days of randomization with second sample obtained within 5 days before randomization. Same laboratory should be used for these assessments.

[c] Screening and Visit 2/Day 0 visits can occur on the same day in the case when historical laboratory values are available for determination of the eligibility. All Visit 2/Day 0 procedures and screening laboratory results needed to confirm eligibility must be completed and documented prior to randomization and initiation of study treatment administration. The test results for the samples taken at Visit 2, from central laboratory or central specialty laboratory, will not be available to be used for the screening. Initiation of study treatment (ie, first dose) will only occur after completion of all required Visit 2/Day 0 procedures, confirmation of eligibility, and completion of randomization. This will be done under the supervision of investigator site personnel. For subjects randomized to receive maribavir or investigator-assigned therapy, therapy must be initiated within 24 hours of randomization.

[d] Symptom-oriented physical examinations other than protocol-specified examinations will be performed when clinically indicated.

[e] Updated medical history on Visit 2/Day 0.

[f] Electrocardiograms other than protocol-specified ECGs will be performed when clinically indicated.

[g] Clinical laboratory test will be performed at a central laboratory for all specified time points during the study including baseline. Central or local laboratory results for hematology/chemistry/serum pregnancy testing can be used for eligibility and their results must be available prior to randomization. Local laboratory β-human chorionic

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

Phase	Screening Phase	Study Treatment Phase[u]									
Study Visit / Rescue Arm Visit	1/NA	2/2R	2A/2AR[w]	3/3R	4/4R	5/5R	6/6R	7/7R	8/8R	9/9R	10/10R (End of Treatment)
Study Week[a]/Rescue Arm Week	-2 to 0	0/0R	0.5/ 0.5R	1/1R	2/2R	3/3R	4/4R	5/5R	6/6R	7/7R	8/8R
Study Day /Rescue Arm Day	-14 to 0	0c/0R	4/4R	7/7R	14/14R	21/21R	28/28R	35/35R	42/42R	49/49R	56/56R

gonadotropin test results can be used for the assessment of pregnancy on Day 0/Week 0. Local laboratory will be used for Visit 2A/2AR (Day 4) potassium and magnesium levels, and Day 4 after starting tacrolimus, cyclosporine, everolimus, or sirolimus if the subject is not taking at V2/2R.

[h] Female subjects of child-bearing potential will have serum pregnancy testing performed at a central or local laboratory. Urine test results are not sufficient for eligibility determination.

[i] HIV status will be used for the evaluation of this criterion. Subjects must have a confirmed negative result within 3 months of study entry or have testing done locally during the screening period. The test result must be available prior to randomization.

[j] Hepatitis B and HCV historical results available within 3 months prior to study treatment initiation will be accepted. If historical values are not available then the test will be repeated at Visit 2/Day 0. The results of test do not have to be available prior to start of dosing.

[k] Blood samples taken at all study visits (processed to obtain plasma), for all CMV DNA tests (quantitation, genotyping), will be tested in the central specialty laboratory. Only during screening period, local specialty laboratory results for CMV DNA quantitation could be used for eligibility assessment; in this case CMV DNA results from central laboratory are not required. At all other visits, CMV DNA test will be conducted at a central specialty laboratory. The screening results, regardless whether from the local or central specialty laboratory, will be utilized for stratification for randomization.

[l] Subjects with tissue invasive CMV disease or CMV syndrome (SOT subjects only) present at Visit 2/Day 0 (baseline) will have serial assessments at all subsequent visits for infection status (no change, improvement, worsening, or resolution of disease/syndrome and associated symptoms) until resolution. All subjects will be assessed at each visit for new tissue invasive disease or CMV syndrome, and any new tissue invasive disease or CMV syndrome will have serial assessments at all subsequent visits for infection status (no change, improvement, worsening, or resolution of disease/syndrome and associated symptoms) until resolution.

[redacted]

[n] If the subject is receiving immunosuppressant drugs (cyclosporine, tacrolimus, sirolimus, or everolimus), as mentioned in Study Protocol Section 7.2.3.5, on Study Day 0, then a blood sample to measure immunosuppressant drug concentration level will be obtained on Visit 2/2R (Day 0) prior to study treatment, Visit 2A/2AR [Day 4 (±1 day)], Visit 3/3R [Day 7 (+2 day)], and on Visit 10/10R (Week 8) If the subject is not receiving immunosuppressant drugs at Day 0, but starts any time after Day 0 while still receiving study treatment, then a blood sample to measure immunosuppressant drug concentration will be obtained 4 days after the first dose of immunosuppressant drug and at the next scheduled study visit. Additional monitoring of immunosuppressant drug levels may be performed at the discretion of the investigator. Tests will be performed at a local laboratory. For more details refer to Section 7.2.3.5 of the Study Protocol.

[o] Pharmacokinetic samples should be obtained and analyzed for only those subjects who are randomized to maribavir treatment arm. For subjects ≥18 years of age randomized to maribavir, a pre-morning dose PK sample should be obtained at all 3 PK visits and a 2-4 hour post-morning dose sample will be collected only at Visit 3/Week 1 and Visit 10/Week 8. There will be no post dose PK sample collected for Visit 6/Week 4. Pharmacokinetic sample collection for adolescent subjects ≥12 to <18 years of age,

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

Phase	Screening Phase	Study Treatment Phase[u]									
Study Visit / Rescue Arm Visit	1/NA	2/2R	2A/2AR[w]	3/3R	4/4R	5/5R	6/6R	7/7R	8/8R	9/9R	10/10R (End of Treatment)
Study Week[a]/Rescue Arm Week	-2 to 0	0/0R	0.5/ 0.5R	1/1R	2/2R	3/3R	4/4R	5/5R	6/6R	7/7R	8/8R
Study Day /Rescue Arm Day	-14 to 0	0c/0R	4/4R	7/7R	14/14R	21/21R	28/28R	35/35R	42/42R	49/49R	56/56R

randomized to maribavir, will be as follows: intensive PK sampling at Visit 3/Week 1 (pre-morning dose and 1, 2, 3, 4, 6, 8 [all ±5 min], and 12 hours [±15 min] post-morning dose); at Visit 6/Week 4 (one pre-morning dose PK sample); at Visit 10/Week 8 (one pre-morning dose and one between 2-4 hour post morning dose PK samples). Additional PK samples will be collected from any subjects with biopsy proven graft-versus-host disease (GVHD) of gastrointestinal (GI) with diarrhea (>300 ml/day) or biopsy proven GVHD of GI with nausea and vomiting or documented acute GVHD of liver (Stage II), total bilirubin >3 mg/dL or biopsy-proven) with diarrhea (>500 ml/day) or biopsy proven acute GVHD of the skin with diarrhea (>500 mL/day) per Boeckh et al., 1998. Refer to Study Protocol Section 7.2.4.1 for more details.

[p] The eligibility of subjects who must discontinue the investigator assigned anti-CMV treatment for lack of anti-viral activity and/or intolerance, will be assessed at Visit 5/Week 3 up to Visit 9/Week 7 for entry into an rescue arm of treatment with maribavir 400 mg BID for up to 8 weeks.

[q] Except at screening, baseline, and end of treatment, IRT will be used for maribavir dispensing. Subjects who are eligible for the rescue arm will be assigned maribavir by the IRT system. The IRT system will be used for stratification and randomization of eligible subjects at baseline. The IRT will be used to manage maribavir.

[r] All dispensed study assigned treatment will be documented on the CRFs and/or other study assigned treatment record. Investigator assigned anti-CMV medication (ganciclovir, valganciclovir, foscarnet, or cidofovir) will also be documented on the CRFs and/or other study treatment accountability records, and may include additional information as required per applicable regulations. The disposition of unused supply of dispensed study assigned treatment and investigator assigned anti-CMV medication that has been prescribed to the subject will be documented in the accountability log.

[s] The study diary will be dispensed at baseline and will be collected at the last follow-up visit. The diary will be used for tracking treatment compliance with medication administered orally during the study treatment phase and it will be used for tracking completion of the [redacted] during the study treatment phase and through the follow-up phase (see Schedule of Assessment 2, Table 2). Note that the diary will only be utilized for study treatments that are given orally. The IV administration will be tracked in the source documents and CRF.

[t] Includes recording of medications and transfusions (packed red blood cells, platelets, fresh frozen plasma). Changes in immunosuppression regimens will also be recorded.

[u] Subjects who prematurely discontinue study treatment will complete the end of treatment procedures described for Visit 10/Study Week 8; these subjects will continue a modified schedule of assessments through the remaining weekly visits scheduled for the study treatment phase and the regular schedule of assessments through the 12-week follow-up phase or if meeting criteria to enter maribavir rescue arm will start 8-week maribavir 400 mg BID treatment. The end of treatment (Visit 10/Study Week 8) sample for immunosuppressant drug concentration level will be collected at the next visit scheduled 1 week after the treatment discontinuation. For subjects entering the Rescue Arm, [redacted] the Visit 2R/Week 0R does not need to be collected. Subjects who discontinue study treatment early will not be asked to complete the following procedures after the end of treatment visit for subsequent visits in the treatment phase: the use of the diary for study treatment compliance, dispense or use of any study treatment, and PK sample collection. After completing the 8-week study treatment phase, subjects will enter the 12-week follow-up phase.

[v] Not required at V2R.

[w] V2A/A-R is only required for subjects taking tacrolimus, cyclosporine, everolimus, or sirolimus at Visit 2/2R.

Table 2 Schedule of Assessment 2: Follow-up Phase

Phase	Follow-up Phase[k,l]							
Visit	**11/11R**	**12/12R**	**13/13R**	**14/14R**	**15/15R**	**16/16R**	**17/17R**	**18/18R (End of Study)**
Study Week (Follow-up Week)[a]	**9(1)/9R (1R)**	**10(2)/10R (2R)**	**11(3)/11R (3R)**	**12(4)/12R (4R)**	**14(6)/15R (6R)**	**16(8)/16R (8R)**	**18(10)/18R (10R)**	**20(12)/20R (12R)**
Study Day (Follow-up Day)	**63(7)/63R (7R)**	**70(14)/70R (14R)**	**77(21)/77R (21R)**	**84(28)/84R (28R)**	**98(42)/98R (42R)**	**112(56)/112R (56R)**	**126(70)/126R (70R)**	**140(84)/140R (84R)**
Physical examination (including weight)								X
Vital signs								X
12-Lead ECG[b]								X
Hematology/Chemistry[c]		X		X		X		X
Urinalysis[c]								X
Immunosuppressant drug concentration level[d]	X							
Invasive bacterial, viral and fungal Infection(s) assessment	X	X	X	X	X	X	X	X
CMV DNA test	X	X	X	X	X	X	X	X
Symptomatic CMV infection assessment[f]	X	X	X	X	X	X	X	X
Transplant status	X	X	X	X	X	X	X	X
GVHD assessment (for HSCT subjects only)	X	X	X	X	X	X	X	X
Comorbidity status evaluation				X		X		X
Study diary[g]				X		X		X
[redacted]				X		X		X

Table 2 Schedule of Assessment 2: Follow-up Phase

Phase	Follow-up Phase[k,l]							
Visit	**11/11R**	**12/12R**	**13/13R**	**14/14R**	**15/15R**	**16/16R**	**17/17R**	**18/18R (End of Study)**
Study Week (Follow-up Week)[a]	**9(1)/9R (1R)**	**10(2)/10R (2R)**	**11(3)/11R (3R)**	**12(4)/12R (4R)**	**14(6)/15R (6R)**	**16(8)/16R (8R)**	**18(10)/18R (10R)**	**20(12)/20R (12R)**
Study Day (Follow-up Day)	**63(7)/63R (7R)**	**70(14)/70R (14R)**	**77(21)/77R (21R)**	**84(28)/84R (28R)**	**98(42)/98R (42R)**	**112(56)/112R (56R)**	**126(70)/126R (70R)**	**140(84)/140R (84R)**
[redacted]				X		X		X
[redacted]	X	X	X	X	X	X	X	X
[redacted]								X
AE monitoring[i]	X	X	X	X	X	X	X	X
SAE monitoring[i]	X	X	X	X	X	X	X	X
Concomitant medications, therapies, and procedures[j]	X	X	X	X	X	X	X	X

AE=adverse event; CMV=cytomegalovirus; ECG=electrocardiogram; GVHD=graft-versus-host disease; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HSCT=hematopoietic stem cell transplant; IRT=interactive response system; R=rescue; SAE=serious adverse event; SF-36=Short Form-36

Note: Subjects in the investigator-assigned anti-CMV treatment arm who discontinue the study treatment phase to enter the maribavir rescue arm will exit after 8 weeks of maribavir 400 mg BID treatment to enter the follow-up phase (visits denoted as "R").

[a] Permissible assessment windows: Study Weeks 9-12 (Follow-up Weeks 1-4) ±2 days; Study Weeks 14-20 (Follow-up Weeks 6-12) ±3 days.

[b] Electrocardiograms other than protocol-specified ECGs will be performed when clinically indicated.

[c] Clinical laboratory testing performed at a central laboratory for all specified time points during the follow-up phase.

[d] Refer to Study Protocol Section 7.2.3.5 for more details.

[e] Blood samples taken at all study visits (processed to obtain plasma), for all CMV DNA tests (quantitation, genotyping) during the follow-up phase will be tested in the central specialty laboratory.

[f] Subjects with tissue invasive CMV disease or CMV syndrome (SOT subjects only) present at Visit 2/Day 0 (baseline) will have serial assessments at all subsequent visits for infection status (no change, improvement, worsening, or resolution of disease/syndrome and associated symptoms) until resolution. All subjects will be assessed at each visit for new tissue invasive disease or CMV syndrome, and any new tissue invasive disease or CMV syndrome will have serial assessments at all subsequent visits for infection status (no change, improvement, worsening, or resolution of disease/syndrome and associated symptoms) until resolution.

Table 2 Schedule of Assessment 2: Follow-up Phase

Phase	Follow-up Phase[k,l]							
Visit	11/11R	12/12R	13/13R	14/14R	15/15R	16/16R	17/17R	18/18R (End of Study)
Study Week (Follow-up Week)[a]	9(1)/9R (1R)	10(2)/10R (2R)	11(3)/11R (3R)	12(4)/12R (4R)	14(6)/15R (6R)	16(8)/16R (8R)	18(10)/18R (10R)	20(12)/20R (12R)
Study Day (Follow-up Day)	63(7)/63R (7R)	70(14)/70R (14R)	77(21)/77R (21R)	84(28)/84R (28R)	98(42)/98R (42R)	112(56)/112R (56R)	126(70)/126R (70R)	140(84)/140R (84R)

[g] The study diary will be used for tracking completion of the [redacted] during the follow-up phase. The study diary will be collected at the last follow-up visit.

[redacted]

[i] Adverse events and SAEs will be monitored and recorded through Visit 18/Week 20/Follow-up Week 12 (end of study) according to Study Protocol Section 7.2.3.6.

[j] All medications, therapies, and procedures used to treat AEs will be recorded through Visit 18/Week 20 (Follow-up Week 12 (end of study).

[k] Subjects who withdraw from the study during the follow-up phase will perform the Visit 18/Week 20 (Follow-up Week 12) end of study procedures.

[l] If the subject is unable to or unwilling to travel to the site for the follow-up visits, these visits may be performed remotely (ie, at the subject's home) by a qualified sponsor or site designee, and only if permitted according to local regulations. Blood sample for DNA quantitation and clinical laboratory assessments will be collected. Adverse events and SAE collection may be completed by telephone follow-up call on the day of the scheduled visit.

2.5 Determination of Sample Size

In Phase 2 Study SHP620-202, the proportion of subjects with undetectable plasma CMV DNA within 6 weeks was 70%, 63%, and 68% for the 400 mg, 800 mg, and 1200 mg BID dose groups, respectively. The proportion of subjects with undetectable plasma CMV DNA within 12 weeks was 70%, 65%, and 75% for the 400 mg, 800 mg, and 1200 mg BID dose groups, respectively. Therefore, it is assumed that at least 60% of maribavir treated subjects will have achieved undetectable plasma CMV DNA at Visit 9/Week 7 and Visit 10/Week 8 when calculating the sample size for Study SHP620-303.

A proportion of approximately 40% is considered as a reasonable estimate of the proportion of subjects with confirmed undetectable plasma CMV DNA at Visit 9/Week 7 and Visit 10/Week 8 in a control group when calculating the sample size. It is believed that the treatment difference of 20% higher in maribavir group compared to control group is larger than a clinically meaningful difference.

In order to demonstrate statistical superiority in the reduction of CMV DNA, it is assumed that the proportion of subjects with confirmed unquantifiable plasma CMV DNA at Visit 9/Week 7 and Visit 10/Week 8 in the maribavir and control groups is 60% and 40%, respectively. A total of 315 subjects is required in the ratio of 2:1 (210 subjects in maribavir group and 105 subjects in the control group) to provide 90% power in hypothesis testing at an alpha level of 0.05 (2-sided test). The sample size is estimated based on a 2-group continuity corrected Chi-square test of equal proportions by using nQuery Advisor 7.0. Considering 10% drop-outs, 351 subjects (234 subjects in maribavir group and 117 subjects in the control group) will be enrolled and randomized.

2.6 Multiplicity Adjustments for Type I Error Control

The hypothesis-testing of the primary and key secondary endpoint will be adjusted for multiple comparisons using a fixed-sequence testing procedure to control the family-wise Type 1 error rate at 2-sided 5% level. The statistical test will be performed sequentially in the order of primary efficacy endpoint, and the key secondary endpoint. First, the primary endpoint analysis will be assessed at α=0.05 (2-sided). If and only after the primary efficacy endpoint is statistically significant, the key secondary endpoint will be assessed at α=0.05 (2-sided).

3. OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to compare the efficacy of maribavir to investigator-assigned anti-CMV therapy in CMV viremia clearance at the end of Study Week 8, in transplant recipients who are refractory or resistant to prior anti-CMV treatment.

3.2 Key Secondary Objective

The key secondary objective of this study is to compare the efficacy of the 2 study treatment arms on CMV viremia clearance and symptomatic CMV infection (tissue-invasive disease and CMV syndrome) improvement or resolution at the end of Study Week 8, and maintenance of this treatment effect through Study Week 16 (8 weeks of post-treatment/follow-up phase).

3.3 Secondary Objectives

The secondary objectives of this study are:

- To compare the efficacy of maribavir to investigator-assigned anti-CMV therapy on CMV viremia clearance after completion of 8 weeks of study treatment in transplant recipients who are refractory or resistant to prior anti-CMV treatment.
- To compare the efficacy of the 2 study treatment arms on CMV viremia clearance and tissue-invasive CMV disease and CMV syndrome improvement or resolution after completion of 8 weeks of study treatment and maintenance of this treatment effect through Study Weeks 12, 16, and 20.
- To assess the maintenance of CMV viremia clearance, and resolution or improvement of tissue invasive CMV disease and CMV syndrome, achieved at the end of Study Week 8, through Weeks 12, and 20.
- To evaluate the incidence of recurrence of 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 CMV viremia in the 2 study treatment arms, when subjects are on-treatment and off-treatment.
- To assess the profile of mutations in the CMV genes conferring resistance to maribavir.
- To evaluate the all-cause mortality.
- To assess the safety and tolerability of maribavir.
- To assess the efficacy, maintenance of the treatment effect, and the safety of maribavir administered as the rescue treatment.
- To characterize the pharmacokinetics of maribavir.

3.4 Exploratory Objectives

The exploratory objectives of this study are:

[redacted]

4. SUBJECT POPULATION SETS

4.1 Enrolled Set

Enrolled Set consists of all subjects who have signed informed consent and some study procedures have begun (e.g., dispensed study treatment, current drug has been withdrawn).

4.2 Randomized Set

Randomized Set consists of all subjects in the enrolled set who have been randomized to the study. Subjects will be analyzed in the treatment group to which they are randomized.

4.3 Modified Randomized Set

Modified Randomized Set consists of all subjects in the enrolled set who have been randomized to the study and have taken any dose of study-assigned treatment. Subjects will be analyzed in the treatment group to which they are randomized.

4.4 Safety Set

The Safety Set consists of all subjects who took any dose of study-assigned treatment. Subjects will be analyzed according to the treatment actually received.

4.5 Per-protocol Set

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. Prior to database lock, the Sponsor medical lead will review the protocol deviations collected throughout the study and determine which of those are relevant major protocol deviations.

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

1. Violations of inclusion criteria 2, 3, and/or 4
2. Early discontinuation defined as discontinuation from study treatment within 72 hours of first dose of study assigned treatment.
3. Received prohibited concomitant medications other than assigned by the randomization while on-treatment
   - Any of the following systemic anti-CMV therapies (except unintentional administration for no longer than 1 day, except cidofovir), if not already administered as investigator anti-CMV treatment of choice:
     - Ganciclovir
     - Valganciclovir
     - Foscarnet
     - Cidofovir
     - Leflunomide

- Artesunate
- Letermovir
- Use of other investigational anti-CMV agent such as CMV specific T-cell transfer (considered investigational)

4. Taking wrong study treatment or receiving no study treatment

4.6 Pharmacokinetic Set

The Pharmacokinetic (PK) Set will consist of all subjects who took any dose of maribavir either as study assigned treatment or as rescue treatment, had plasma sample drawn and tested for maribavir concentrations.

- The adolescent PK Set will consist of all subjects ≥12 to <18 years of age in the PK Set.

4.7 Rescue Set

The Rescue Set will consist of all subjects who entered rescue arm and received any dose of maribavir as rescue therapy.

The Randomized Set and PP Set will be used for efficacy analyses with the Randomized Set as the primary analysis set and the PP Set as the supportive one.

5. SUBJECT DISPOSITION

This section describes subject disposition for both the analysis sets and the study status.

The number of subjects in the following analysis sets will be summarized by treatment group and overall. Percentages will be provided (except the enrolled set) using the Randomized Set as the denominator.

- Enrolled Set
- Randomized Set
- Modified Randomized Set
- Safety Set
- PP Set
- PK Set
- Adolescent PK Set (age ≥12 to <18 years)
- Rescue Set

For subjects randomized to the IAT group, the number and percentage of subjects in each type of treatment will be provided.

For subject study status after receiving the study assigned treatment, the number and percentage of the subjects in the following categories will be presented by treatment group and overall using the Randomized Set.

- Subjects who completed the 8 weeks of study treatment, or discontinued treatment early and by reason
- Subjects who completed 8 visits for the 8-week treatment phase
- Subjects who entered rescue treatment
- Subjects who did not switch to rescue treatment, their study status at the end of study, the number and percentage of subjects who completed the study or prematurely discontinued from the study and by reason.

For subjects who entered rescue treatment phase, the number and percentage of the subjects in the following categories will be provided.

- Subjects who completed rescue treatment or discontinued rescue treatment early and by reason
- Subjects who completed 8 visits for the 8-week rescue treatment phase
- Subjects study status at the end of study, the number and percentage of subjects who completed the study or discontinued early and by reason

A listing of all screen failures (ie, subjects who were screened and enrolled but not randomized) will be presented along with reasons for screen fail and details of any AEs.

In addition, the number of subjects enrolled and randomized will be summarized by region, country and site.

6. PROTOCOL DEVIATIONS

Protocol deviations are identified throughout study and categorized (major/significant or minor/nonsignificant) following the study specific Deviation Rules Document. Protocol deviations related to COVID-19 pandemic will be captured.

A summary of the number and percentage of subjects with any protocol deviations, major and minor, will be produced using the Randomized Set. A summary of the number and percentage of subjects with any COVID-19 related protocol deviations, major and minor, will also be produced using the Randomized Set. All protocol deviation data will be listed by subject using the Randomized Set. Additionally, all protocol deviations related to COVID-19 will be presented by region, country, site and subject.

7. 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 safety and efficacy sections (refer to Section 10 and Section 11).

Demographic and baseline characteristics will be determined using the screening visit or last observation on or prior to the first dose date of study assigned treatment.

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

The following demographic characteristics will be summarized: age, age group (12-17, 18-44, 45-64, and ≥65 years old), sex, ethnicity, race, weight, height, and BMI.

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

- Current transplant type (SOT/HSCT)
  - If SOT, by organ type, and additional characteristics specific to each organ type
  - If HSCT, by
    - Underlying disease,
    - Recurrence of underlying disease (yes, no),
    - Type of HSCT transplant (autologous, allogenic),
      - If allogenic HLA match type,
      - If allogenic haploidentical (yes, no)
    - Stem cell source,
    - Current graft status at baseline,
    - Type of preparative conditioning regimen
- History of previous transplants (yes, no)
  - If yes, transplant type(s) prior to current transplant
  - If HSCT, number of previous HSCT and reason for previous HSCT
- CMV serostatus overall and by transplant type (SOT, HSCT)
- CMV DNA category (high, medium, low) used in randomization from IRT
- CMV DNA category (high, medium, low) based on baseline central laboratory results
- Presence of CMV mutation resistant to ganciclovir/foscarnet/cidofovir per investigator (yes, no)
- Presence of CMV mutation resistant to ganciclovir/foscarnet/cidofovir per central laboratory result (yes, no)
- Is current CMV infection the first episode post-transplant (yes, no)
- Have history of CMV tissue invasive disease (yes, no) and by type
- Category of current CMV infection based on investigator's assessment (CMV Syndrome for SOT subjects only, tissue invasive disease, asymptomatic)

  - Symptoms present for CMV Syndrome
  - Tissue invasive disease type
- Symptomatic CMV infection (CMV tissue invasive disease or CMV syndrome) confirmed by EAC
- Is net immunosuppression use changed prior to start of study treatment, specifically due to current CMV infection (yes, no)
  - If yes, strategies used
- Prior anti-lymphocyte use (yes, no)
- Acute GVHD status at baseline (presence, absence, and grade)
- Chronic GVHD status at baseline (presence, absence, and grade)
- Prior use of CMV prophylaxis (yes, no)
- Hepatic impaired subjects (no impairment and by grade)
- Renal impaired subjects (no, mild, moderate, severe)
- Baseline total WBC from hematology panel (<2.7, ≤2.7 and <7, ≤7 10^9/L)
- Baseline CD4+CD69+, and CD8+CD69+ T cells from immune function assay (<0.5%, ≤0.5% and <2%, ≤2%)

Baseline characteristics treated as continuous variable:

- Days from onset of current CMV infection to first dose of study assigned treatment
- Baseline CMV DNA levels from central laboratory
- The nucleated cell number transplanted, the number of CD34+ cells transplanted for the current HSCT

The hepatic impairment is defined based on the baseline Total Bilirubin to be aligned with CTCAE V4.03 for toxicity grading:

- ≤upper limit of normal (ULN) – No impairment
- >ULN to <1.5x ULN: Grade 1
- ≥1.5x ULN to <3x ULN: Grade 2
- ≥3x ULN: Grade 3 or 4

The renal impairment is defined based on the baseline creatinine clearance per Cockcroft-gault equation:

- No [creatinine clearance >80 mL/minute]
- Mild [creatinine clearance 50-80 mL/minute]
- Moderate [creatinine clearance 30-<50 mL/minute]
- Severe [creatinine clearance <30 mL/minute]

Medical history will be summarized by system organ class by treatment group and overall.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

The extent of exposure and treatment compliance will be summarized using the Safety Set.

8.1 Exposure to Study Assigned Treatment

Exposure data are recorded in both the patient eDiary and the eCRF for study drug administered orally, and CRF only for study drug administered intravenously (IV). The dose adjustment and dose interruption for study drugs are collected on the eCRF.

It is noted that there were reports of eDiary malfunction due to issues such as device or internet connection during the study resulting in some data loss. Exposure to maribavir treatment for the treatment phase will be measured in the following ways:

- Exposure duration will be calculated as the number of days from the date of first dose to the date of the last dose of study treatment plus 1
- Actual exposure days to maribavir will be calculated as the number of days on which at least 1 dose of study drug was taken from the available eDiary data.
- Total number of maribavir doses taken will be calculated as the cumulative number of doses taken as recorded in the eDiary

The above exposure will also be summarized in the set of subjects without any eDiary issue to assess the impact by eDiary.

Exposure to maribavir received as the rescue therapy will also be calculated and summarized separately using the above definition.

For the investigator-assigned anti-CMV treatment group, it is up to the study investigators to choose and prescribe an anti-CMV drug of their choice from the available products utilized for treatment of CMV infection/disease in clinical practice, as endorsed in published guidance documents, institutional guidelines, and other published literature (Kotton et al. 2013; Tomblyn et al. 2009). The IAT group may utilize 1 or 2 of the following 4 anti-CMV agents: (change from ganciclovir to valganciclovir or vice versa will be allowed):

- Ganciclovir
- Valganciclovir
- Foscarnet
- Cidofovir

For a subject receiving 1 or 2 anti–CMV agents at the time of enrollment, the investigator may either change therapy at the time of randomization/treatment initiation or the subject may remain on the same therapy as the investigator assigned anti-CMV agent, if randomized to this study treatment arm. After randomization, changes to the investigator treatment of choice could include: change in dosing or change in dosing regimen, but will not include an addition of or switch to another anti-CMV agent (switching between valganciclovir and ganciclovir is allowed). If the treatment was continued or was started (post-randomization) as 2 anti-CMV

agents, withdrawal of one agent while continuing with the second one will be possible. Combination therapy of cidofovir with foscarnet is prohibited.

Dose and dose regimen of the investigator-assigned anti-CMV treatment will be at the discretion of the investigator following clinical practice. Adjustment of the dose (increase or decrease) could be done for either efficacy or safety, as deemed appropriate by the investigator. Reason for dose adjustment will be recorded in eCRF.

Given the varied dosing intervals for each agent and the possible combination, exposure for these anti-CMV treatments in the treatment phase will be defined as below.

- Exposure duration for ganciclovir, valganciclovir, and foscarnet will be calculated as the number of days from the date of first dose to the date of the last dose of study treatment plus 1; exposure duration for cidofovir as monotherapy will be calculated as the number of days from the date of first dose to the date of the last dose of cidofovir plus 14. If combination treatment is used, the exposure duration will be the longer of the two calculated treatment durations.
- Actual exposure days to study drug will be calculated as the number of days on which any dose of study drug was taken or administered including days during an extended dosing interval (eg, Q48 hour for ganciclovir/valganciclovir, every other week for cidofovir). If combination treatment is used, the actual exposure days to study drug will be the longer of the two calculated treatment durations. The actual exposure days to valganciclovir will be calculated as the number of days on which at least 1 dose of study drug was taken per the eDiary.

Exposure will be summarized by treatment group and IAT type using the Safety Set. Additionally, exposure by study assigned treatment will be provided for the following subgroups.

- Race (white, black or African American, Asian, Others)
- Sex (male, female)
- Age group,
    - ≥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)
- Transplant type (SOT, SCT)
- Presence of CMV mutation associated with resistance to ganciclovir/foscarnet/cidofovir per central laboratory result (yes, no)
- Symptomatic infection (yes, no) as confirmed by EAC
- Renal impaired subjects (no, mild, moderate/severe)
- Hepatic impaired subjects (yes, no)

Exposure to maribavir received as rescue therapy will be summarized separately using the Rescue Set.

8.2 Measurement of Treatment Compliance

The dosing compliance for study-assigned treatment (maribavir or investigator-assigned anti-CMV treatment group) is defined as the number of actual exposure days divided by the exposure duration days multiplied by 100.

The number and percentage of subjects with dose change and type of change as recorded on eCRF will be provided.

The Safety Set will be used for all drug exposure and compliance information, dose change, and type of change will be presented chronologically in data listing, sorted by treatment type (ie, maribavir, ganciclovir, valganciclovir, foscarnet, cidofovir, and each combination type) and subject, and will include the route of administration, date and time of dose administration, and tablet/dose administered as applicable for each treatment type. Drug exposure and compliance information for maribavir as rescue therapy will be summarized and provided in a data listing using the Rescue Set.

9. PRIOR AND CONCOMITANT MEDICATION AND PROCEDURE

9.1 Prior and Concomitant Medication

The version of World Health Organization (WHO) Drug Dictionary dated September 2013 or in effect at the time of analysis will be used to classify prior and concomitant medications by Anatomical Therapeutic Chemical (ATC) class and preferred term.

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

Concomitant medication during the on-treatment period 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 on or after the study treatment initiation and before the end of the on-treatment period. The on-treatment observation period starts at the time of study treatment initiation through 7 days after the last dose of study treatment or through 21 days after the last dose of cidofovir. For subjects who transfer from the study treatment to either maribavir rescue or to a nonstudy anti-CMV treatment, the on-treatment observation period starts at the time of the study treatment initiation until the maribavir rescue treatment initiation or until the nonstudy anti-CMV treatment initiation, whichever is earlier.

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

Concomitant medication during the on-rescue treatment period, and post-rescue treatment period will be defined similarly.

Any technical details related to computation, dates, imputation for missing dates are described in Section 18.6.

Prior and concomitant medication usage will be summarized by the number and percentage of subjects receiving each medication by ATC Level III and preferred term by treatment group and overall 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. Post-treatment anti-CMV medication usage will be summarized by treatment group and IAT type (valganciclovir/ganciclovir, foscarnet) using the Safety Set.

Additionally, concomitant medications in the following specific categories will be summarized by treatment group and overall using the Safety Set.

- Growth factor use
- Blood product use

Similarly, the above summary of concomitant medications will be repeated for the on-rescue treatment and post-rescue treatment period using the Rescue Set.

All prior, concomitant, post-treatment medication, concomitant medication to rescue treatment, and post rescue treatment medications will be provided in by-subject data listing.

9.2 Prior and Concomitant Procedure

A study concomitant procedure is any therapeutic and diagnostic intervention (eg, 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 therapeutic and diagnostic intervention with the start date prior to the date of the first dose of study treatment.

Concomitant procedure during the on-treatment period, post-treatment procedure in the follow-up period will be defined similarly as that of the concomitant medications or post-treatment medications respectively.

Concomitant procedure during the on-rescue treatment period, and post-rescue treatment procedures will be defined similarly.

All prior, concomitant, post-treatment procedures, concomitant procedure to rescue treatment, and post rescue treatment procedure will be provided in by-subject data listings.

10. EFFICACY ANALYSES

Unless specifically noted otherwise, all statistical tests and confidence intervals will be two-sided at α=0.05. It is noted that the phrase "statistically significant" will be applied to only analyses of the primary and key secondary efficacy endpoints with adjustment for multiplicity (see Section 2.6).

Summary descriptive statistics will include the number of subjects (N), mean, standard deviation, median, minimum and maximum (range) values for continuous variables, and number and percentages for categorical variables. The denominator for the percentages will be based on the number of subjects in the analysis set unless otherwise specified. Time-to-event endpoints will be summarized using Kaplan-Meier estimation and ninety-five percent (95%) confidence intervals will be presented for the estimated 25%, 50%, and 75% times estimates.

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

Unless otherwise specified, all efficacy analyses will be based on results from central laboratory; for tissue invasive disease symptoms evaluation, the adjudicated results by EAC will be used for the efficacy analysis.

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 (refer Section 18.3). The strata level based on the central laboratory baseline plasma CMV DNA concentration for the efficacy analysis are defined as:

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

It is noted that low CMV DNA group includes subjects with baseline central laboratory (Day 0) CMV DNA <910 IU/mL. This is to account for all subjects enrolled on study after meeting eligibility criteria per the investigator and taking into consideration viral load fluctuation, differences in sampling time, specimen type, and testing methods. Baseline plasma CMV DNA concentration based the central laboratory may differ from the CMV DNA concentration used in eligibility and randomization, which required subjects to have a documented CMV infection in whole blood or plasma, with a screening value of ≥2730 IU/mL in whole blood or ≥910 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory qPCR or comparable quantitative CMV DNA test within 14 days prior to randomization and the second sample within 5 days from the same laboratory and same sample type.

Confirmed CMV viremia clearance: defined as plasma CMV DNA concentration below the lower limit of quantification (<LLOQ; ie, <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.

Recurrence of the Symptomatic CMV infection: defined as the presence of signs or symptoms of the tissue invasive CMV disease or CMV syndrome (same or new symptomatology) confirmed as per Ljungman et al. (2017), after the period of resolution of the symptomatic infection in subjects symptomatic at baseline.

Subjects in the investigator-assigned treatment arm who are unable to continue taking investigator-assigned anti-CMV treatment due to the inadequate anti-viral activity and/or intolerance to the assigned treatment (as evaluated starting at Visit 5/Week 3) may be evaluated for entry into a maribavir rescue arm. The data collected post- maribavir rescue initiation, will be included in separate secondary analyses for efficacy and exploratory analysis for PK. Summary of all safety analyses will be provided separately for the maribavir rescue arm.

All efficacy measurements assessed after the initiation of rescue therapy or alternative anti-CMV treatment will be excluded from the primary study assigned treatment efficacy analysis unless otherwise specified. Efficacy after the initiation of rescue therapy will be summarized separately as specified. Efficacy measurements after the initiation of rescue therapy or alternative anti-CMV treatment will be indicated in listings.

Unless otherwise specified, for analysis purposes, the study week (Week 0 through Week 20) for all efficacy measurements on-treatment phase and follow-up phase will be determined based on the clinical visits. Efficacy measurements (Schedule of Assessment 1, Table 1, and Schedule of Assessment 2, Table 2, Section 7.2.2 of Protocol), assessed during the treatment phase and follow-up phase before receiving alternative anti-CMV treatment or rescue treatment, are included in the efficacy analysis to assess effect of the study-assigned treatment unless otherwise specified. If variation from the scheduled days of assessment, unscheduled visit, or early withdrawal from the treatment or study is found, a 4-day time window will be used for weekly assessment, and a 7-day time window will be used for biweekly assessment with the caveat that one measurement is counted only once for one week, and assessment done on or before the first dose of study treatment is considered for baseline determination. If two measurements are in the same week, the measurement closest to the scheduled visit from study start will be used for the summary.

10.1 Primary Efficacy Endpoint and Analysis

10.1.1 Primary Efficacy Endpoint

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.

Confirmed CMV viremia clearance at the end of Study Week 8 (Visit 10) is defined as plasma CMV DNA concentrations <LLOQ (ie, <137 IU/mL), when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test at a central specialty laboratory, in 2 consecutive postbaseline samples separated by at least 5 days, regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy (see Table 3).

Table 3 Assessments of Virological Responders at Study Week 8

Scenario	CMV DNA Weeks on Study					
	Week 6	**Week 7**	**Week 8**	**Week 9***	**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, otherwise nonresponder
5	-	NA	-	+/-/NA	Yes	2 consecutive '-' as shown by available data and both '-' at Week 6 and Week 8 for missing Week 7, otherwise nonresponder
6	-	NA	NA	-	Yes	2 consecutive '-' as shown by available data at Week 6 and Week 9 and both '-', otherwise nonresponder

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

*Week 9 data only to be used if Week 8 data are unavailable or missing.

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

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

"-" = CMV DNA concentration <LLOQ (<137 IU/mL)

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

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

Plasma CMV DNA assessments after starting alternative anti-CMV treatment or rescue treatment are not evaluable for the assessment of study assigned treatment effect. The CMV DNA assessment on the same date as the alternative anti-CMV treatment will be included in the evaluation as the procedure is to be done prior to the start of alternative anti-CMV treatment. Subjects who discontinue study assigned treatment early are to complete the treatment phase

assessment as described in Section 4.5 of the Protocol. The response categorization based on the available data is summarized in Table 4.

Table 4 Summary of Response Categorization for Primary Endpoint

Data at Week 7 and Week 8	Responder
Available, or missing but can be imputed using adjacent week/s data	Yes/no based on 2 consecutive samples separated by at least 5 days at Week 8 (See Table 3)
Not evaluable/missing due to rescue or alternative anti-CMV treatment	No
Missing but achieved confirmed viremia clearance at time of early discontinuation	No
Missing without achieving confirmed viremia clearance at time of early discontinuation	No

Table 5 Estimand for Primary Efficacy Endpoint

Attributes	Planned
Population	Transplant recipients (HSCT or SOT) with a current CMV infection that is refractory or resistant to treatment with currently available anti-CMV therapies (ie, ganciclovir, valganciclovir, foscarnet, or cidofovir).
Variable (or endpoint)	Proportion of responders, defined as subjects with confirmed CMV viremia clearance at Study Week 8 regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy, and without alternative anti-CMV treatment
Strategy for addressing intercurrent events	Composite strategy is used. The following intercurrent events are considered: 1. If a subject takes alternative anti-CMV treatment or maribavir as rescue treatment before Study Week 8, assume non-response 2. If a subject had missing data due to early discontinuation to confirm viremia clearance at Study Week 8, assume non-response
Population-level summary	Difference in proportion of responders at Study Week 8 between maribavir and IAT treatment groups

10.1.2 Analysis of Primary Efficacy Endpoint

The null hypothesis and alternative hypothesis for the primary endpoint (H1) to be tested are:

$$H1_{0:}\ P1_T - P1_C = 0$$

vs

$$H1_{1:}\ P1_T - P1_C \neq 0$$

$P1_T$: proportion of responder in maribavir treatment group who achieve confirmed viremia clearance at end of Study Week 8
$P1_C$: proportion of responder in IAT group who achieve confirmed viremia clearance at end of Study Week 8

The proportion of responders (ie, subjects with confirmed CMV viremia clearance 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) will be calculated for each treatment group. The difference in proportion of responders between treatment groups will be obtained using Cochran-Mantel-Haenszel (CMH) weighted average across all strata (see Section 10 for strata definitions), and tested using CMH method, with transplant type and baseline plasma CMV DNA concentration as two stratification factors. The 95% confidence limits of the weighted average of difference across strata will be provided using the normal approximation. If the minimum number of subjects in a response category in a treatment group, for example, in the high viral load group, is less than 5, the high and intermediate viral load groups will be collapsed into 1 stratum level.

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 and the adjusted difference and 95% CI in proportion of responders between treatment groups will be obtained and tested using minimum risk weight method of Mehrotra and Railkar (2000) instead of the CMH method, stratifying by transplant type and baseline plasma CMV DNA concentration. If the p-value from the test of adjusted difference in proportion of responders between treatment groups is ≤0.05 and the adjusted proportion of responders from maribavir is higher, it will be concluded that maribavir is more efficacious compared to the control group. Unadjusted difference in proportion of responders between treatment groups and the 95% confidence limits using the normal approximation will be provided.

The analysis of the primary efficacy endpoint will be conducted using Randomized Set as the primary and PP Set as supportive according to the randomized treatment per intent-to-treat principle. The analysis will also be repeated using the Modified Randomized Set as supportive. If there are subjects who were randomized but did not receive any dose of study assigned treatment, the analysis will be conducted according to the randomized treatment.

The time to failure to achieve the primary endpoint of response at Study Week 8 due to missing CMV measurements, receipt of rescue medication, or receipt of alternative anti-CMV treatment will be presented using descriptive statistics. In addition, the number and percentage of subjects who failed the primary endpoint will be presented by reason (eg, received rescue or alternative anti-CMV treatment, early discontinuation and primary reason of study discontinuation).

10.1.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

The following sensitivity and supplementary analysis for the primary efficacy endpoint will be conducted using the Randomized Set.

1. Subjects who discontinue study treatment early without CMV DNA measurement available for evaluation of effect at Week 8, but who meet the criteria of confirmed CMV viremia clearance at the time of discontinuation (defined as 2 consecutive post baseline assessments of CMV DNA target <LLOQ, separated by at least 5 days) will be included as responders (see Table 6). The analysis of this response will be conducted following the same method as described for the primary endpoint of response at Study Week 8.

Table 6 Response Categorization in Sensitivity Analysis for Primary Endpoint

Data at Week 7 and Week 8	Responder
Available, or missing but can be imputed using adjacent week/s data	Yes/no based on 2 consecutive samples separated by at least 5 days at Week 8 (See Table 3)
Not evaluable/missing due to rescue or alternative anti-CMV treatment	No
Missing but achieved confirmed viremia clearance at time of early discontinuation	Yes
Missing without achieving confirmed viremia clearance at time of early discontinuation	No

2. The primary endpoint of response will also be analyzed using multivariable logistic regression model to control for baseline stratification factors and other important baseline characteristics. The list of baseline characteristics to be considered will include but will not be limited to:

   - Transplant type (HSCT, SOT)
   - CMV DNA level (high, intermediate, low)
   - Presence of CMV mutation associated with resistance to ganciclovir/foscarnet/cidofovir per central laboratory result (yes, no)
   - CMV serostatus (D+R-, D+R+ or D-R+, D-R-)
   - Prior Anti-lymphocyte use (yes, no)
   - Immune function status as measured by baseline total WBC from hematology panel, CD4+CD69+, and CD8+CD69+ T cells from immune function assay if sample size is sufficient
   - Enrolling Region (North America, Europe, Asia)
   - Prior use of CMV prophylaxis (yes, no).

Below model selection approach will be followed:

a) Fit a logistic model including treatment, transplant type, CMV DNA level, and each baseline characteristic covariate, and interaction terms between baseline covariate and treatment, baseline covariate and transplant type, baseline covariate and CMV DNA level. Baseline covariates or covariates with interaction term significant at 0.25 level will be identified. Summary of such univariate analysis for each covariate will be provided.
b) Fit a multivariable logistic model including the baseline covariates and the identified interaction terms from step 1 using the backward selection to eliminate non-significant variables at level of 0.05. Check for change of coefficients ($\Delta\beta$), if it is more than 20%, the deleted variables will be added back to the model one at a time for examination of biological meaning, and the model is iteratively reduced using the backward selection. The final model will include the variable/s statistically significant at level of 0.05 (Categorical Data Analysis, Alan Agresti, 2013). The fit of the final model will be assessed including goodness of fit and regression diagnostics. If any baseline variable's interaction term is significant, then this baseline variable is also included in the model, regardless of its p-value. Treatment, transplant type, and CMV DNA level will be fixed in the model selection.
c) Provide parameter estimates from the final model.

3. The analysis of the primary efficacy endpoint will be repeated using the CMV DNA level and transplant type used for randomization rather than CMV DNA level from the central laboratory results and transplant type as the stratification factors in the analysis. This is to evaluate the impact to the primary analysis of treatment effect due to the difference in strata data used in randomization and analysis.
4. The analysis of the primary efficacy endpoint will be repeated by excluding subjects who discontinue early from the analysis set. The following definitions of early discontinuation are defined to explore the impact of early discontinuation to the primary efficacy analysis: discontinue study early regardless of reason within 72 hours, and 7, 14, 21, and 28 days of starting the study-assigned treatment. This is to evaluate the impact of early discontinuation on the primary analysis of treatment effect.
5. Response within 8 weeks of study is defined as subjects who met the criteria of confirmed CMV viremia clearance defined as 2 consecutive postbaseline assessments of CMV DNA target <LLOQ, separated by at least 5 days any time in treatment phase. The analysis of this response within Study Week 8 will be conducted following the same method as described for the primary endpoint of response at Study Week 8. This is to evaluate the treatment effect based on the ability to achieve viremia clearance.
6. Response at Study Week 8 in the subset of subjects who received 8 weeks of study-assigned treatment will be conducted following the same method as described in the primary analysis. This is to evaluate the treatment effect as measured by response at Week 8 for those who were able to receive 8 weeks of treatment.
7. Response (defined as 2 consecutive postbaseline assessments of CMV DNA target <LLOQ, separated by at least 5 days) at end of Study Week 8 regardless of the use of alternative anti-CMV treatment for the IAT treatment group will be conducted following the same

method as described for the primary endpoint of response at Study Week 8. This is to assess the efficacy without the potential confounding of dose limiting toxicity for the IAT group.

8. To evaluate the impact of the difference in the CMV DNA used for enrollment (based on either central or local laboratory assay, plasma or whole blood sample in the screening period) and the baseline CMV DNA from the central laboratory prior to receiving the first dose of study assigned treatment, the following analyses will be conducted.

    a. Repeat the analysis of the primary efficacy endpoint in the set of subjects who had baseline CMV DNA from the central laboratory >LLOQ.

    b. Repeat the analysis of the primary efficacy endpoint in the set of subjects who had baseline CMV DNA from the central laboratory ≥910 IU/mL.

9. To assess the impact of COVID-19 pandemic, the primary endpoint definition in Table 3 will be followed except for missing data due to the COVID-19 pandemic. 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. The primary endpoint definition in Table 3 has considered missed visit (2 or less) scenarios around Week 8. With COVID-19 pandemic, 3 or more consecutive weeks of missed visits around Week 8 may occur. For such scenario, available CMV DNA level at Week 5 and/or 10 data will be included to assess the response at Week 8 following Table 3.
   Subjects with missing data post-baseline to confirm response at Week 8 due to COVID-19, will have the missing CMV DNA level imputed using the multiple imputation (MI) with the Markov chain Monte Carlo (MCMC) method. The imputation seed will be 1812 and the number of impute time will be 5. CMV DNA results reported as "Not detected or <LLOQ" will be imputed as half of the LLOQ value (ie, 137/2=68.5), and the log10 transformation will be applied to CMV DNA levels in the calculation.
   Once missing data are filled in, response at Study Week 8 will be assigned following Table 3. The imputed data sets will be analyzed using the CMH test for the adjusted difference in proportion of response controlling for two stratification factors, transplant type and baseline plasma CMV DNA level as in the primary analysis.
   This sensitivity analysis will be conducted only if there are ≥5% of subjects with missing data to confirm response at Week 8 due to COVID-19.

Table 7 Response Categorization in COVID-19 Impact Sensitivity Analysis for Primary Endpoint Using Multiple Imputation

Data at Week 7 and Week 8	Responder
Available, or missing but can be imputed using adjacent week/s data	Yes/no based on 2 consecutive samples separated by at least 5 days at Week 8 (See Table 3)
Not evaluable/missing due to rescue or alternative anti-CMV treatment	No

Table 7 Response Categorization in COVID-19 Impact Sensitivity Analysis for Primary Endpoint Using Multiple Imputation

Data at Week 7 and Week 8	Responder
Missing but can be assessed using available Week 10 or Week 5 data due to COVID-19 pandemic	Yes/no based on 2 consecutive samples separated by at least 5 days including data from Week 5 and Week 10 to account for missed visits due to COVID-19 pandemic
Missing without data to confirm response at Week 8 unrelated to COVID-19 pandemic	No
Missing without data to confirm response at Week 8 related to COVID-19	Yes/no based on CMV DNA levels from multiple imputation

10. To assess the impact of COVID-19 pandemic, additional sensitivity analysis for the primary endpoint using worst case scenario will be conducted. The primary endpoint definition in Table 3 will be followed except for missing data due to the COVID-19 pandemic. 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. The primary endpoint definition in Table 3 has considered missed visit (2 or less) scenarios around Week 8. With COVID-19 pandemic, 3 or more consecutive weeks of missed visits around Week 8 may occur. For such scenario, available CMV DNA level at Week 5 and/or 10 data will be included to assess the response at Week 8 following Table 3. Subjects with missing data to confirm response at Week 8 due to COVID-19, will have response assigned as non-responder if a subject was receiving maribavir and responder if a subject was receiving IAT as the study assigned treatment (see Table 8). The analysis of this response assignment will be conducted following the same method as described for the primary efficacy endpoint.

Table 8 Response Categorization in COVID-19 Impact Sensitivity Analysis Using Worst Case for Primary Endpoint

Data at Week 7 and Week 8	Responder
Available, or missing but can be imputed using adjacent week/s data	Yes/no based on 2 consecutive samples separated by at least 5 days at Week 8 (See Table 3)
Not evaluable/missing due to rescue or alternative anti-CMV treatment	No
Missing but can be assessed using available Week 10 or Week 5 data due to COVID-19 pandemic	Yes/no based on 2 consecutive samples separated by at least 5 days including data from Week 5 and Week 10 to account for missed visits due to COVID-19 pandemic

Table 8 Response Categorization in COVID-19 Impact Sensitivity Analysis Using Worst Case for Primary Endpoint

Data at Week 7 and Week 8	Responder
Missing without data to confirm response at Week 8 unrelated to COVID-19 pandemic	No
Missing without data to confirm response at Week 8 related to COVID-19 pandemic	Yes for subjects in the IAT group, no for subjects in the maribavir group

10.1.4 Subgroup Analyses of the Primary Efficacy Endpoint

The proportion of responders at Study Week 8 and the corresponding 95% CI will be summarized by treatment group for the following subgroups. Subgroups may be collapsed to have adequate sample size except for age group. The difference in proportion of responders between treatment groups and the 95% confidence limits will be calculated using methods similar to the primary efficacy analysis, stratifying for any factors used in the primary analysis that remain applicable. Subgroup analysis results will be summarized in a forest plot. The subgroup analyses for the primary efficacy endpoint will include the following:

- Transplant type (SOT, HSCT, and kidney transplant)
- CMV DNA viral load (high, intermediate, low)
- Symptom status (symptomatic or asymptomatic) at baseline as adjudicated by EAC
- Presence of CMV mutation resistant to ganciclovir/foscarnet/cidofovir per central laboratory result (yes, no)
- Age group
  - ≥18 to <45 years of age
  - ≥45 to <65 years of age
  - ≥65 years of age
- Enrolling regions (North America, Europe, Asia)
- Gender (male, female)
- Prior Anti-lymphocyte use (yes, no)
- Maribavir versus individual IAT type if sample size is adequate

10.2 Key Secondary Efficacy Endpoint and Analysis

10.2.1 Key Secondary Efficacy Endpoint

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

- Achievement of CMV viremia clearance and resolution or improvement of tissue-invasive CMV disease or CMV syndrome for subjects symptomatic at baseline or achievement of clearance of viremia and no symptoms of tissue invasive CMV disease or CMV syndrome for subjects asymptomatic at baseline at the end of Study Week 8, followed by maintenance of this treatment effect for an additional 8 weeks off treatment (ie, 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. CMV infection symptom control include:

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

The investigator will perform the initial diagnosis of tissue-invasive CMV disease or CMV syndrome for the symptomatic subjects at baseline and new occurrence of tissue invasive CMV disease or CMV syndrome for the asymptomatic subjects at baseline through the study, and will continue with the assessment of the infection status (ie, no change, improvement, worsening, or resolution) at subsequent visits throughout the study. All investigator-assessed cases of tissue invasive CMV disease or CMV syndrome will be reviewed and adjudicated by an independent EAC both for the confirmation of the diagnosis at baseline and new symptomatic CMV infection and for the outcome (ie, no change, improvement, worsening, or resolution). EAC adjudicated cases will be used for the efficacy analyses.

Criteria for defining the key secondary efficacy endpoint are:

- First being a responder 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 or CMV syndrome status (ie, resolution or improvement of tissue invasive CMV disease or CMV syndrome for subjects symptomatic at baseline or no symptoms of tissue invasive CMV disease or CMV syndrome for subjects asymptomatic at baseline).

  AND

- Maintenance of this treatment effect (both CMV viremia clearance and tissue-invasive disease or CMV syndrome 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 9).

Table 9 Assessments of Responders for Key Secondary Endpoint

Response (both virological response and symptomatic CMV infection control) at Study Week 8	CMV DNA Assessment Week							Key secondary endpoint responder*	Rationale
	9	10	11	12	14	16	18[1]		
Yes	+/-	+/-	+/-	+/-	+/-	+/-	+/-/NA	No	Any 2 consecutive "+" during FU by Week 16
Yes	+/-	+/-	+/-	+/-	+/-	-	+/-/NA	Yes	Week 16 is "- "and no 2 consecutive "+"during FU
Yes	+/-	+/-	+/-	+/-	+/-	+	+/-/NA	No	Week 16 is '+' and Week 18 is "+" or "NA", criteria of 2 consecutive "+" not met
Yes	+/-	+/-	+/-	+/-	+/-	+	-	Yes	Week 16 is '+' and 2 consecutive "+" criteria is not met based on Week 18 data
Yes	+/-	+/-	+	-	-	NA	-	Yes	Week 16 is missing, 2 consecutive '+' criteria not met based on Week 14 and 18 data
Yes	+/-	+/-	+	-	-	NA	+/NA	No	Week 16 is missing, 2 consecutive '+' criteria may be met based on available Week 18 data
Yes	+/-/NA	+/-/NA	+/-/NA	+/-/NA	NA	NA	+/-/NA	No	Lack of data to show maintaining effect through Week 16
No								No	

[1]Week 18 data will be used toto confirm not having CMV viremia recurrence through Week 16 if Week 16 data is not available.

*Must also meet the criterion of CMV infection symptom control to be a responder.

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

"-" = CMV DNA concentration <LLOQ (<137 IU/mL)

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

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

Only CMV viremia data on or prior to date of receiving nonstudy CMV treatment or rescue treatment will be included in the assessment.

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. Responder categorization for maintenance through Week 16 is also summarized in Table 10 below.

Table 10 Summary of Response Categorization for Key Secondary Endpoint

Data at Week 16	Key secondary endpoint responder*
Available, or missing but adjacent data are available	Yes/no based on no 2 consecutive "+"during FU (see Table 9)
Not evaluable or missing due to rescue or alternative anti-CMV treatment	No
Missing with or without CMV viremia clearance maintained at time of discontinuation	No

*Must first be a responder at the end of Study Week 8 with viremia clearance and symptom control, and also meet the criterion of CMV infection symptom control to be a responder.

Table 11 Estimand for Key Secondary Efficacy Endpoint

Attributes	Planned
Population	Transplant recipients (HSCT or SOT) with a current CMV infection that is refractory or resistant to treatment with currently available anti-CMV therapies (ie, ganciclovir, valganciclovir, foscarnet, or cidofovir)
Variable (or endpoint)	Proportion of responders, defined as subjects who achieved confirmed viremia clearance achieved and CMV infection symptom control at Study Week 8 regardless of whether study-assigned-treatment was discontinued before the stipulated 8-weeks of treatment and maintain through Study Week 16 and no alternative anti-CMV treatment
Strategy for addressing intercurrent events	Composite strategy is used. The following intercurrent events are considered: 1. If a subject takes alternative anti-CMV treatment or maribavir as rescue treatment before Study Week 16, assume non-response 2. If a subject discontinues study early 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
Population-level summary	Difference in proportion of responders for the key secondary endpoint between SHP620 and IAT treatment groups

10.2.2 Analysis of the Key Secondary Efficacy Endpoint

The null and alternative hypothesis for the key secondary endpoint (H2) to be tested:

$$H2_0: P2_T - P2_C = 0$$

vs

$$H2_1: P2_T - P2_C \neq 0$$

$P2_T$: proportion of responders, ie, subjects with confirmed viremia clearance and symptom control at end of Study Week 8 and maintain it through Week 16 in maribavir group

$P2_C$: proportion of responders, ie, subjects with confirmed viremia clearance and symptom control at end of Study Week 8 and maintain it through Week 16 in IAT group

The proportion of responders for the key secondary endpoint will be calculated for each treatment group. The difference in proportion of responders between treatment groups will be obtained and tested using the same method as described for the primary efficacy endpoint. The EAC's adjudicated tissue-invasive disease or CMV syndrome symptoms and outcome will be used for the analysis.

The hypothesis-testing of the primary and key secondary endpoint will be adjusted for multiple comparisons using a fixed-sequence testing procedure to control the family-wise Type 1 error rate at 5% level (see Section 2.6).

If the proportion of responders for the primary efficacy endpoint is higher in the maribavir group and the test of adjusted difference in proportion of responders between treatment groups is statistically significant, and the proportion of response for the key secondary efficacy endpoint is higher in maribavir group and the test is significant at 0.05 level, it will be concluded that the treatment effect is more durable for maribavir as compared to the control group.

The analysis of the key efficacy endpoint will be conducted using the Randomized Set as the primary and PP Set as supportive. The analysis will be repeated using the Modified Randomized Set as supportive if there are randomized subjects who did not receive any dose of study assigned treatment; subjects will be analyzed according to the randomized treatment.

10.2.3 Sensitivity and Supplementary Analyses of the Key Secondary Efficacy Endpoint

1. Subjects who discontinue study early without CMV DNA measurement available for evaluation of study drug effect at Week 16, however, they meet the criteria of confirmed CMV viremia clearance defined as 2 consecutive post baseline assessments of CMV DNA target <LLOQ, separated by at least 5 days, at the time of discontinuation, and meet the criterion of CMV symptom control will be included as responders for the key secondary endpoint (see Table 12). The analysis of this response will be conducted following the same method as described for the key secondary endpoint of response at Study Week 16.

Table 12 Response Categorization in Sensitivity Analysis for Key Secondary Endpoint

CMV DNA Data at Week 16	Key secondary endpoint responder*
Available, or missing but adjacent are available	Yes/no based on no 2 consecutive "+"during FU (see Table 9)
Not evaluable or missing due to rescue or alternative anti-CMV treatment	No
Missing with CMV viremia clearance maintained at time of discontinuation	Yes
Missing without CMV viremia clearance maintained at time of discontinuation	No

*Must first be a responder at the end of Study Week 8 with viremia clearance and symptom control, and also meet the criterion of CMV infection symptom control to be a responder.

2. The analysis of the key secondary efficacy endpoint will be repeated by using the CMV DNA level and transplant type used for randomization rather than the CMV DNA level based on central laboratory values and transplant type as the stratification factors in the analysis.
3. The treatment effect between treatment groups for the key secondary efficacy endpoint will be estimated using multivariable logistic regression method after controlling for important baseline characteristics. The list of baseline characteristics to be considered and the model selection steps will follow the sensitivity analysis described above for the primary efficacy endpoint.
4. 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.
5. 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 maintain such effect through Study Week 16, regardless the use of alternative anti-CMV treatment for the IAT treatment group. The proportion of alternative response at Study Week 16 will be analyzed following the same method as described above for the key secondary endpoint. This is to evaluate the treatment effect at Week 16 without the potential confounding of dose limiting toxicity for the IAT group.
6. To evaluate the impact of the difference in the CMV DNA used for enrollment (based on either central or local laboratory assay, plasma or whole blood sample in the screening period) and the baseline from the central laboratory prior to receiving the first dose of study assigned treatment, the following analyses will be conducted.
    a. Repeat the analysis of the key secondary efficacy endpoint in the set of subjects who had baseline CMV DNA from the central laboratory >LLOQ.
    b. Repeat the analysis of the key secondary efficacy endpoint in the set of subjects who had baseline CMV DNA from the central laboratory ≥910 IU/mL.
7. To assess the impact of COVID-19 pandemic, the key secondary endpoint definition in Table 9 will be followed except for missing data due to the COVID-19 pandemic. If there are ≥5% of subjects with missing data due to COVID-19 to confirm maintenance effect through

Week 16, the missing CMV DNA levels will be imputed using the MI method, and the CMV infection control adjudicated by EAC prior to study discontinuation will be assumed for Week 16 and the maintenance effect through Week 16 will be assigned as in Table 13. The analysis will follow the same method as the primary efficacy endpoint as described in Section 10.1.3.

Table 13 Response Categorization in COVID-19 Impact Sensitivity Analysis for Key Secondary Endpoint Using Multiple Imputation

CMV DNA Data at Week 16	Key secondary endpoint responder*
Available, or missing but adjacent are available	Yes/no based on no 2 consecutive "+" during FU (see Table 9)
Not evaluable or missing due to rescue or alternative anti-CMV treatment	No
Had minimum two available CMV DNA data from Week 9 through Week 16 including Week 16	Yes/No
Missing without data to confirm response at Week 16 unrelated to COVID-19 pandemic	No
Missing without data to confirm response at Week 16 related to COVID-19 pandemic	Yes/no based on CMV DNA levels from multiple imputation

*Must first be a responder at the end of Study Week 8 with viremia clearance and symptom control, and also meet the criterion of CMV infection symptom control to be a responder.

Summary of EAC's assessment of symptomatic CMV infection (tissue-invasive disease or CMV syndrome symptoms) will be provided.

10.2.4 Subgroup Analyses

The proportion of responder and the corresponding 95% CI for the key secondary efficacy endpoint will be summarized by treatment group for the following subgroups. Subgroups may be collapsed to have adequate sample size. 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.

- Transplant type (SOT, HSCT, and kidney transplant)
- CMV DNA viral load (high, intermediate, low)
- Symptom status (symptomatic or asymptomatic) at baseline as adjudicated by EAC
- Presence of CMV mutation resistant to ganciclovir/foscarnet/cidofovir per central laboratory result (yes, no)
- Age group

- ≥18 to <45 years of age
- ≥45 to <65 years of age
- ≥65 years of age

- Enrolling regions (North America, Europe and Asia)
- Gender (male, female)
- Prior Anti-lymphocyte use (yes, no)
- Maribavir versus individual IAT type if sample size is adequate

10.3 Other Secondary Efficacy Endpoints and Analysis

The analysis of the secondary efficacy endpoints will be conducted using the Randomized Set and PP Set unless otherwise specified. Secondary efficacy endpoints will be summarized by treatment arm, and, if indicated, analyzed statistically at α=0.05 (2-sided), without adjustment for multiple comparisons.

10.3.1 The Achievement of the Confirmed CMV Viremia Clearance After 8 Weeks of Receiving Study-Assigned Treatment

Subjects who achieved confirmed CMV viremia clearance after receiving 8 weeks study-assigned treatment at Week 8, 12, 16, 20 will be classified as responders (a binary response) for the respective timepoint.

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.

10.3.2 The Achievement of the Confirmed CMV Viremia Clearance and CMV Infection Symptom Control After Receiving 8 Weeks of Study-Assigned Treatment and Maintaining the Effect Over Time

The achievement of the confirmed CMV viremia clearance and CMV infection symptom control at Week 8, and maintained through Week 12, 16, and 20 after receiving 8 weeks of study-assigned treatment will be determined as below.

A subject is counted as a responder (a binary response) 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 CMV infection symptom control
    - resolution or improvement of tissue invasive CMV disease or CMV syndrome for subjects symptomatic at baseline,
    - or maintaining no symptoms of tissue invasive CMV disease or CMV syndrome for subjects asymptomatic at baseline
- and received 8 weeks of study-assigned treatment

At Week 12, 16, and 20, a subject is counted as a responder if the effect of viremia clearance and CMV infection symptom control achieved after 8 weeks of study treatment is maintained.

The analysis of achievement of the confirmed CMV viremia clearance and CMV infection symptom control at Study Week 8, 12, 16, 20 after receiving 8 weeks of study-assigned treatment will be conducted following the same method as described for the primary endpoint.

10.3.3 The Maintenance of the CMV Viremia Clearance and CMV Infection Symptom Control Achieved at the End of Study Week 8 Through Weeks 12 And 20

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.

10.3.4 The Recurrence of CMV Viremia

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. Although the recurrence of CMV viremia prior to Week 8 may simply

represent fluctuations in the viral load during the course of treatment, it will be analyzed as well as the more clinically meaningful recurrence of CMV viremia after Week 8.

- 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

Additionally, the above recurrence rates will be calculated in the subset of subjects who received 8 weeks of study-assigned treatment.

10.3.5 The Recurrence of CMV Viremia During and Off-Study-Assigned 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
    - While off study-assigned treatment

10.3.6 The Maribavir CMV Resistance Profile

Analysis of maribavir CMV resistance will be included in the separate Resistance Analysis Plan.

10.3.7 All-Cause Mortality

All-cause mortality by the end of study regardless of the use of rescue treatment or alternative anti-CMV treatment will be analyzed. The time to all-cause mortality by the end of the study participation in days will be calculated as stop date (event date of death due to any cause or censored date at the last contact) – randomization date +1. The time to all-cause mortality on study in days will be summarized descriptively (minimum, median, and maximum) for all-cause mortalities and using the Kaplan-Meier (KM) method, and compared using the log-rank test. Treatment difference (hazard ratio, and its 95% CI) between maribavir and IAT treatment groups will be estimated using the stratified Cox's regression model with transplant type and baseline plasma CMV DNA level as two stratification factors.

Additionally, the analysis will be repeated for all-cause mortality on study after receiving study assigned treatments before rescue or alternative anti-CMV treatment. All-cause mortality on study after receiving study assigned treatments before rescue or alternative anti-CMV treatment in days will be calculated as stop date (date of death due to any cause before rescue or alternative anti-CMV treatment or censored date at the start of rescue treatment or alternative anti-CMV treatment or last contact, whichever is earlier) – randomization date +1.

The mortality status for all subjects will be provided in a data listing.

10.3.8 Assessment of Efficacy for Maribavir Rescue Arm

The assessment of efficacy for maribavir rescue arm will be conducted using the rescue arm analysis set.

10.3.8.1 The Confirmed Clearance of Plasma CMV DNA at the End of 8 Weeks of Maribavir Rescue Treatment Phase

The number and percentage and the corresponding 95% CI of subjects who achieved the CMV viremia clearance (a binary response) at the end of 8 weeks of maribavir rescue treatment phase will be calculated, regardless of whether the rescue treatment was discontinued before the end of the stipulated 8 weeks of therapy.

10.3.8.2 The Achievement of Viremia Clearance and Disease Control for Maribavir Rescue Treatment

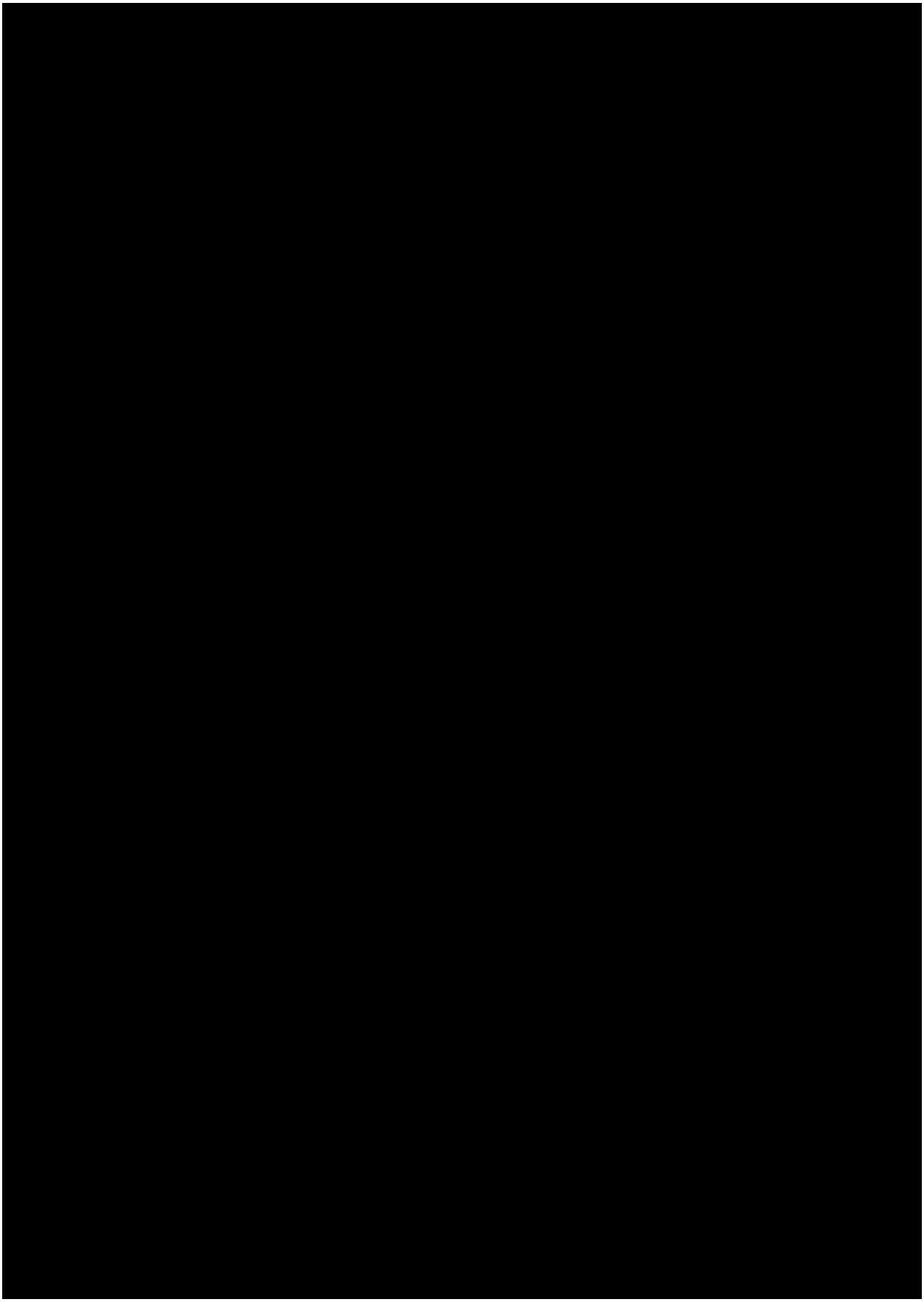
Subjects who achieved viremia clearance and CMV infection symptom control at Study Week 8 after starting the maribavir rescue treatment and followed by maintenance of the treatment effect for an additional 8 weeks (as evidenced by sustained clearance of viremia and improvement or resolution of symptoms and no new symptom development between end of treatment and up to Week 16) is categorized as a responder.

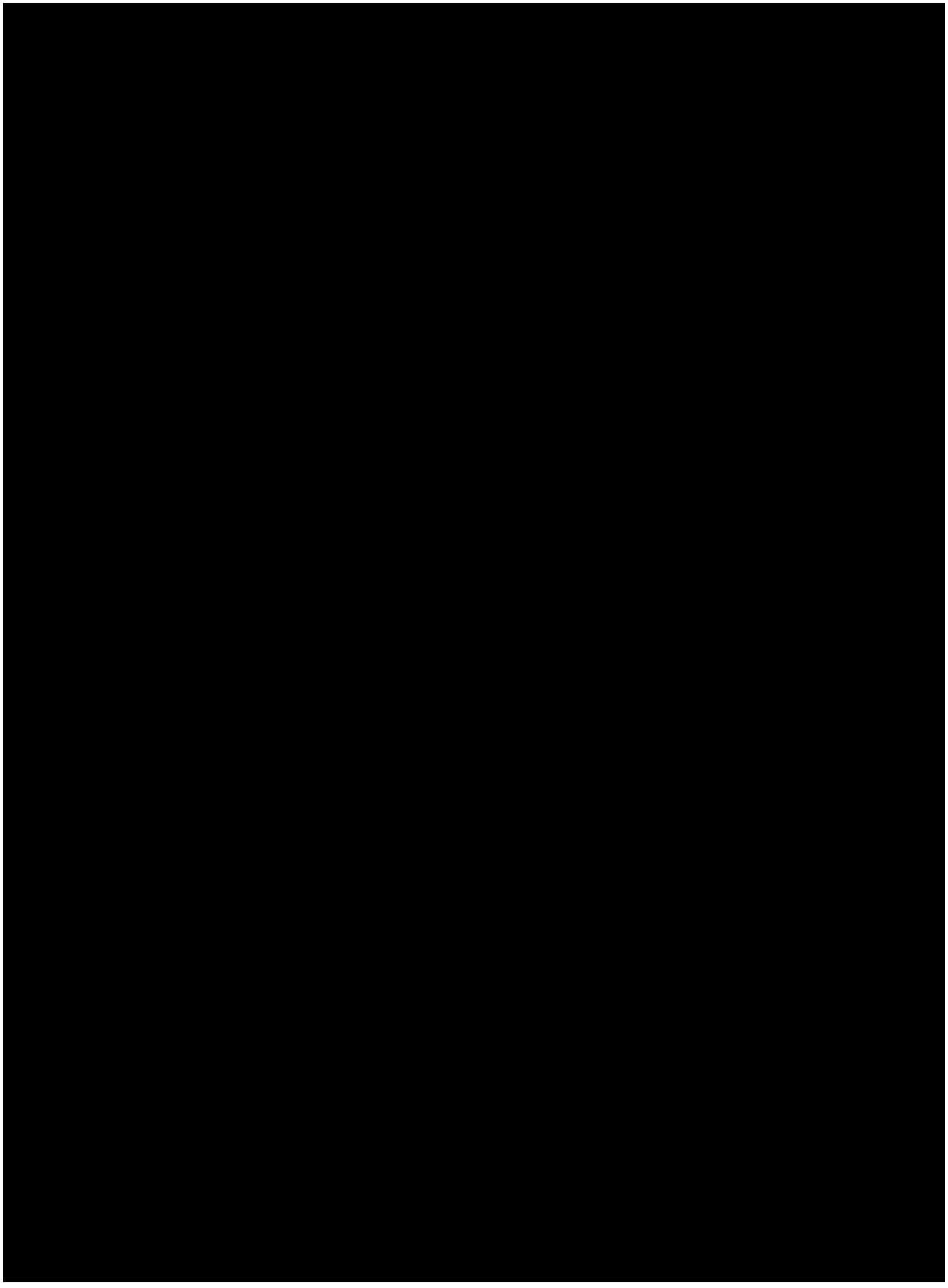
The number and percentage and the corresponding 95% CI of subjects who achieved viremia clearance and CMV infection symptom control at Week 8 and maintain the effect through Week 16 after maribavir rescue treatment will be summarized.

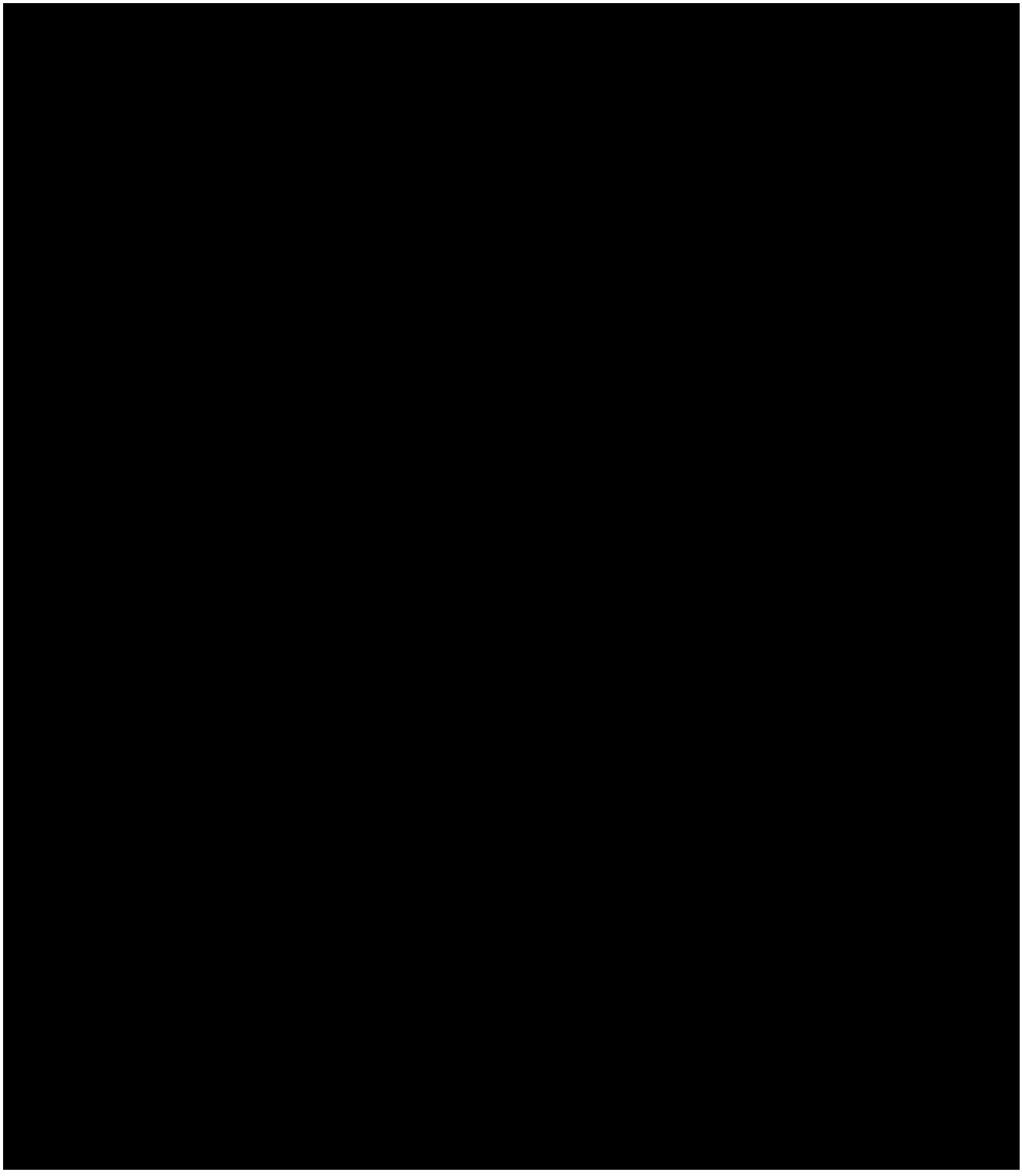
Additionally, the number and percentage and the corresponding 95% CI of subjects who achieved viremia clearance and infection symptom control at Study Week 8, and maintain the effect through Week 12, 20 after maribavir rescue treatment will be summarized.

10.4 Exploratory Efficacy Endpoint(s) and Analyses

[redacted]







11. SAFETY ANALYSES

The primary analysis of safety will be based on the "treatment-emergent" principle. This analysis will comprise the basis upon which conclusions will be drawn regarding the safety profile.

Safety evaluation will be made during the periods such as screening phase, treatment phase, and follow-up phase (See Figure 1 of the protocol). Baseline assessments will be the last assessment on or before the first dose date of study treatment. The adverse events (AEs) that occur from the time of ICF signature to first dose will be collected but will not be evaluated in the safety analyses. They will be listed as pretreatment adverse events. Two observation periods are defined for the purpose of safety analyses for the study assigned treatment using the Safety Set:

1) The on-treatment observation period starts at the date of study treatment initiation through 7 days after the last dose of study treatment, or through 21 days after the last dose of cidofovir (if cidofovir is the IAT). For subjects who transfer from the study treatment to either maribavir rescue or to a nonstudy anti-CMV treatment, the on-treatment observation period ends at the 7 days after the last dose of study treatment or through 21 days if cidofovir is used, or until initiation of maribavir rescue treatment or nonstudy anti-CMV treatment, whichever is earlier. The on-treatment observation period will serve as the primary period for analysis of safety.
2) The overall-study observation period starts at the date of study treatment initiation through the end of the follow-up phase of the study for subjects that do not receive maribavir rescue therapy, and the overall-study observation period starts at the date of study treatment initiation through the time before receiving maribavir rescue therapy for subjects who receive maribavir rescue therapy

The safety endpoints include the following:

- Treatment-emergent AEs and treatment-emergent SAEs, overall study AEs and overall study SAEs
- Clinical laboratory evaluations

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

Safety analyses for the maribavir rescue arm will be provided separately using the Rescue Set. Similarly, the following observation periods are defined for the safety analysis of rescue treatment.

1) The on-rescue treatment period starts at the rescue treatment initiation through 7 days after the last dose of rescue treatment or the start of alternative anti-CMV treatment, whichever is earlier.
2) The on-rescue overall observation period starts at the rescue treatment initiation through the end of study.

Safety endpoints will be summarized descriptively for the on-treatment period and overall-study period, on-rescue treatment period and on-rescue treatment overall observation period, as appropriate.

11.1 Adverse Events

All AEs will be recorded from the time the informed consent is signed through 30 days after the last dose of study assigned treatment. This includes events occurring during the screening phase of the study, regardless of whether or not study treatment is administered. Following the 30-day capture period for all AEs, only those AEs deemed related to study assigned treatment or other protocol-mandated procedures and all SAEs (regardless of causality assessment) will be collected until the defined follow-up period.

All SAEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained.

Adverse events will be coded using MedDRA Version 23 (March 2020).

An AE (classified by preferred term) that has a start date on or after the first dose of study treatment or if it has a start date before the date of first dose of study treatment, but increases in severity after first dose of study treatment will be considered treatment emergent AE (TEAE) for the observation period.

If an AE onset date (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 onset date 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 18.7, Section 18.8, and Section 18.9.

If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to study treatment.

11.1.1 Treatment-emergent Adverse Event

The following TEAE summaries will be produced for the on-treatment observation period, overall-study observation period for the study assigned treatment and IAT type, respectively using the Safety Set.

- 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 withdrawal from study, fatal AEs and AEs of special interest (AESI) as well as the total number of events for each category

- Summary of TEAE by system organ class (SOC) and preferred term, including the number and percentage of subjects with a TEAE, as well as the total number of events in each treatment group
- Summary of TEAE by preferred term in descending order of frequency for maribavir treatment group
- Summary of TEAE by maximum severity, SOC, and preferred term
- Summary of TEAEs related to study treatment by SOC and preferred term
- Summary of treatment-emergent SAEs by SOC and preferred term
- Summary of treatment-emergent SAEs by maximum severity, SOC and preferred term
- Summary of treatment-emergent SAEs considered related to study drugs by SOC and preferred term
- Summary of TEAE leading to study treatment discontinuation by SOC and preferred term
- Summary of TEAE related to study treatment leading to study treatment discontinuation by SOC and preferred term
- Summary of TEAE leading to withdrawal from study by SOC and preferred term
- Summary of TEAE related to study treatment leading to withdrawal from study by SOC and preferred term
- Summary of TEAE leading to death by SOC and preferred term
- Summary of TEAE related to study treatment leading to death by SOC and preferred term
- Summary of TEAEs related to study treatment by maximum severity, SOC, and preferred term

TEAEs of the rescue treatment will be analyzed in a similar fashion. Selected summaries of TEAE of the rescue treatment for the on-rescue treatment observation period and on-rescue treatment overall observation period using the Rescue Set will be provided.

11.1.2 Adverse Events of Special Interest (AESIs)

The severity grading of AESIs are listed below (see Section 8.1.4 of study protocol for more details):

- **AESIs with severity grading based on CTCAE Version 4.03**
    - Tissue invasive CMV
    - Taste disturbance (dysgeusia)
    - Nausea, Vomiting, Diarrhea
    - Neutropenia
    - CMV syndrome (applicable only in SOT subjects)

- **AESIs with 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 (HSCT subjects):
  - Acute Graft-versus-host-disease
  - Chronic Graft-versus-host-disease
- Graft rejection (acute, chronic, or failure)

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 class, and PTs for the on-treatment period and overall-study period. The following summaries will be provided for AESIs for the study assigned treatment and IAT type using the Safety Set for the on-treatment and overall-study periods:

- Summary of frequently occurring TEAEs of special interest by AESI class, preferred term in descending order for maribavir treatment group
- Summary of TEAEs of special interest by maximum severity, AESI class, and preferred term
- Summary of TEAEs of special interest by AESI class and preferred term
- • Summary of TEAEs of special interest related to study treatment by class and preferred term
- Summary of TEAEs of special interest related to study treatment by AESI class, preferred term in descending order of frequency for maribavir treatment group
- Summary of TEAEs of special interest related to study treatment by maximum severity, AESI class, and preferred term
- Summary of serious TEAEs of special interest by AESI class, and preferred term
- Summary of serious TEAEs of special interest related to study treatments by AESI class, and preferred term

11.1.2.1 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 or as rescue 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 maribavir 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.

11.1.2.2 Renal Disorder TEAEs

The following summaries of sponsor-defined renal disorder TEAEs will be provided for the study assigned treatment and IAT type 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)

11.1.3 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,
  - ≥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)
- Transplant type (SOT, HSCT)
- Presence of CMV mutation resistant to ganciclovir/foscarnet/cidofovir per central laboratory result (yes, no)
- Symptomatic infection (yes, no) as confirmed by EAC

- Renal impaired subjects (no, 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 and IAT type 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, Symptomatic infection by EAC 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, Symptomatic infection by EAC 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.

11.2 Clinical Laboratory Variables

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. Local laboratory results will be provided in data listings.

The following outputs will be provided for the overall-study observation period for the study assigned treatment by visit; the last observation while on study treatment and the last observation on the overall-study observation period will be included unless otherwise specified. The analysis will be repeated for the rescue arm, as appropriate.

- Summary of actual and change from baseline of hematology and chemistry laboratory values for continuous variables by treatment group and visit using descriptive statistics in tables and change from baseline will be presented using the box plots
  - Additionally, summary of actual and change from baseline for the following lab parameters by treatment group, IAT type (ganciclovir/valganciclovir, foscarnet), and visit using descriptive statistics, and the respective change from baseline for these laboratory parameters will also be presented using the box plots.

    To evaluate bone marrow effects:
    - Hemoglobin
    - Leukocytes
    - Lymphocytes

- Neutrophils
- Platelets
- Reticulocytes

To evaluate electrolyte abnormalities:

- Calcium
- Phosphate
- Magnesium
- Potassium

To evaluate renal toxicity:

- Creatinine
- Urea nitrogen

- Furthermore, the summary and box plots for creatinine and urea nitrogen will be repeated by renal impairment (no, mild, moderate/severe) at baseline
- The summary and box plots for creatinine and urea nitrogen will also be presented for the subset of subjects who received kidney transplant

- Summary of actual and change from baseline of immunosuppressant drug level for subjects who received immunosuppressant drug at baseline by treatment group and visit using descriptive statistics
- Summary of categorical urinalysis laboratory parameter results by treatment group and visit
- Summary of clinically significant (yes/no) laboratory (hematology, chemistry, and urinalysis) results as determined by the study investigator by treatment group and visit

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

- Hematology: ANC, Hgb, platelet, WBC, ALC
- Chemistry: Serum sodium, potassium, glucose, creatinine, calcium, phosphorus, magnesium, uric acid, creatinine phosphokinase, total bilirubin, ALT, AST, gamma−glutamyltransferase (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 [1.0×10^9/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.

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.

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 and IAT type (valganciclovir/ganciclovir, foscarnet) for decreasing ANC, Hgb, platelet, WBC, ALC, and increasing creatinine.

11.3 Vital Signs

Vital sign values will be considered potentially clinically significant (PCS) if they meet the observed value criteria or the change from baseline criteria listed in Table 14. The number and percentage of subjects with PCS post-baseline values will be tabulated by treatment group and visit. The percentages will be calculated relative to the number of subjects with baseline and post-baseline assessment. The numerator is the total number of subjects with at least 1 PCS post-baseline vital sign value. A supportive listing of subjects with post-baseline PCS values will be provided including the subject number, site, baseline, and post-baseline PCS values. All vital signs data will be presented in a by-subject listing.

Table 14 Criteria for Potentially Clinically Significant Vital Signs

	Criteria	
Vital Sign Parameter	**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	

11.4 Electrocardiogram (ECG)

A 12-lead electrocardiogram (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. Each ECG will include heart rate, RR duration, PR duration, QT duration, and QRS duration. The corrected QT interval (QTc) will be calculated using the Fridericia's formula. The investigator will be responsible for providing the interpretation for all ECGs in terms of clinical significance to the subject. A summary of investigator's interpretation of ECG results will be provided.

In addition, ECG variable values will be considered PCS if they meet or exceed the upper limit values listed in Table 15. The number and percentage of subjects with post-baseline PCS values will be tabulated by treatment group and visit. The percentages will be calculated relative to the number of subjects with available non-PCS baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCS post-baseline ECG value. A listing of all subjects with post-baseline PCS value will be provided including the subject number, site, baseline, and post-baseline PCS values.

Table 15 Criteria for Potentially Clinically Significant ECG Values

ECG Parameter	Criteria Observed Value
Heart Rate (bpm)	≤50
	≥100
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

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

11.5 Treatment with Hemopoietic Growth Factors, Blood, and Blood Products Transfusions

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

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

12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

12.1 Pharmacokinetics Population

The PK Set and adolescent PK Set are defined in Section 4.6.

12.2 Pharmacokinetic Methods

All summaries and analyses of the pharmacokinetic data will be based on the PK Set and adolescent PK Set as applicable.

12.2.1 Concentration Data

In adult subjects of at least 18 years old who will receive maribavir treatment or maribavir rescue treatment, sparse blood samples at predose (C_{min}) and 2-4 hour postdose administration at Week 1, Week 4, and Week 8 will be collected. For subjects ≥12 to <18 years of age, an intensive PK sampling will be performed at Week 1 and sparse PK sampling similar to adults (≥18 years) will be performed at Week 4 and Week 8. PK samples will be analyzed for the determination of plasma maribavir concentrations.

It is noted that eDiary malfunctions occurred during the study resulting in some loss of dosing date and time data. Some of the plasma maribavir concentrations are impacted because 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 concentrations dataset will include all plasma maribavir concentrations, and the impacted plasma maribavir concentrations will have the PK sampling time be imputed according to the sparse sampling or intensive sampling schedule (primary concentration dataset). The impacted maribavir concentrations will be evaluated individually to confirm the appropriateness of this method, and previous dosing pattern 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).

12.2.2 Handling BLQ Values

The following procedures will be used for plasma concentrations below the LLOQ:

- Samples that are below LLOQ are treated as zero in the calculation of summary statistics (eg, mean, SD, etc) for the plasma concentrations at individual time points.
- 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 values will not be imputed.

12.2.3 Pharmacokinetic Parameters

Pharmacokinetic endpoints for maribavir treatment either from treatment phase or rescue treatment are as follows:

For all subjects who received maribavir treatment:

- Maribavir C_{min} (predose 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
- Vz/F: apparent volume of distribution

12.3 Statistical Analysis of Pharmacokinetic Data

Maribavir concentrations will be listed by subject, visit and planned sampling time for all subjects as well as adolescent subjects only. Maribavir concentrations will also be summarized by visit and nominal time using descriptive statistics (number of observations, mean, SD, coefficient of variation, median, maximum, minimum) for all subjects as well as adolescent subjects only.

A scatter plot of all reportable maribavir concentration vs actual sampling time will be generated using the primary concentration dataset with PK Set. This will be repeated using the secondary concentration dataset using the PK Set. A listing of subjects with maribavir concentration below LLOQ will be provided along with the Week 8 efficacy response.

C_{min} calculated using the primary concentration dataset will be listed and summarized by visit using the PK Set. C_{min} calculated using the secondary concentration dataset will be listed and summarized by visit using the PK Set. This will be repeated separately using the adolescent PK Set if it has at least 6 subjects. For adolescent, $AUC_{(0\text{-}tau)}$, C_{max}, T_{max}, CL/F, and Vz/F at Week 1 will be listed and summarized if the adolescent PK Set has at least 6 subjects to provide number of observations, mean, SD, coefficient of variation, median, maximum, minimum, geometric mean, and coefficient of variation of geometric mean.

12.4 Analyses of Pharmacokinetic/Pharmacodynamic Relationships

C_{min} values at Week 1, Week 4, and Week 8 will be averaged for use in the analysis model. C_{min} values that are below LLOQ will be assigned ½ LLOQ for these analyses.

PK/pharmacodynamic (PD) relationship analysis will be based on the PK Set using PK parameter (C_{min}) derived from the primary concentration dataset. The analysis will be repeated for the PK Set using C_{min} calculated from the secondary concentration dataset only if the difference between the C_{min} calculated from the primary concentration data and the secondary concentration data are more than 10% as a sensitivity analysis. Furthermore, if there are more than 10% difference in the number of subjects between the PK Set and the supportive PK Set (defined as all subjects in PK Set who are also in the PP Set), then the PK/PD relationship analysis will be repeated using the supportive PK Set.

Analysis on the relationship between C_{min} of maribavir and efficacy endpoints of interest will be conducted by logistic regression analysis and graphical exploration using the PK Set (primary), and supportive PK Set if needed. Efficacy endpoints of interest will include the primary efficacy endpoint, key secondary efficacy endpoint, other secondary and exploratory efficacy endpoints as listed below to the extent data allow:

- Primary efficacy endpoint:
  - Confirmed CMV viremia clearance at Study Week 8 (response=yes/no)
- Key secondary efficacy endpoint:
  - Achievement of the confirmed CMV viremia clearance and CMV infection control at Study Week 8 followed by maintenance through Study Week 16 (response=yes/no)
- Secondary efficacy endpoint:
  - CMV recurrence any time on study
- Exploratory efficacy endpoint:
  - Time to first CMV viremia clearance
  - Time from the first CMV viremia clearance to CMV viremia recurrence

A logistic regression model will be fitted using response (primary and key secondary efficacy endpoints as listed above) as the dependent variable and C_{min} of maribavir as the independent variable. Probability of confirmed CMV viremia clearance response at Week 8 versus maribavir C_{min} will be plotted. Box plot of confirmed CMV viremia clearance response at Week 8 and of maribavir C_{min} will be provided. Scatter plots of time from first CMV viremia clearance to CMV viremia recurrence versus maribavir C_{min} and time to first CMV viremia clearance versus maribavir C_{min} will be displayed. In addition, Kaplan-Meier estimates of time from first CMV viremia clearance to CMV viremia recurrence, time to first CMV viremia clearance using maribavir C_{min} (above median and below median) will be graphically presented.

A list of subjects with average maribavir trough concentrations that are below LLOQ and viremia response, and recurrence will be provided. A categorical treatment summary table of C_{min} (below LLOQ or >LLOQ) versus the response will be included.

12.5 PK and PK/PD Analysis to Be Performed Separately from Clinical Study Report

In a separate analysis and report, maribavir concentrations will be analyzed by population PK analysis approach using nonlinear mixed effect model approach using NONMEM v7 or above. Impact of subject demographics (eg, age, gender, race, body weight) and other subject characteristics (eg, hepatic impairment, renal impairment, concurrent medications, subject population) in 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; relationship between post hoc maribavir PK parameter estimates (AUC, C_{max}, and C_{min}) and efficacy and safety measures of interest will be explored. This analysis may be conducted by combining maribavir PK data from other Phase 2 and Phase 3 studies.

13. OTHER ANALYSES

Exploratory endpoints of [redacted] are included under Section 10.

14. INTERIM ANALYSIS

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. No formal interim analysis for efficacy will be performed. For further details of the DMC, see Section 15.

15. DATA MONITORING/REVIEW COMMITTEE

An independent DMC is established to assess the data for safety and to ensure the validity and scientific merit of the trial. It is anticipated that the DMC meetings will be conducted approximately every 6 months. Detailed plans for the DMC's purpose and responsibilities are described in the DMC charter and its statistical analysis plan.

16. COMPUTER METHODS

Statistical analyses will be performed using Version 9.3 (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).

17. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Changes noted in SAP Amendment 1

No major change to the analyses specified in the DATA MANAGEMENT AND STATISTICAL METHODS section of the original protocol.

The following changes in STATISTICAL METHODS section were incorporated in protocol amendment 5 dated 11 July 2018.

- Update definition of CMV infection symptoms to include CMV syndrome in addition to tissue invasive disease to be followed for symptom control (resolution or improvement of tissue invasive disease or CMV syndrome for those with symptoms at baseline or no new tissue invasive disease or CMV syndrome for those asymptomatic at baseline)
- Update the overall-study observation period for safety analysis to stop at the start of the rescue treatment only so that all safety observation on study will be summarized either in the overall-study observation period minus the period on-rescue treatment or in the overall-rescue arm observation period

Changes noted in SAP Amendment 2

Analyses specified in the DATA MANAGEMENT AND STATISTICAL METHODS section of the study protocol amendment 6 dated 7 December 2018 are being followed. In addition to clarifications, specification of more sensitivity or supplementary analyses or subgroup analysis of key efficacy and safety parameters, the following change is included in this SAP amendment under Section 10.4.3 (Time from first CMV viremia clearance to CMV viremia recurrence).

The endpoint of CMV viremia recurrence requiring alternative treatment after Week 8 is added in this SAP amendment. The CMV viremia recurrence is 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. Recurrence by this laboratory definition may not be clinically meaningful due to usual viral load fluctuations. However, a viral load recurrence requiring alternative treatment as determined by the investigator is clinically meaningful. Therefore, the endpoint of CMV viremia recurrence requiring alternative treatment after Week 8 is added in Section 10.4.3 to evaluate the time from CMV viremia clearance at Week 8 to CMV viremia recurrence requiring alternative treatment after Week 8 for those who achieved confirmed CMV viremia clearance at Week 8 (ie, responder for the primary efficacy endpoint).

Changes noted in SAP Amendment 3

Noteworthy changes since SAP Amendment 2 are noted in the table below. Other minor editorial revisions (including changes for consistency and clarity) are not described in this table.

Table 16 Noteworthy Changes since SAP Amendment 2

Section Number	Section Title	Description
4.5	Per protocol set	Clarify rule of prohibited concomitant medication is to be determined while on treatment, not while on treatment phase
6	Protocol deviation	Add listing to present all COVID-19 related protocol deviation
7	Baseline characteristic	Add definitions of renal impairment and hepatic impairment Add summary of baseline WBC, CD4, CD8
8	Extent of exposure	Update the sensitivity analysis to focus on the set of subjects without impact due to eDiary issue as identified from protocol deviation log
9	Prior and Concomitant Medication and Procedure	Replace the summary of post-treatment medication with summary of post-treatment anti-CMV treatment
10	Efficacy Analysis	Explicitly state the viral load strata based on central laboratory result used in the analysis
10.1.3	Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint	Update COVID-19 sensitivity analyses
10.1.4	Subgroup Analysis of the Primary Efficacy Endpoint	Add kidney transplant type to the subgroup analysis
10.2.3	Sensitivity and Supplementary Analyses of the Key Secondary Efficacy Endpoint	Update COVID-19 sensitivity analysis
10.2.4	Subgroup Analysis of the Primary Efficacy Endpoint	Add kidney transplant type to the subgroup analysis
10.4.3	Time from the First CMV Viremia Clearance to CMV Viremia Recurrence	Clarify keeping viral load measurements after the start of rescue or alternative anti-CMV treatment in the recurrence assessment
11.1	Adverse Events	Add analyses of time to resolution for dysgeusia and similar events and clarify summaries for subgroup analysis
11.2	Clinical Laboratory Variables	Add summary of selected lab parameters by IAT type, and by renal impairment subgroup, and kidney transplant subgroup
17	Changes to Analyses Specified in Protocol	Added summary of changes since last SAP version
18	Data Handling Conventions	Added a section for baseline for efficacy and safety endpoints

18. DATA HANDLING CONVENTIONS

18.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, minimum, maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category. Percentages will be presented as whole numbers.

The number of decimal places to present data and p-values will follow Shire standards.

18.2 Derived Efficacy Endpoints

Efficacy endpoints are defined under Section 10.

18.3 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).

In this study, the time information of oral administration of maribavir or valganciclovir are recorded using the patient eDiary. The administration of study-assigned treatment administered intravenously are recorded on the eCRF with date only information. There were subjects who received either maribavir or valganciclovir and had the study procedure time on Day 0 after the first dose administration time as recorded in the eDiary. For these subjects, study procedures (including laboratory assessments, vital signs, ECGs, [redacted]) after the first dose time on Day 0 will be used as baseline. For adverse events, if AE start/stop date and time were recorded on eCRF and dose administration time were available as recorded on eDiary for maribavir and valganciclovir, the time information will be used in the determination of the onset period of an AE; if either time information was unavailable, only the date information will be used in the determination of the onset period of an AE.

18.4 Repeated or Unscheduled Assessments of Safety Parameters

It is possible that repeat or unscheduled assessments are made for some safety variables (eg, 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.

18.5 Missing Date of Study Assigned Treatment

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.

18.6 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, or procedure, incomplete (ie, 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.

18.6.1 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 study assigned treatment, then the day and month of the date of the first dose of study assigned treatment 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 study assigned treatment, 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 study assigned treatment, 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 study assigned treatment, then the day of the date of the first dose of study assigned treatment will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of study assigned treatment or if both years are the same but the month is before the month of the date of the first dose of study assigned treatment, 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 study assigned treatment or if both years are the same but the month is after the month of the date of the first dose of

study assigned treatment, then the first day of the month will be assigned to the missing day.

18.6.2 Incomplete Stop Date

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

Missing Day and Month

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

18.7 Missing Date Information for Adverse Events

For AEs, the default is to only impute incomplete (ie, 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.

It is noted that AE eCRF page has fields for AE start/stop date and time as part of the standard AE capture, but the AE start/stop time were not mandated to be collected or be queried since CRF Completion Guide version 4. If the AE start/stop date and time were collected, the information will be used to compare with the dose administration time (if collected), if not, only date information will be used.

18.7.1 Incomplete Start Date

Follow same rules as in Section 18.6.1.

18.7.2 Incomplete Stop Date

When required per the protocol, follow the same rules as in Section 18.6.2.

18.8 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of study assigned treatment, 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 study assigned treatment, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

18.9 Missing Relationship to Investigation Product for Adverse Events

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

18.10 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, a character string being reported for a numerical variable, the appropriately determined coded value will be used in the statistical analysis (see Table 17). However, the actual values as reported in the database will be presented in data listings.

Table 17 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	<2	0
Urinalysis: Glucose	≥55	Positive
	≤0	Negative
Urinalysis: pH	≥8.0	8.0

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