CLINICAL STUDY PROTOCOL

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

Protocol Version and Date:

Amendment 6: 07 Dec 2018

PROTOCOL: SHP620-303

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.
DRUG:	SHP620
IND:	IND 051001
EUDRACT NO.:	2015-004725-13
SPONSOR:	Shire ViroPharma, Incorporated 300 Shire Way, Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	**Multicenter**
PROTOCOL HISTORY:	Amendment 6: 07 December 2018 Amendment 6.1: 07 December 2018 Amendment 5.1: 20 August 2018 (Germany, Singapore, Switzerland) Amendment 5: 11 July 2018 Amendment 4: 26 March 2018 Amendment 3.1: 10 October 2017 (Germany and Singapore) Amendment 3: 01 March 2017 Amendment 2.1 : 18 May 2017 (Germany) Amendment 2 (Version 3.0): 01 December 2016 Amendment 1 (Version 2.0): 08 July 2016 Original Protocol (Version 1.0): 25 April 2016

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire ViroPharma, Incorporated) Approval

Signature: [redacted]	**Date:** [redacted]
[redacted], MD	

Investigator's Acknowledgement

I have read this protocol for Shire ViroPharma, Incorporated Study SHP620-303.

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.

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: _____
(please hand print or type) _____
_____
_____

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Amendment 6 to protocol SHP620-303 incorporates the following major changes:

- Specified that any subject not tested for HIV within 3 months prior to screening must be tested during screening by a local laboratory and must have a negative HIV test result available before randomization.

- Removed Hematopoetic Cell Transplant Comorbidity Index from assessments, and deleted corresponding appendix describing the tool. Specified Karnofsky Performance Status and Lansky scales as the only assessment tools for evaluation of comorbidity status.

- Reduced minimum washout period prior to the first dose of study treatment for letermovir from 14 days to 3 days.

- For subjects failing to attain viral clearance, added Visit 18/Week 20 (previously only Visit 16/Week 16) CMV DNA assessment result above the pre-defined cut off to necessitate CMV genotyping.

- Identified specific dated SmPCs as reference safety information for investigator-assigned treatments

- Removed requirement of duplicate SAE and pregnancy reporting to PPD/CRO and Medical Monitors, removed corresponding erroneous contacts, updated name of Shire Global Drug Safety Department, and removed individual names of medical contacts at PPD.

- Clarified that a product quality complaint from any site should be directed to a single central e-mail address.

Noteworthy changes to the protocol are captured in the table below. Other minor editorial revisions (including changes for consistency and clarity) are not described in this table.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **6**	**Amendment Date** **07 Dec 2018**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Modified SAE and pregnancy reporting procedure and limited contact information to only Shire Global Drug Safety; removed specific contact information and names of CRO medical monitors, and updated name of Shire Global Drug Safety Department.		Emergency Contact Information; Section 8.2.2; Section 8.2.4
Clarified that a product quality complaint from any site should be directed to a single central e-mail address.		Product Quality Complaints
Specified need for negative HIV test result within prior 3 months before randomization after exclusion criterion 8 to better ensure HIV negativity for all randomized subjects..		Synopsis, Section 3.1, Study Schedule Table 1, footnote i.; Section 4.2; Section 7.1.1, Section 7.2.3.5; Section 7.2.5; Table 5
Reduced minimum washout period prior to the first dose of study treatment for letermovir from 14 days to 3 days to facilitate enrollment.		Synopsis, Section 4.2
Removed Hematopoetic Cell Transplant Comorbidity Index from Study Schedules, Procedures, and appendices as inappropriate assessment for the study. Specified Karnofsky Performance Status and Lansky scales as the only assessment tools for evaluation of comorbidity status.		Table 1, Table 2, Section 7.1.2, Section 7.1.3, Section 7.2.2.7, Appendix 5
Specified Summary of Product Characteristics versions to be used as reference safety information for investigator-prescribed medications to promote consistent reporting of treatment-related events		Section 8.2.1
For subjects failing to attain viral clearance, added Visit 18/Week 20 (previously only Visit 16/Week 16) CMV DNA assessment result above the pre-defined cut off to necessitate CMV genotyping.		Section 7.1.3

See Appendix 1 for protocol history.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the "Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol" within 24 hours to the Shire Global Drug Safety Department. The fax number and e-mail address are provided on the form (sent under separate cover).

Fax: [redacted]
e-mail: [redacted]

For protocol- or safety-related issues <u>during normal business hours 8:00am - 5:00pm (local time per region)</u>, the investigator must contact the PPD medical monitor:

<u>Hotline numbers (24 hours a day/7 days a week):</u>

North America: [redacted]

Europe, Middle East, Africa (EMEA)/Asia-Pacific (APAC): [redacted]

<u>Fax numbers</u>:

North America: [redacted] and [redacted]

EMEA/APAC: [redacted]

<u>E-mail</u>:

North America: RTP Safety Mailbox (SM) - [redacted]

EMEA ASIA Safety Central Mailbox (SM) - [redacted]

For protocol- or safety-related issues outside of normal business hours, the Investigator must contact:

Hotline numbers (24 hours a day /7 days a week): North America - [redacted]; EMEA /APAC - [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please report the Product Quality Complaint to: [redacted]

Telephone number (provided for reference if needed):

300 Shire Way, Lexington, MA 02421 USA

[redacted]

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ABBREVIATIONS

AAG	alpha-1-1acid-glycoprotein
AE	adverse event
AESI	adverse events of special interest
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
BAL	bronchoalveolar lavage
BID	twice daily
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CoD	Certificates of Destruction
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
EAC	Endpoint Adjudication Committee
EC	ethics committee
ECG/EKG	electrocardiogram
EIND	emergency investigational new drug
[redacted]	[redacted]
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus

HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HSA	human serum albumin
HSCT	hematopoietic stem cell transplant
HSV	herpes simplex virus
IAT	investigator-assigned anti-CMV treatment
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IRT	interactive response technology
IVIg	intravenous immunoglobulin
KPS	Karnofsky Performance Status
LLOQ	lower limit of quantification
OTC	over-the-counter
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	per os (oral)
qPCR	quantitative polymerase chain reaction
QTc	corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SOT	solid organ transplant
TEAE	treatment-emergent adverse event
TID	3 times daily
ULN	upper limit of normal
US	United States
VZV	varicella zoster virus

DEFINITIONS

Term	Definition
Confirmed viremia clearance	Defined as plasma cytomegalovirus (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.
Rebound of CMV viremia	Defined as increase in viral DNA load for >1 log10 above nadir without prior clearance of viremia.
Recurrence of 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 symptomatic CMV infection in subjects symptomatic at baseline.
Refractory	Documented failure to achieve >1 log10 (common logarithm to base 10) decrease in CMV DNA level in whole blood or plasma after a 14 day 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	Documented failure to achieve >1 log10 (common logarithm to base 10) decrease in CMV DNA level in whole blood or plasma after a 14 day 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.

Term	Definition
Symptomatic subjects	Eligible enrolled subjects who have tissue-invasive CMV disease or CMV syndrome (SOT subjects only) at baseline, as determined by the investigator.
Asymptomatic subjects	Eligible enrolled subjects who do not have tissue-invasive CMV disease or CMV syndrome (SOT subjects only) at baseline, as determined by the investigator.

STUDY SYNOPSIS

Protocol number: SHP620-303	**Drug:** Maribavir
Title of the study: 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.	
Number of subjects (total and for each treatment arm): Approximately 413 subjects will be screened to randomize approximately 351 subjects in a 2:1 ratio (234 [maribavir treatment]: 117 [investigator-assigned anti-CMV treatment (IAT)])	
Investigator(s): A multicenter study to be conducted at approximately 140 sites worldwide.	
Site(s) and Region(s): Approximately 140 sites in North America, Europe, and Asia Pacific.	
Study period (planned): 2016-2019	**Clinical phase:** 3

Primary Objective:

To compare the efficacy of maribavir to investigator-assigned anti-CMV therapy on CMV viremia clearance at the end of Study Week 8, in transplant recipients who are refractory or resistant to prior anti-CMV treatment.

Key Secondary Objective:

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).

Secondary Objectives:

- 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 symptomatic CMV infection (tissue invasive 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 (4 weeks post-treatment period), 16 (8 weeks post-treatment/follow-up phase), and 20 (12 weeks post-treatment).
- To assess the 2 study treatment arms for maintenance of CMV viremia clearance, and resolution or improvement of tissue invasive CMV disease, achieved at the end of Study Week 8, through weeks 12 (4 weeks of post treatment period), and 20 (12 weeks post treatment).
- To evaluate the incidence of recurrence of 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 any time during the study.
- To evaluate the incidence of recurrence of CMV viremia in the 2 study treatment arms when patients 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.

Exploratory Objectives:

[redacted]

Rationale:

The population of hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients whose CMV infections are refractory to available antiviral treatment (ie, ganciclovir, valganciclovir, foscarnet, or cidofovir) is an area of high unmet medical need. Some patients refractory to anti-CMV treatment are found to harbor virus with mutations conferring resistance to a particular drug.

Maribavir is a potent member of a new class of drugs, the benzimidazole ribosides, which bind to viral serine/threonine kinase (UL97) that plays a role in nuclear viral egress, viral replication, or regulation of host cell cycle. Favorable results from a Phase 2 study support the safety, tolerability, and anti-viral activity of maribavir as a potential option for the treatment of CMV infections that are refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir, including CMV infections with confirmed resistance to anti-CMV agents, in HSCT and SOT recipients. Consequently, Study SHP620-303 has been designed to further assess the efficacy of maribavir 400 mg twice daily (BID) treatment compared to investigator-assigned anti-CMV treatment in HSCT and SOT recipients with refractory CMV infections, including confirmed resistance to prior anti-CMV treatment.

The study will enroll pediatric subjects ⩾12 to <18 years of age. Inclusion of adolescent patients in the study is based on the population PK modeling that showed that the same systemic exposures are reached in individuals ⩾35 kg dosed with 400 mg BID of maribavir. Maribavir metabolism and excretion are not expected to differ in adolescents and adults, as the primary metabolism is through liver enzymes CYP3A4, CYP 2C19 and CYP 1A2 that reach adult levels in children of 1-2 years of age (Lu et al. 2014). It is not expected that the bioavailability and systemic exposure to maribavir in adolescent subjects of 12-18 years of age is different from adults at the same oral dose.

Study treatment

<u>Investigational product, dose, and mode of administration:</u>

Maribavir

The sponsor will provide maribavir 200 mg strength tablets, which will be administered orally (PO) at 400 mg twice daily (BID).

<u>Investigator-assigned anti-CMV drugs:</u>

Ganciclovir

Valganciclovir

Foscarnet

Cidofovir

Investigators will choose and administer/prescribe the anti-CMV agent best suited to treat the respective subject's CMV infection based on their clinical judgment. The anti-CMV agents of choice include the following commercially available drugs: ganciclovir, valganciclovir, foscarnet, or cidofovir. In clinical practice, these agents are utilized for treatment of CMV infection/disease and endorsed by published guidelines (Kotton et al. 2013; Tomblyn et al., 2009), and by local institutional guidelines. The dose of these agents will be determined by the Investigator.

Methodology:

This is a multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of maribavir treatment compared to investigator-assigned anti-CMV treatment in HSCT and SOT recipients with CMV infections that are refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir, including CMV infections with confirmed resistance to 1or 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 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 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 a 14 day 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 a 14 day 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 the 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 agent; this assessment will be based on the results from the central specialty laboratory and utilized for analysis. Subject enrollment will be monitored to achieve an approximate target of 60% of subjects who have a CMV infection with documented resistance to any of the anti-CMV agents (ganciclovir, valganciclovir, foscarnet, or cidofovir) according to the central specialty results from samples taken at baseline.

The subjects randomized to maribavir treatment arm will discontinue the 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. Addition of or switch to another anti-CMV agent will be declared as a failure for the purpose of study analysis. After randomization changes to the investigator treatment of choice could include, change in dosing, dosing regimen, but will not include an addition of or switch to another anti-CMV agent. Note that changes between 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 IU/mL and <273000 IU/mL in whole blood or ⩾9100 IU/mL and <91000 IU/mL in plasma, and low viral load <27300 IU/mL and ⩾2730 IU/mL in whole blood or CMV DNA <9100 IU/mL 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 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 and CMV syndrome at the end of the 8-week study treatment phase and

during the follow-up phase for subjects with symptomatic infection present at baseline. "***Asymptomatic 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 (absence or presence) 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 (below), 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.

Screening Phase

Approximately 413 subjects will be screened during an approximately 2-week screening phase to establish eligibility for study participation. Historical laboratory results for tests specified in the Schedule of Assessment 1 may be used during screening for the assessment of the eligibility, including local CMV DNA quantification test results. If local laboratory results are not available, the central laboratory assessments may be conducted. All clinical laboratory results required for eligibility verification must be available prior to randomization.

Study Treatment Phase

Approximately 351 eligible subjects with refractory or resistant CMV infection will be stratified and then randomized at Visit 2/Day 0 to receive either maribavir or investigator-assigned anti-CMV treatment (IAT) (collectively, study-assigned treatment) for 8 weeks.

The screening and Visit 2/Week 0/Day 0 visits can occur on the same day in the case when historical local laboratory results are available for determination of eligibility.

All Visit 2/Day 0 procedures and screening laboratory results needed to confirm eligibility must be completed and documented prior to randomization and study treatment administration. The whole blood/plasma samples for CMV DNA quantification, hematology, and chemistry testing must be taken for all patients at Visit 2/Week 0/Day 0. The test results of these assays will not be available prior to the start of treatment. 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.

Subjects Randomized to Maribavir Treatment

Depending on the time of the first maribavir dose on Visit 2/Day 0, a second dose should be administered on Visit 2/Day 0 provided that doses can be separated by a minimum of 8 hours; otherwise, only 1 dose will be administered on Visit 2/Day 0. Maribavir will then be administered (preferably) every 12 hours (q12h). When q12h dosing is not feasible, the doses should be separated by a minimum of 8 hours. Since 200 mg strength maribavir tablets will be utilized, subjects will be required to take 2 tablets of maribavir q12h as shown below.

Maribavir Dosing Regimen

Regimen	AM	PM
400 mg BID	200 mg × 2 tablets	200 mg × 2 tablets

Subjects will take the maribavir 400 mg BID dose for the 8 weeks of the study treatment phase.

Subjects Randomized to Investigator-Assigned Anti-CMV Therapy

Investigator-assigned anti-CMV treatment strategies for the 8 weeks of the study treatment phase must only utilize up to 2 available anti-CMV agents from the following: ganciclovir, valganciclovir, foscarnet, or cidofovir (foscarnet and cidofovir in combination is prohibited).

After randomization, changes to the investigator treatment of choice could include, change in dosing, change in dosing regimen, but will not include a switch to or an addition of another anti-CMV agent (switching between valganciclovir and ganciclovir is allowed). The rationale for dose adjustment will be documented. Investigational anti-CMV agents are not permitted.

Subjects will follow the investigator's prescribed anti-CMV treatment. Subjects will remain on their investigator-assigned anti-CMV therapy for the 8 weeks of the study treatment phase. Subjects may stop treatment at the discretion of the investigator, for lack of confirmed viremia clearance and/or intolerance to the assigned treatment. Subjects may be assessed for rescue arm eligibility at the investigator's discretion. Intolerance to assigned treatment without clear evidence of virologic and/or clinical failure will not qualify a patient for the rescue arm. Viremia clearance should be based on the results from the same laboratory used for randomization. Subjects may be assessed for entry into a rescue arm, starting at Visit 5/Week 3 (after a minimum 3 weeks of treatment), for treatment with maribavir 400 mg BID for 8 weeks. Subjects must meet 1 of the following criteria to be eligible to enter the maribavir rescue arm:

1. Subject has increased whole blood or plasma CMV viremia levels of $\geqslant$1 $\log_{10}$ from baseline as measured by the local or central specialty laboratory qPCR assay (results from the same laboratory will be compared). Local specialty laboratory results must be documented.

2. Subjects with tissue invasive CMV disease must meet both criteria after being on treatment for at least 3 weeks:
   - Subject whole blood or plasma CMV DNA has decreased <1 $\log_{10}$ from baseline as measured by the local or specialty laboratory qPCR assay (results from the same laboratory will be compared). Local specialty laboratory results must be documented.
   - Symptomatic subject's presenting tissue invasive CMV disease did not improve, or worsened as assessed by the investigator OR subject who was asymptomatic at baseline developed tissue invasive CMV disease.

3. No CMV viremia clearance was achieved (results from the same laboratory will be assessed) necessitating continued anti-CMV treatment AND the subject has demonstrated intolerance to the investigator-assigned anti-CMV treatment as evidenced by 1 of the conditions:
   - Acute increase in serum creatinine, at least 50% increase from the baseline value, attributed to treatment (cidofovir, foscarnet) toxicity
   - Development of hemorrhagic cystitis when on treatment with cidofovir or foscarnet
   - Development of neutropenia (absolute neutrophil count [ANC <500/mm^3 [0.5 x 10^9/L]) when on treatment with ganciclovir or valganciclovir

The transition into the rescue arm will be allowed after the study medical monitor has reviewed the investigator's request and has approved the subject's eligibility for the rescue arm. Blood sample taken for CMV DNA test at the

first visit of the maribavir rescue treatment period will be used as the 'baseline' assessment for the purpose of the analyses of the response to maribavir rescue treatment (including resistance analyses). Subjects who are unable to continue taking investigator-assigned anti-CMV treatment due to the lack of anti-viral activity and/or intolerance to the assigned treatment and who do not meet the eligibility criteria to enter the maribavir rescue arm will be treated as deemed appropriate by the investigator.

The investigator may also choose to interrupt therapy for a maximum of 7 consecutive days, or up to 2 study treatment interruptions for a total of up to 7 days. This will not result in permanent study treatment discontinuation. If study drug is interrupted for any reason and subsequently resumed, the end of the study drug administration period would remain fixed at a maximum of 8 weeks after the date of the start of treatment.

All subjects will undergo study-specific evaluations weekly during the study treatment phase. All subjects who complete the study treatment phase through Visit 10/Week 8 will enter the 12-week follow-up phase.

Subjects who prematurely discontinue study treatment in the investigator assigned treatment arm, and are not transferred to the maribavir rescue arm, will complete the end of treatment procedures described for Visit 10/Study Week 8 in the Schedule of Assessment 1. These subjects will continue on 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. The end of treatment sample for immunosuppressant drug concentration level will be collected at the next visit scheduled 1 week after the treatment discontinuation. Subjects who discontinue maribavir 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 duration specified for the study treatment phase, subjects will enter the 12-week follow-up phase. During the period after the study treatment discontinuation, and until the end of the study, subjects might be administered an anti-CMV treatment for lack of efficacy, recurrence of CMV viremia, or for worsening or new onset of CMV disease as deemed necessary by the investigator. Subjects who withdraw from the study during the follow-up phase will perform the end of study evaluations and procedures for Visit 18/Week 20 (Follow-up Week 12) as soon as possible.

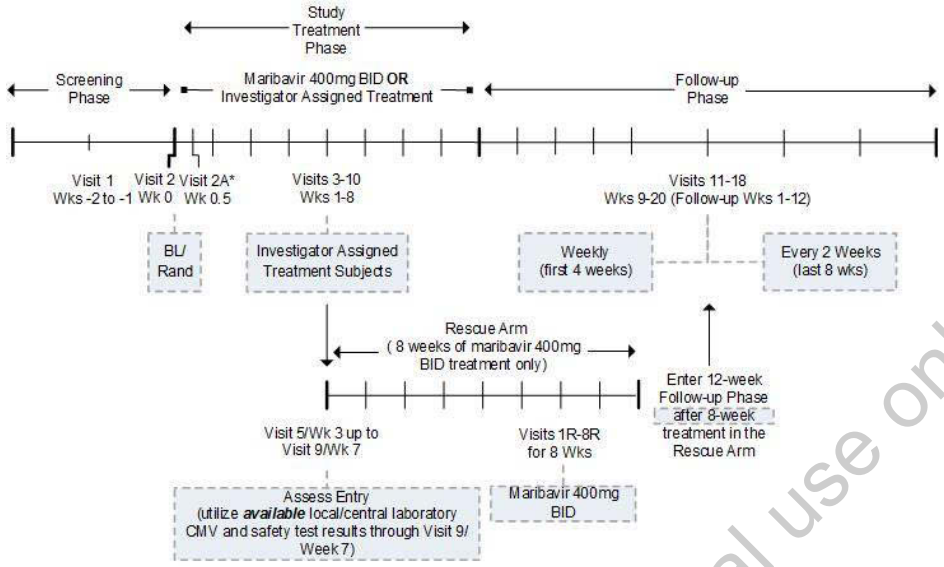
Subjects who withdraw consent during the study treatment phase will be asked to undergo all end of treatment evaluations and procedures listed for Visit 10/Week 8. Subjects who withdraw from the study during the follow-up phase will undergo all end of study evaluations and procedures listed for Visit 18/Week 20 (Follow-up Week 12) as soon as possible and whenever possible, prior to initiation of any nonstudy anti-CMV treatment (as deemed by the investigator) for lack of efficacy, recurrence of CMV viremia, or for worsening or new onset of CMV disease; no further follow-up will be performed.

Subjects who are transferred to maribavir rescue arm will complete the end of treatment evaluations listed for Visit 10/Week 8 prior to being transferred. They will be treated with maribavir for 8 weeks and will follow the procedures in the manner similar to that followed by subjects in the maribavir treatment arm, as indicated in the Schedule of Assessment 1 (visits denoted with letter R). After the completion of 8 weeks of maribavir rescue treatment, subjects will enter the 12-week follow-up phase and will follow the procedures indicated in the Schedule of Assessment 2.

Follow-up Phase

Study-specific evaluations including central specialty laboratory CMV testing and safety assessments will occur weekly for the first 4 weeks, then every 2 weeks for the final 8 weeks of the 12-week follow-up phase. Refer to Schedule of Assessment 2 for a complete list of the evaluations.

Study Design Flow Chart



*Visit 2A/A-R is only required for subjects taking tacrolimus, cyclosporine, everolimus, or sirolimus at Visit 2/2R.
BID=twice daily; BL=baseline; R=rescue; Rand=randomized; wks=weeks

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

Notable Study Evaluations during Study Treatment Phase and Follow-up Phase

CMV DNA Quantitation

Blood samples will be assessed at a central specialty laboratory for the quantitation of CMV DNA in plasma using the COBAS® AmpliPrep/COBAS® TaqMan® CMV Test. Central Specialty laboratory plasma CMV DNA results will be reported to the investigator site as available. Additional CMV DNA testing at local specialty laboratories may be performed at more frequent intervals or use additional assay methods at the discretion of the investigator.

Confirmed CMV viremia clearance will be 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 or the recurrence of CMV viremia will be 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. Every attempt should be made to collect the 2 consecutive plasma samples and monitor results to confirm recurrence.

CMV genotyping and phenotyping

Visit 2/Day 0 plasma samples will be used for CMV DNA genotyping to identify mutations in the viral UL97 and UL54 genes known to confer resistance to commercially available anti-CMV agents. In addition, viral UL27 gene will be tested. During the study, CMV genotyping will be conducted when the CMV DNA viral load is above a predefined cut off level (validated for this assay) in cases of failure to clear viremia during treatment, cases of recurrence of viremia on and off treatment and cases of viremia rebound if >1 $\log_{10}$ above nadir while on treatment

(***rebound*** is defined as increase in viral DNA load for >1 $\log_{10}$ above nadir without prior clearance of viremia). The entire UL97, UL27, and UL54 CMV genes will be sequenced in every sample that meets the criteria for genotyping, including the baseline samples. Additionally, virus susceptibility testing will be performed on selected de novo CMV variant sequences of the relevant gene of maribavir treated subjects by recombinant resistance phenotyping. Details of the analysis will be specified in the resistance analysis plan.

Symptomatic CMV Infection Assessment

Tissue-invasive CMV disease will be defined as described by Ljungman et al. (2002 and 2017). The gold standard for diagnosing CMV tissue invasive disease is the identification of CMV inclusions in the infected cells of the tissues OR identification of CMV in biopsy tissue samples. However, in some cases both diagnostic methods are required when tissue samples have a high chance of being contaminated by body fluids that shed virus (bronchoalveolar lavage [BAL], urine or stool). In some subjects, when it is not possible to obtain a tissue biopsy, a culture of CMV from body fluids or CMV DNA quantitation (for selected cases) may be used to confirm diagnosis, with a lower level of confidence in diagnosis. CMV syndrome (in SOT subjects only) will also be defined as described by Ljungman et al. (2017), and requires at least 2 of 6 signs and symptoms to be present (see Appendix 3 for full description of criteria).

All subjects will be monitored for the occurrence of CMV tissue invasive disease and CMV syndrome throughout the study. For *symptomatic* subjects who present with tissue invasive CMV disease and CMV syndrome at baseline, the investigator will document the initial diagnosis of CMV tissue invasive disease and CMV syndrome at Visit 2/Day 0 (ie, absence or presence at baseline) and all serial assessments of infection status (ie, no change, improvement, worsening, or resolution) at all subsequent visits in the study. Case charts documenting the symptomatic infection diagnosis (present at baseline or new symptomatic infection) and follow-up infection status at study visits will be provided for adjudication to an independent Endpoint Adjudication Committee. The roles, responsibilities, and rules governing operation of the independent Endpoint Adjudication Committee will be fully documented in an Endpoint Adjudication Committee charter.

The ***recurrence of symptomatic CMV infection*** will be 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 symptomatic CMV infection in subjects symptomatic at baseline.

In subjects asymptomatic at baseline, the occurrence of new CMV tissue invasive disease or CMV syndrome after start of study treatment will be initially assessed by the investigator followed by adjudication by the EAC.

Inclusion and exclusion criteria:

Inclusion Criteria:

1. The subject must be able to provide written, personally signed, and dated informed consent to participate in the study before completing any study-related procedures. As applicable, a parent/both parents or legally authorized representative (LAR) must provide signature of informed consent and there must be documentation of assent by the subject before completing any study-related procedures.

2. The subject must be a recipient of hematopoietic stem cell or solid organ transplant.

3. The subject 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 results. Both samples should be taken within 14 days prior to randomization with second sample obtained within 5 days prior to randomization. The same laboratory and same sample type (whole blood or plasma) must be used for these assessments.

4. The subject must have a current CMV infection that is refractory to the most recently administered of the four anti-CMV treatment agent(s). Refractory is 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 a 14 day or longer treatment period with IV ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir.

- Subjects who have documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir must also meet the definition of refractory CMV infection.

5. The investigator must be willing to treat the subject with at least 1 of the available anti-CMV drugs (ganciclovir, valganciclovir, foscarnet, or cidofovir). Note: Combination therapy with foscarnet and cidofovir is **not permitted** in the IAT arm due to the potential for serious nephrotoxicity.

6. The subject must be ⩾12 years of age at the time of consent.

7. The subject must weigh ⩾35 kg.

8. The subject must have all of the following results as part of screening laboratory assessments (results from either the central laboratory or a local laboratory can be used for qualification):
    a. Absolute neutrophil count (ANC) ⩾1000/mm^3 [1.0 x 10^9/L]
    b. Platelet count ⩾25000/mm^3 [25 x 10^9/L]
    c. Hemoglobin ⩾8g/dL
    d. Estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2 as assessed by Modification of Diet in Renal Disease (MDRD) formula for subjects ⩾18 years of age or Schwartz formula for subjects <18 years of age (see Appendix 12 for the formulae).

9. The subject must have a negative serum β-human chorionic gonadotropin (β-HCG) pregnancy test at screening, if a female of child bearing potential. Additional urine pregnancy tests may be done per institutional requirements; however they are not sufficient for eligibility determination. Sexually active females of child bearing potential must agree to comply with any applicable contraceptive requirements of the protocol. If male, must agree to use an acceptable method of birth control, as defined in the protocol, during the study treatment administration period and for 90 days afterward if treated with maribavir, ganciclovir, valganciclovir, or cidofovir and for 180 days afterward if treated with foscarnet.

10. The subject must be able to swallow tablets, or receive tablets crushed and/or dispersed in water via a nasogastric or orogastric tube.

11. The subject must be willing and have an understanding and ability to fully comply with study procedures and restrictions defined in the protocol.

12. The subject must be willing to provide necessary samples (eg, biopsy) for the diagnosis of tissue invasive CMV disease at baseline as determined by the investigator.

13. The subject must have a life expectancy of ⩾8 weeks.

Exclusion Criteria:

Subjects must not:

1. Have a current CMV infection that is considered refractory or resistant due to inadequate adherence to prior anti-CMV treatment, to the best knowledge of the investigator.

2. Require ganciclovir, valganciclovir, foscarnet, or cidofovir administration for conditions other than CMV when study treatment is initiated (example: herpes simplex virus (HSV) coinfection requiring use of any of these agents after the randomization) or would need a coadministration with maribavir for CMV infection. NOTE: A

subject who is not continuing with the same anti-viral drug(s) (ganciclovir, valganciclovir, or foscarnet) for the study treatment (if randomized to the investigator assigned anti-CMV treatment arm), must discontinue their use before the first dose of study drug. If subject is currently being treated with cidofovir and is assigned another anti-CMV therapy by the investigator, the subject must discontinue its use at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment.

3. Be receiving leflunomide, letermovir, or artesunate when study treatment is initiated. NOTE: subjects receiving leflunomide must discontinue the use at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment. Subjects receiving letermovir must discontinue at least 3 days prior to the first dose of study treatment. Subjects receiving artesunate must discontinue the use prior to the first dose of study treatment.

4. Have severe vomiting, diarrhea, or other severe gastrointestinal illness within 24 hours prior to the first dose of study treatment that would preclude administration of oral/enteral medication.

5. Have known hypersensitivity to the active substance or to an excipient for a study treatment.

6. Have tissue invasive CMV disease with central nervous system involvement, including the retina (eg CMV retinitis).

7. Have serum aspartate aminotransferase (AST) >5 times upper limit of normal (ULN) at screening, or serum alanine aminotransferase (ALT) >5 times ULN at screening, or total bilirubin ⩾3.0 x ULN at screening (except for documented Gilbert's syndrome), by local or central lab. Note: Subjects with biopsy confirmed CMV hepatitis will not be excluded from study participation despite AST or ALT >5 times ULN at screening.

8. Have known positive results for human immunodeficiency virus (HIV). Subjects must have a confirmed negative HIV test result within 3 months of study entry or, if unavailable, be tested by a local laboratory during the screening period.

9. Require mechanical ventilation or vasopressors for hemodynamic support at the time of enrollment.

10. Be female and pregnant or breast feeding.

11. Have previously received maribavir.

12. Have received any investigational agent with known anti-CMV activity within 30 days before initiation of study treatment or CMV vaccine at any time.

13. Have received any unapproved agent or device within 30 days before initiation of study treatment.

14. Have active malignancy with the exception of nonmelanoma skin cancer. Subjects who have had a HSCT and who experience relapse or progression of the malignancy, as per investigator's opinion are not to be enrolled.

15. Be undergoing treatment for acute or chronic hepatitis C.

16. Have any clinically significant medical or surgical condition that in the investigator's opinion could interfere with the interpretation of study results, contraindicate the administration of the assigned study treatment, or compromise the safety or well-being of the subject.

Maximum duration of subject involvement in the study:

- Planned duration of screening phase: Up to 2 weeks
- Planned duration of study treatment phase: 8 weeks
- Planned duration of follow-up phase: 12 weeks
- Planned duration of maribavir rescue arm including follow-up (as applicable): Up to 29 weeks

Endpoints and statistical analysis:

Subject Population Sets:

- The enrolled set will consist of all subjects who have signed an informed consent and have begun some study procedures.
- The randomized set will consist of all subjects in the enrolled set who have been randomized to the study. Subjects will be analyzed in the treatment group to which they are randomized.
- The safety set will consist of all subjects who have taken any dose of study treatment. Subjects will be analyzed according to the treatment actually received.
- The per-protocol (PP) set will consist of all subjects in the randomized set who do not have predefined major protocol deviations that may affect the primary efficacy assessment.
- The pharmacokinetic set will consist of all subjects in the safety set who had plasma samples drawn and tested for maribavir concentrations.
  - The adolescent pharmacokinetic set will consist of all subjects ⩾12 to <18 years of age in the safety set who had plasma samples drawn and tested for maribavir concentrations.

The randomized set and the 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.

Sample Size Justification:

In Study SHP620-202, the proportion of subjects with undetectable plasma CMV DNA was 70%, 63%, and 68% for the 400 mg, 800 mg, and 1200 mg BID dose groups, respectively, within 6 weeks. The proportion of subjects with undetectable plasma CMV DNA was 70%, 65%, and 75% for the 400 mg, 800 mg, and 1200 mg BID dose groups, respectively, within 12 weeks. 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.

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 the investigator assigned treatment 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.

For the proposed trial, 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.

Primary Efficacy Endpoint:

The primary efficacy endpoint (a binary response) for the study is confirmed clearance of plasma CMV DNA (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 during the treatment period, the subject must have received exclusively study-assigned treatments.

Confirmed CMV viremia clearance at the end of Study Week 8 (Visit10) 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 examples table below).

Assessments of Virological Responders at Study Week 8

Scenari	CMV DNA Weeks on Study				Response	Rationale
	Week 6	Week 7	Week 8	Week 9*		
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 starting alternative anti-CMV treatment, withdrawal from study, etc.

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

Note: 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, prior to the start 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 (CMV viremia clearance) =2 consecutive post baseline assessments of CMV DNA target <LLOQ, separated by at least 5 days.

Statistical Methodology for Primary Efficacy Endpoint:

The difference in proportion of subjects with confirmed CMV viremia clearance, at the end of Study Week 8, between treatment groups (maribavir and investigator's choice of anti-CMV treatment) will be obtained using Cochran-Mantel-Haenszel (CMH) weighted average across all strata, and assessed using CMH test with transplant type and baseline plasma CMV DNA concentration as 2 stratification factors. The baseline plasma CMV DNA levels will be the last central laboratory assessment before the first dose of study treatment. If the p-value from the CMH test is $\leqslant 0.05$ and the proportion of response from maribavir is higher, it will be concluded that maribavir is more efficacious compared to the control group.

Subjects in the investigator-assigned treatment arm who are unable to continue taking investigator-assigned anti-CMV treatment due to the lack of 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. Subjects who take rescue medication will be considered as failures for primary efficacy analyses. 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. The same is applicable for patients who might be discontinued from maribavir treatment due to intolerance. Subjects who discontinue due to intolerance and without viremia clearance at Study Week 8 will be considered failures in both treatment arms.

Key Secondary Endpoint:

The key secondary endpoint of this study is:

- Achievement of CMV viremia clearance and resolution or improvement of symptomatic CMV infection (tissue invasive CMV disease or CMV syndrome (in SOT subjects only) 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 (resolution or improvement of tissue invasive disease or CMV syndrome for symptomatic subjects at baseline, or no new symptoms for subjects asymptomatic at baseline) to be declared at the end of Study Week 8, and maintenance of such effect through Week 16, the subject must have received exclusively a study-assigned treatment.

The investigator will perform the initial diagnosis of tissue-invasive CMV disease or CMV syndrome (absence or presence) 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 through the study. All investigator-assessed cases of tissue invasive CMV disease and CMV syndrome will be reviewed and adjudicated by an independent 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).

Endpoint Adjudication Committee adjudicated tissue invasive CMV disease and CMV syndrome will be used for the efficacy analyses.

Statistical Methodology for Key Secondary Endpoint:

The key secondary endpoint will be analyzed using the same approach as the primary endpoint.

Multiplicity adjustment:

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 α=5% level. The testing will be done in the order of primary efficacy endpoint, and the key secondary endpoint. First, the primary endpoint analysis

(CMV viremia clearance at Week 8) will be assessed at α=0.05. If and only after this is statistically significant, the key secondary endpoint of response based on maintaining CMV viremia clearance and resolution or improvement/no new development in symptoms at the end weeks of study through Follow-up Week 16 will be assessed at α=0.05. If this is statistically significant, it will be concluded that effect of maribavir is more sustainable compared to the control group at Follow-up Week 16 (ie, 8 weeks off treatment).

Subgroup Analyses:

Analyses for the primary and key secondary endpoints will be conducted for the following subgroups (inclusive, but not limited to):

- Subjects symptomatic at baseline
- SOT/HSCT recipients
- CMV DNA concentration levels (high, medium, low)
- Resistant (yes/no)
- Adolescents ⩾12 to <18 years of age (exploratory analysis: may be conducted if sample size is adequate)

The secondary efficacy endpoints of this study are as follows:

- The achievement of the confirmed CMV viremia clearance after 8 weeks of receiving study-assigned treatment.
- The achievement of the confirmed CMV viremia clearance and CMV infection symptom control after receiving 8 weeks of study-assigned treatment, followed by maintenance of this treatment effect through study weeks 12 (4 weeks post-treatment period), 16 (8 weeks post treatment/follow-up phase), and 20 (12 weeks post treatment).
- The maintenance of the CMV viremia clearance, and CMV infection symptom control, at the end of Study Week 8, through Weeks 12, and 20, regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy.
- The recurrence of CMV viremia during the first 8 weeks of the study, in the follow-up period of 12 weeks, and at any time during the 20 weeks of the study, regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy.
- The recurrence of CMV viremia during study-assigned treatment and in the follow-up after the subject is discontinued from study-assigned treatment.
- The maribavir CMV resistance profile.
- All causes mortality by the end of the study (Visit 18/Week 20 [Follow-up Week 12]).

The secondary efficacy endpoints assessed for the maribavir rescue treatment arm are as follows:

- The clearance of plasma CMV DNA at the end of 8 weeks after starting maribavir rescue treatment.
- Achievement of viremia clearance at the end of 8 weeks after starting maribavir rescue treatment and resolution or improvement of tissue invasive CMV disease or CMV syndrome for subjects who are symptomatic at the start of maribavir treatment or subjects who are asymptomatic at the start of maribavir treatment remain symptom free, followed by maintenance of the treatment effect for an additional 8 weeks when off maribavir rescue treatment (as evidenced by sustained clearance of viremia and improvement or resolution of tissue invasive CMV disease or CMV syndrome and no new tissue invasive CMV disease or CMV syndrome development between end of treatment and up to Week 16).

The exploratory efficacy endpoints are as follows:

[redacted]

Pharmacokinetic endpoints for maribavir treatment and maribavir rescue treatment are as follows:

Secondary endpoint:

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

Exploratory endpoints:

[redacted]

Safety endpoints and analysis:

The safety analyses will include evaluation and procedures to meet the secondary objective of assessing the safety and tolerability of maribavir.

Safety evaluation will be made during the periods as illustrated in the Study Design Flow Chart, ie, screening phase, treatment phase, and follow-up phase.

Two observation periods are defined for the purpose of analyses:

- 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 if cidofovir is used. For subjects who transfer from the study treatment to either maribavir rescue or to a nonstudy CMV treatment, the on treatment observation period starts at the time of the study treatment initiation through 7 days after the last dose of study treatment (or through 21

days if cidofovir is used), or until the maribavir rescue treatment initiation or until the nonstudy CMV treatment initiation, whichever is earlier. This will serve as the primary analysis of safety.

- The overall-study observation period minus the period on rescue arm starts at the time of study treatment start through the end of the study. For subjects who receive maribavir rescue therapy, the overall-study observation period minus the period on rescue arm starts at the time of study treatment start through the time before receiving maribavir rescue therapy.

Similar observation periods are defined for the safety analysis of the maribavir rescue arm. The events 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.

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

Safety endpoints will be summarized descriptively for the on treatment period, and overall-study period, as appropriate. Baseline assessments will be the last assessment before the first dose of study treatment. The safety set will be used to analyze the safety data. Summary of all safety analyses will be provided separately for the maribavir rescue arm.

The safety endpoints include the following:

- TEAEs and treatment-emergent serious adverse events (SAEs), overall study AEs and overall study SAEs
- Clinical laboratory evaluations

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

The number of events, incidence, and percentage of TEAEs and overall-study AEs will be displayed for each treatment group by system organ class (SOC) and by Preferred Terms using the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries in terms of severity and relationship to study medication will also be provided. Treatment-emergent SAEs will be summarized separately in a similar fashion. Summaries of AEs causing discontinuation of study medication, withdrawals, AEs leading to death, SAEs, and adverse events of special interest (AESI) will be provided.

Adverse events of special interest, eg, tissue invasive CMV disease, dysgeusia, events of nausea, vomiting, and diarrhea, neutropenia, increased immunosuppressant drug concentration levels, graft rejection, opportunistic infections, and GVHD will be analyzed according to primary System Organ Classes (SOCs) and Preferred Terms (PTs). Additional grading of events of special interest will be applicable. Summary tables with SOCs and PTs will be generated presenting the number and percentage of subjects by AE, severity, seriousness, and relationship to study medication.

Usage of concomitant medications will be summarized descriptively for each of the treatment groups and the maribavir rescue treatment group for the on treatment period and overall-study period. Treatment of hemopoietic growth factors, blood and blood transfusion products will be summarized separately.

Change from baseline in vital signs and clinical laboratory tests will be summarized for each treatment group with descriptive statistics at each assessment visit. Summary and shift tables will be produced for selected laboratory parameters based on National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE v4.0)

Abnormal physical examination findings will be listed.

Summary of electrocardiogram (ECG) findings will be provided by treatment groups.

An independent data monitoring committee (DMC) will be established to assess the data for safety and to ensure the validity and scientific merit of the trial. Detailed plans for the DMC's purpose and responsibilities will be described in the DMC charter and the statistical analysis plan.

STUDY SCHEDULES

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**	**0[c]/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
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	X	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**	**0[c]/0R**	**4/4R**	**7/7R**	**14/14R**	**21/21R**	**28/28R**	**35/35R**	**42/42R**	**49/49R**	**56/56R**
Technology[q]											
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
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

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**	**0[c]/0R**	**4/4R**	**7/7R**	**14/14R**	**21/21R**	**28/28R**	**35/35R**	**42/42R**	**49/49R**	**56/56R**

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 (Section 5.1).

[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 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]

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**	**0[c]/0R**	**4/4R**	**7/7R**	**14/14R**	**21/21R**	**28/28R**	**35/35R**	**42/42R**	**49/49R**	**56/56R**

[n] If the subject is receiving immunosuppressant drugs (cyclosporine, tacrolimus, sirolimus, or everolimus), as mentioned in 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.

[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, 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 premorning dose PK sample); at Visit 10/Week 8 (one premorning 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 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 investigational product will be documented on the CRFs and/or other investigational product 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 investigational product 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. [redacted] . 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

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**	**0[c]/0R**	**4/4R**	**7/7R**	**14/14R**	**21/21R**	**28/28R**	**35/35R**	**42/42R**	**49/49R**	**56/56R**

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[e]	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
[redacted]				X		X		X
[redacted]	X	X	X	X	X	X	X	X
[redacted]								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]								
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

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").

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

[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 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.

[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 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

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)

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.

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Cytomegalovirus (CMV) is a beta herpesvirus that commonly infects humans; serologic evidence of prior infection can be found in 40-100% of various adult populations (de la Hoz et al., 2002). However, serious disease occurs almost exclusively in individuals with compromised immune systems. Cytomegalovirus remains a significant problem for patients undergoing various types of transplants that are associated with the use of potent immunosuppressive chemotherapy, including hematopoietic stem cell transplants (HSCT) and solid organ transplants (SOT) (de la Hoz et al., 2002; Razonable and Emery, 2004).

In addition to the direct effects that manifest as CMV organ disease or symptomatic infection, CMV also is known to have several potential indirect effects. These indirect effects include an increased incidence of opportunistic infections, an association between CMV and graft-versus-host disease (GVHD) predominately in HSCT patients, and associations between CMV and graft rejection or other allograft pathology in SOT patients, and reduced patient survival (Rubin, 1989; Hodson et al., 2005; Ljungman et al., 2006). Such organ-specific associations with CMV include bronchiolitis obliterans in lung recipients, vanishing bile duct syndrome in liver recipients, accelerated transplant vasculopathy in heart recipients and transplant glomerulopathy, transplant renal artery stenosis or increased risk of transplant rejection (Razonable and Emery, 2004; Legendre and Pascual, 2008; Richardson et al., 1981; Pouria et al., 1998; Farrugia and Schwab, 1992). These effects are believed to be mediated by the virus's ability to modulate the immune system, either directly or secondary to the host antiviral response through regulation of cytokine, chemokine, and/or growth factor production.

Cytomegalovirus prevention strategies (prophylaxis or preemptive therapy) for various high-risk transplant subjects exist, however, CMV infection or disease can still occur within the early (initial ~3 months) or later post-transplantation time periods (Boeckh et al., 2003; Legendre and Pascual, 2008). Cytomegalovirus viremia is considered one of the most important predictors of development of CMV disease (Emery et al., 2000; Humar et al., 1999). In kidney transplant recipients, the highest incidence of symptomatic CMV infection (syndrome) or disease occurs in CMV-seronegative recipients who receive a kidney from a CMV-seropositive donor (D+/R-) (Paya et al., 1989; Kanj et al., 1996; Singh et al., 2004; Winston et al., 1995).

Although the currently available systemic anti-CMV agents, intravenous (IV) or oral ganciclovir, oral valganciclovir (a prodrug of ganciclovir with improved bioavailability), IV foscarnet, and IV cidofovir are generally effective, their use is limited by their respective toxicities; bone marrow suppression caused by ganciclovir/valganciclovir and renal impairment caused by foscarnet or cidofovir (Boeckh et al., 2003; Ljungman et al., 2001; Reusser et al., 2002; Salzberger et al., 1997). These toxicities are of particular concern in transplant patients, in whom the bone marrow has been ablated or significantly suppressed (HSCT patients), who receive ongoing immunosuppressants to prevent organ rejection (SOT patients) or GVHD (in HSCT patients), or who may require the use of other therapies that are potentially toxic to the kidneys or other organs (SOT and HSCT patients).

Development of anti-viral resistance to currently available anti-CMV agents is also an ongoing clinical problem in solid organ and stem cell transplantation leading to graft loss and even mortality for some transplant patients. As described by Limaye et al., 2000, ganciclovir resistance developed in 7% D+/R- kidney, liver, and pancreas recipients who were prophylaxed with 3 months of oral ganciclovir. Ganciclovir-resistant disease accounted for 20% of CMV disease, occurred late (a median of 10 months after transplantation), was associated with higher intensity of immunosuppression, and was considered a clinically serious concern (Avery, 2007).

There are no approved therapies for the treatment of CMV infection or CMV disease in transplant recipients, and no approved treatment for CMV infection or disease that is resistant or refractory to currently available therapies in any population. Maribavir is currently under development for the treatment of CMV infection or disease, including those resistant or refractory to ganciclovir, valganciclovir, foscarnet, or cidofovir, in transplant recipients.

1.2 Product Background and Clinical Information

Maribavir is a potent and selective, orally bioavailable antiviral drug with a novel mechanism of action against CMV (Chulay et al., 1999) and a favorable nonclinical and clinical safety profile. It is a potent member of a new class of drugs, the benzimidazole ribosides (Williams et al., 2003). In side-by-side in vitro assays it is 3- to 20-fold more potent than ganciclovir and cidofovir, and at least 100-fold more potent than foscarnet (Biron et al., 2002; Drew et al., 2006). Unlike currently available anti-CMV agents that inhibit CMV deoxyribonucleic acid (DNA) polymerase, maribavir inhibits the CMV UL97 serine/threonine kinase by competitively inhibiting the binding of adenosine triphosphate (ATP) to the kinase ATP-binding site (Biron et al., 2002; Williams et al., 2003; Krosky et al., 2003; Wolf et al., 2001; Kern et al., 2004); the dominant phenotypic inhibitory effect of maribavir is on viral DNA assembly and egress of viral capsids from the nucleus of infected cells (Biron et al., 2002). Except for ganciclovir, maribavir does not antagonize the effects of other anti-viral (anti-CMV) agents. Since ganciclovir is dependent on its initial phosphorylation by the viral UL97 kinase, maribavir may antagonize its clinical efficacy. Maribavir is active in vitro against strains of CMV that are resistant to ganciclovir, foscarnet, or cidofovir.

1.2.1 Pharmacokinetics, metabolism, and drug-drug interactions

Results from the Phase 1 studies demonstrated that following oral administration, maribavir was rapidly and well absorbed with mean peak plasma concentrations generally achieved between 1 and 3 hours post dose. After administration of single and multiple doses (both twice daily [BID] and 3 times daily [TID] regimens) over 28 days, total maribavir plasma concentrations increased with increasing dose proportionally up to 900 mg. At dose levels $\geqslant$900 mg BID, there was no apparent increase in maximum observed plasma concentration (C_{max}) levels, and above this level, the increase in area under the plasma concentration versus time curve (AUC) may be less than dose proportional. Maribavir demonstrates time-independent pharmacokinetics (PK). Pharmacokinetic data obtained in Phase 2 studies were similar to the data observed in healthy volunteers.

Administration of maribavir in conjunction with food resulted in a 28% decrease in C_{max} without a significant effect on AUC when compared to administration under fasting conditions.

Bioavailability of a 100 mg tablet was unaffected by crushing the tablet or changes in gastric pH. Maribavir was bound to plasma proteins, namely human serum albumin (HSA), lipoproteins, and alpha-1-1acid-glycoprotein (AAG). The fraction of unbound maribavir was estimated at approximately 1.5% in healthy subjects and 0.96% in transplant patients. The apparent plasma elimination half-life for unchanged maribavir was approximately 5-7 hours. Maribavir is metabolized primarily in the liver through CYP3A4 pathway with the formation of the primary metabolite, VP44469. Renal clearance is a minor route of elimination of maribavir.

A mass balance study in healthy male and female subjects following administration of a single 400 mg oral dose of [^{14}C] maribavir resulted in fecal recovery of radiolabel that averaged about 14% and recovery of radiolabel in the urine that averaged about 61%. In plasma, the predominant drug-related species was unchanged maribavir, representing approximately 65% of total radioactivity and VP 44469 represented approximately 9% of urine and feces. The apparent plasma elimination half-lives for total radioactivity and unchanged maribavir were approximately 66 and 7 hours, respectively.

In vitro studies indicated that CYP 3A4 (a hepatic metabolizing enzyme) is the primary enzyme involved in the formation of VP 44469 from maribavir; CYP 2C19 and CYP 1A2 may also be involved in VP 44469 formation. Based on an in vitro study, UGT1A1, UGT1A3, UGT2B7, and possibly UGT1A9 were involved in the glucuronidation of maribavir however intrinsic clearance was too low to be quantified. These data suggests the contribution of glucuronidation to the overall clearance of maribavir is considered to be low and the potential for maribavir as the victim of drug interactions when coadministered with UGT inhibitors/inducers is expected to be low. In vitro studies also demonstrated that maribavir is not an inhibitor of CYP3A4, CYP2A6, CYP2B6, CYP2C8, CYP2D6, or CYP2E1. It is potentially a weak inhibitor of CYP 1A2, 2C9, and 2C19. VP 44469 is not an inhibitor of CYP enzymes. Maribavir is a substrate as well as an inhibitor of P-glycoprotein with an IC50 of 33.7 µM (P-gp: a transporter protein). Maribavir is a weak inhibitor for UGT1A1, UGT1A3, UGT1A9, and UGT2B7 enzymes with IC50 values at 32.2µM, 184µM, 123µM, and 153 µM, respectively. Maribavir has no inhibitory effect on UGT1A4 and UGT1A6 at up to 500 µM.

Clinical studies conducted to evaluate the potential of drug-drug interactions demonstrated the following:

- Concomitant administration of maribavir (400 mg BID) with tacrolimus, a substrate of CYP 3A4 and P-gp, resulted in increased tacrolimus C_{max} and AUC by 38% and 51%, respectively.
- Maribavir did not have a clinically significant effect on the activity of CYP 1A2, CYP 3A, CYP 2C9, or CYP 2D6; however, it inhibited CYP2C19 activity (based on plasma omeprazole/5-OH omeprazole ratio). A follow-up clinical study indicated maribavir had no effect on the PK of voriconazole (a CYP2C19 substrate). Maribavir did not affect digoxin (a sensitive P-gp probe) AUC, however, it increased Cmax by 24.8%.
- Concurrent administration of rifampin, an inducer of CYP 3A4 and P-gp, and maribavir significantly reduced plasma concentrations of maribavir, resulting in a 61% reduction in AUC, reduced half-life, and significantly increased clearance, most likely due to

induction of hepatic and intestinal CYP 3A4, and possible enhancement of P-gp transport.

- Concomitant administration of antacid had no effect on maribavir exposure.
- Concomitant administration of ketoconazole increased maribavir AUC and C_{max} by 46% and 10%, respectively.

The effect of renal impairment on maribavir pharmacokinetic was evaluated in a single dose (400 mg) study with 12 subjects with normal renal function (creatinine clearance >80 mL/minute), 10 subjects with mild/moderate renal impairment (creatinine clearance 30-80 mL/minute), and 9 subjects with severe renal impairment (creatinine clearance <30 mL/minute). Mean pharmacokinetic parameter estimates based on total or unbound plasma drug concentrations for subjects with normal renal function, mild/moderate renal impairment, and severe renal impairment were similar. Based on the results from this study, renal impairment does not affect the PK of maribavir; dose adjustment for subjects with mild to severe renal impairment is not needed. There is no experience with the use of maribavir in subjects receiving peritoneal dialysis or hemodialysis. Due to the high plasma protein binding of maribavir, dialysis is unlikely to reduce plasma concentrations of maribavir significantly.

The effect of hepatic impairment on the pharmacokinetic of maribavir was evaluated in a single-dose study (200 mg) with 10 subjects with normal hepatic function and 10 subjects with moderate hepatic impairment based on a Child-Pugh Class B classification. Moderate hepatic impairment results in a modest increase in total plasma maribavir C_{max} and AUC values (and modestly reduced clearance values) when compared to subjects with normal hepatic function. However, C_{max} and AUC values based on unbound plasma concentrations of maribavir were comparable among these groups.

In Study 1263-200 (a Phase 2 study of maribavir for CMV prophylaxis), based on total drug concentrations in plasma, steady-state AUC values in HSCT recipients were 19-66% higher than AUC values in healthy subjects. This difference can be explained based on the differences in plasma protein binding in healthy subjects and transplant patients. In Study 1263-202 (SHP620-202), a Phase 2 study of maribavir for CMV treatment, the PK parameters (AUC and C_{max}) at 400 mg BID dose were comparable to that in the healthy subjects.

1.2.2 Efficacy

Once the safety and tolerability of maribavir was established across a wide range of doses (up to 2400 mg/day for 28 days) in 15 Phase 1 studies, the clinical development plan focused on maribavir as an anti-CMV agent for the prevention of CMV disease in transplant patients. Results from the Phase 3 trials for CMV prevention, where maribavir was administered at 100 mg BID for up to 12 weeks in HSCT recipients and up to 14 weeks in liver transplant recipients, failed to reduce the incidence of endpoint adjudication committee confirmed CMV disease within 6 months following HSCT when compared with placebo (Study 1263-300), and failed to show noninferiority to ganciclovir with respect to the incidence of endpoint adjudication committee confirmed CMV disease within 6 months following liver transplantation (Study 1263-301).

Maribavir was used for treatment of CMV infections in 6 transplant recipients (5 SOT, 1 HSCT) under individual emergency investigational new drug (EIND) applications in the United States (US) (Avery et al., 2010). All patients had previously been treated with multiple other anti-CMV drugs, and 4 out of 6 had known genotypic CMV resistance to 1 or more of those CMV drugs. For all 6 patients, oral maribavir treatment was initiated at a dose of 400 mg BID. In 2 patients, the dose was increased to 800 mg BID. The duration of treatment was individualized for each patient based on response. Maribavir appeared to be safe and well-tolerated, as it was administered for prolonged periods of time (4 out of 6 patients were dosed >6 months). Three patients reported 7 serious adverse events (SAEs), all of which were considered to be unrelated to maribavir.

Within 6 weeks of starting maribavir treatment, all subjects had a >1 log decrease in blood CMV DNA, and 4 of the 6 patients had no detectable CMV. Cytomegalovirus viremia persisted in 2 patients despite dosing >6 months; 1 of these patients had unusually low exposure to maribavir based on trough blood levels. The other patient in whom CMV viremia persisted had a very high baseline CMV DNA level. The genotypic analysis for this patient revealed the presence of UL97 maribavir-resistance mutations T409M and H411Y (Strasfeld et al., 2010).

Subsequently, in Europe, more than 200 patients received maribavir through a named patient program (NPP), and in France, through the authorized therapeutic-use procedure. Data from only a small subset of the French NPP were reported. These data were consistent with the US EIND experience. Additional details regarding these patients are available in the maribavir investigator's brochure.

The data obtained from the small number of patients in EIND and NPP, suggested that maribavir was associated with a reduction in CMV DNA in the blood in the majority of subjects, and could be a useful component for the treatment of CMV infections that are resistant or refractory to currently available anti-CMV therapies. As a result, two Phase 2 studies were conducted to assess the safety, tolerability, and anti-CMV activity of maribavir for treatment of CMV infections: Study SHP620-202 in transplant recipients with CMV infections or disease that are resistant or refractory to treatment with anti-CMV agents conducted in the US and Study 1263-203 (SHP620-203) in transplant recipients with wild-type CMV infections who do not have CMV organ disease (asymptomatic) conducted in Europe. In both these studies subjects received 1 of 3 dose strengths: 400, 800, or 1200 mg BID, and both studies demonstrated favorable anti-CMV activity for besides showing that was well-tolerated with no safety concerns at all doses evaluated.

The primary efficacy endpoint for Study SHP620-202 was confirmed undetectable plasma CMV DNA within the 6 weeks after starting study drug treatment, defined as 2 consecutive postbaseline, on treatment undetectable result (<200 copies/mL) separated by at least 5 days. Overall, 67% of subjects achieved confirmed undetectable plasma CMV DNA within 6 weeks. Among maribavir groups, there was no strong evidence of dose strength differentiation in the proportion of subjects achieving the endpoint. Among subjects with ⩾1 investigator-reported CMV genetic mutation associated with resistance to ganciclovir/valganciclovir or foscarnet at baseline, 43/71 (61%) achieved confirmed undetectable plasma CMV DNA within 6 weeks after starting treatment with maribavir.

Secondary efficacy endpoints for Study SHP620-202 included CMV recurrence, defined as achievement of undetectable plasma CMV DNA in at least 2 consecutive samples separated by at least 5 days at any time after Day 1, followed by detectable plasma CMV DNA in at least 2 consecutive samples separated by at least 5 days. Overall, 30/86 (35%) maribavir subjects had a CMV recurrence at any time during the study (Note: Percentage is based on the number of subjects achieving undetectable CMV DNA). Twenty-four of the 30 subjects had a CMV recurrence while on study drug. Thirteen of these 24 subjects developed UL97 mutations previously described to confer resistance to maribavir that were not present prior to study drug dosing. The remaining 6 maribavir subjects had a CMV recurrence after the end of treatment with study drug.

The primary efficacy endpoint for Study SHP620-203 was confirmed undetectable plasma CMV DNA within 3 and 6 weeks after starting study drug treatment, defined as 2 consecutive postbaseline, on treatment undetectable results (<200 copies/mL) separated by at least 5 days. The proportion of subjects with undetectable plasma CMV DNA within 3 and 6 weeks after starting study drug treatment was numerically higher in the maribavir group than the valganciclovir group. Among the 3 maribavir dose strength groups, there was no difference in the proportion of subjects achieving the endpoint. In the subgroup of subjects whose transplant type was HSCT, a numerically higher percentage of subjects in the overall maribavir group (75%) than the valganciclovir group (48%) achieved confirmed undetectable plasma CMV DNA within 6 weeks. Although the percentage of subjects with high baseline plasma CMV DNA (⩾ 10000 copies/mL) was similar between the overall maribavir and valganciclovir groups (34% vs. 33%), a numerically higher percentage of maribavir subjects (77%) achieved confirmed undetectable plasma CMV DNA within 6 weeks compared with valganciclovir (65%).

Secondary efficacy endpoints for Study SHP620-203 included CMV recurrence; this was assessed within 6 weeks after starting study drug treatment and within the study participation period. Overall, 22/98 (22%) maribavir subjects and 5/28 (18%) valganciclovir subjects experienced a CMV recurrence within the study participation period (Note: Percentages are based on the number of subjects achieving undetectable CMV DNA). Four of the 22 maribavir subjects recurred while on study drug (2 subjects each in the 400 mg BID and 800 mg BID groups). All 4 of these subjects developed UL97 mutations previously described to confer resistance to maribavir that were not present prior to study drug dosing. The remaining 18 maribavir subjects and all 5 valganciclovir subjects experienced a CMV recurrence after the end of study drug treatment.

Phase 3 registration trials are underway based on the results from these Phase 2 studies for CMV treatment.

1.2.3 Safety

Maribavir has been administered across a broad range of oral doses from 50-2400 mg/day. Clinical safety experience has been obtained from 15 Phase 1 studies in adult healthy volunteers, special populations (subjects with renal and hepatic impairment, and stable renal transplant recipients), and HIV-infected subjects. A definitive QT study demonstrated no clinically significant repolarization effect of maribavir administered orally at single doses of 100 mg and

1200 mg in healthy subjects. In addition, no other significant electrocardiographic effects of maribavir were found.

Maribavir had a favorable safety and tolerability profile in both the Phase 2 and Phase 3 trials for CMV prophylaxis. Adverse events (AEs) were most commonly associated with gastrointestinal (GI) disorders (eg, diarrhea, dysgeusia, nausea, and vomiting). These events were generally of mild or moderate intensity. There were no signals of clinically significant effects of maribavir on vital signs, ECG parameters, or laboratory findings in the studies conducted for CMV prophylaxis.

In both Phase 2 studies for treatment of CMV infection (Studies SHP620-202 and SHP620-203), subjects received maribavir at 1 of 3 dose strengths: 400, 800, or 1200 mg BID, and both studies demonstrated that maribavir was well-tolerated with no safety concerns at all doses evaluated. In Study SHP620-202, treatment-emergent AEs (TEAEs) that occurred were events already observed in previous studies (ie, dysgeusia, GI events, elevated immunosuppressant drug levels, and rash) and there were no additional safety concerns raised from this study. In Study SHP620-203, TEAEs that occurred at a higher frequency in maribavir subjects compared with valganciclovir were events already observed in previous studies with maribavir (ie, dysgeusia, GI events, and elevated immunosuppressant drug levels). Analyses of clinical laboratory, vital signs, and ECG data did not identify any clinically meaningful differences across the maribavir treatment groups.

Based on the Phase 2 CMV treatment and Phase 3 CMV prophylaxis studies, the adverse drug reactions (ADRs) associated with maribavir use are: abdominal pain, abdominal pain upper, decreased appetite, diarrhea, dizziness, dysgeusia, fatigue, headache, immunosuppressant drug level increased, nausea, and vomiting.

To date, maribavir has shown an overall favorable safety profile in placebo-controlled studies, open-label studies, and in studies that compared maribavir with other CMV therapies (ganciclovir, valganciclovir) for prophylaxis and for CMV treatment in HSCT and SOT patients. Treatment effect on viral load reduction (confirmed undetectable plasma CMV DNA: 67% of subjects within 6 weeks in Study SHP620-202; 60.5% of subjects in 3 weeks and 77.3% of subjects in 6 weeks in Study SHP620-203) seen in Phase 2 treatment studies coupled with acceptable safety and tolerability establish the positive benefit-risk profile and warrant further investigation of maribavir in the treatment of refractory CMV infections in transplant recipients.

Refer to the latest version of the maribavir investigator's brochure for the most detailed and most current information regarding the drug metabolism, pharmacokinetics, efficacy and safety of maribavir.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

The population of transplant recipients whose CMV infections are resistant or refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir, including the pediatric population, is a significant unmet medical need. There are limited treatment options for these patients and no anti-viral drugs specifically approved for this purpose. Strategies to treat resistant or refractory CMV infections include minimizing immunosuppression when possible; increasing the dose of, combining, or switching among the available anti-viral drugs (ie, ganciclovir/valganciclovir, foscarnet, cidofovir); and the use of adjunctive treatments as intravenous immunoglobulin (IVIg), cytomegalovirus immune globulin (CMV Ig), adoptive infusions of CMV-specific T-cells, altering the immune suppressive regimen to mTOR inhibitors (sirolimus and everolimus), use of medications such as leflunomide, and artesunate (Kotton et al., 2013; Nishihori et al., 2015). No robust data are available on the effectiveness of these strategies reinforcing the need for an effective anti-CMV agent.

Results from the Phase 2 study SHP620-202 support the safety, tolerability, and anti-viral activity of maribavir for the treatment of resistant or refractory CMV infections in transplant recipients. Study SHP620-202 was a multicenter, randomized, dose-ranging, parallel-group study of maribavir for the treatment of CMV infections that were resistant or refractory to treatment with ganciclovir, valganciclovir, or foscarnet in HSCT and SOT recipients. Study subjects were randomized in a 1:1:1 allocation ratio to receive oral maribavir at 1 of 3 dose strengths (400 mg BID, 800 mg BID, or 1200 mg BID) for up to 24 weeks. While there was no strong evidence of differentiation among the 3 maribavir dose strengths, all maribavir doses were similarly effective at clearing CMV viremia based on the proportion of subjects with confirmed undetectable plasma CMV DNA within 6 weeks after starting study drug treatment. Maribavir was also generally well-tolerated across the dose range studied; commonly reported adverse events, such as dysgeusia and gastrointestinal events (eg, nausea, vomiting, diarrhea), were consistent with the known maribavir safety profile.

This Phase 3 study is designed to further assess and demonstrate the efficacy and safety of maribavir, dosed at 400 mg BID, compared to investigator-assigned anti-CMV treatment (IAT) of choice for the treatment of CMV infections that are resistant or refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir in HSCT and SOT recipients.

2.2 Rationale for the Study Design

This study will assess the efficacy and safety of maribavir for the treatment of refractory CMV infections, including those with documented resistance to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir, on the basis of clearance of CMV viremia. Improvement or resolution of tissue invasive CMV disease and CMV syndrome will also be assessed as applicable. Based on published literature, ganciclovir-resistant disease accounted for 20% of CMV disease, occurred late (a median of 10 months after transplantation), was associated with higher intensity of immunosuppression, and is a clinically serious concern (Avery, 2007). As there are limited treatment alternatives and no anti-CMV agents specifically approved to treat

resistant or refractory CMV infections, treatment with maribavir may address the unmet medical need for this population.

Investigator assigned anti-CMV treatment with 1 or 2 of the 4 anti-CMV drugs (ganciclovir, valganciclovir, foscarnet, or cidofovir) with additional strategies when deemed necessary by investigator (eg, change in the dose of the anti-CMV drug, reduction of immunosuppressant, addition of IVIG or CMV Ig) is the active control group for this study. The subject on single or dual therapy with anti–CMV agents at the time of enrollment, may either change therapy at the time of randomization/treatment initiation or remain on the same therapy as the investigator assigned anti-CMV treatment, if randomized to this study arm. If the treatment was continued or started as 2 anti-CMV agents, withdrawal of 1 agent, while continuing the second one will be possible.

While there are no approved therapies for the treatment of CMV infections, and those that are resistant or refractory to currently available anti-CMV agents, published CMV treatment guidelines include recommendations for the treatment of such infections (Kotton et al., 2013).

In HSCT recipients, when CMV replication is detected above the predefined threshold during the monitoring of CMV infection, the pre-emptive treatment is generally given for a minimum of 2 weeks with further extension until CMV becomes undetectable. There is a difference in practice regarding the minimum duration of therapy. Valganciclovir (previously ganciclovir) is often used for pre-emptive therapy, although foscarnet can be used as well (Busca et al., 2007; Reusser et al., 2002). However, foscarnet is associated with nephrotoxicity, and requires intravenous hydration and frequent electrolyte monitoring (Reusser et al., 2002); cidofovir is used much less due to substantial side effects including nephrotoxicity and myelosuppression (Tomblyn et al., 2009). Ganciclovir or valganciclovir use is associated with bone marrow toxicities that specifically in the HSCT recipients are a considerable clinical issue. Although these agents are used widely they are not approved for the CMV treatment indication. Furthermore, the use of a comparator arm in the context of a pivotal Phase 3 trial will provide for a more rigorous interpretation of virologic response to maribavir.

Study subjects will be randomized to receive either maribavir or investigator-assigned anti-CMV treatment for 8 weeks during the study treatment phase. In the SHP620-202 study (HSCT and SOT recipients with resistant or refractory CMV infections), the majority of maribavir subjects achieved confirmed undetectable plasma CMV DNA levels by Week 6 of study drug treatment, while CMV recurrence occurred at rates not unexpected for a population with such an overwhelmingly severe illness and concurrent lack of host immune responsiveness. A fixed duration, 8-week treatment regimen, in this Phase 3 study will account for a longer duration of treatment need in patients of certain transplant types (ie, lung transplant) consistent with clinical practice as well as secondary prophylaxis of recurrence after achieving undetectable plasma CMV DNA levels; furthermore, in the context of a clinical trial, the 8-week treatment duration will allow to standardize the duration for measuring the primary efficacy endpoint.

While the currently available anti-CMV agents ganciclovir, valganciclovir, foscarnet, and cidofovir may be considered in clinical practice to treat refractory or resistant CMV infections, their use is limited by their respective toxicities, most notably bone marrow suppression caused

by ganciclovir/valganciclovir and nephrotoxicity caused by foscarnet or cidofovir. Such toxicities can also worsen existing bone marrow suppression associated with transplant related maintenance with immunosuppressive therapy. Recognizing such safety limitations as well situations where no treatment effect is observed, subjects randomized to investigator-assigned anti-CMV treatment will be afforded the opportunity to enter into a maribavir rescue arm (for 8 weeks of treatment) based on objective criteria relative to a lack of anti-CMV activity (impact on viremia) after a certain duration of therapy, with or without intolerance to their assigned treatment.

The clearance of CMV viremia (plasma CMV DNA clearance) is considered a surrogate marker that may correlate to direct clinical benefit for the treatment of CMV infection or disease. While no registration trials for the treatment of established CMV infection in transplant patients have been conducted the VICTOR study (Asberg et al., 2007) of IV ganciclovir versus oral valganciclovir for the treatment of CMV disease in SOT recipients demonstrated that clearance of CMV viremia was highly correlated with resolution of CMV disease. This correlation was further evidenced with the subsequent analysis of VICTOR study plasma samples using the COBAS® AmpliPrep/COBAS® TaqMan® CMV Test, a test calibrated to the World Health Organization International Standard for Human CMV for Nucleic Acid Amplification Techniques. These recent findings, together with the maribavir Phase 2 study results, support a primary efficacy endpoint weighted on the CMV viremia clearance to demonstrate the efficacy of maribavir for the treatment of resistant or refractory CMV infections. Clinicians consider CMV viremia clearance when evaluating the success of therapy hence the CMV plasma/blood monitoring protocols are employed in patients with high risk of CMV infection or reactivation of latent CMV infection, and information of the viral load guide the decision for the pre-emptive treatment in the absence of the symptomatic disease.

Primary endpoint based on CMV viremia clearance will be assessed at the end of Study Week 8 as on treatment clearance is the most relevant assessment to determine anti-viral treatment effect. Assessment of treatment effect durability will be measured as key secondary and secondary endpoints. Although important from the clinical stand point, recurrence of CMV DNA after treatment is more influenced by other factors such as host immune status, other comorbidities, immunosuppressive treatments for prevention of transplant rejection than by the effectiveness of the anti-CMV drug treatment. In addition, CMV viremia clearance and clinical benefit of maribavir on tissue invasive CMV disease or CMV syndrome improvement or resolution after 8 weeks of treatment and maintenance of this treatment effect through the study will be evaluated in subjects with tissue invasive CMV disease. As there are currently no approved therapies for the treatment of CMV infections in the pediatric transplant recipient population, this study will initiate the assessment of maribavir use in the pediatric population by enrolling adolescent subjects ⩾12 to <18 years of age.

2.3 Rationale for Dose Selection

Results from the Phase 2 studies SHP620-202 (HSCT and SOT recipients with resistant or refractory CMV infections) and SHP620-203 (HSCT and SOT recipients with asymptomatic CMV infection) demonstrated comparable efficacy across the 400 mg BID, 800 mg BID, and 1200 mg BID maribavir dose groups in the clearance of CMV viremia within up to 6 weeks after

starting study drug treatment. In study SHP620-202, however, a numerically higher CMV viremia clearance rate and lower CMV recurrence rate were observed for the 400 mg BID group compared to the 800 mg and 1200 mg BID groups. In both Phase 2 studies, the most common treatment-emergent adverse events (TEAEs) included dysgeusia, events of nausea, vomiting, and diarrhea, and elevated immunosuppressant drug concentration levels. There was a dose-dependence for dysgeusia and elevated immunosuppressant drug concentration levels. These findings (comparable efficacy and better safety profile with the 400 mg dose) support the further evaluation of 400 mg BID maribavir for the treatment of CMV.

Investigators will determine the anti-CMV therapy best suited to treat the respective subject's CMV infection. Anti-CMV therapeutic strategies for this Phase 3 study will be limited to commercially available anti-viral (anti-CMV) agents, including ganciclovir, valganciclovir, foscarnet, and cidofovir that are utilized for treatment of patients in clinical practice. Subjects will be then randomly assigned (2:1) to either maribavir or investigator choice of treatment.

Currently available maribavir pharmacokinetics, PK modeling and extrapolation of systemic exposure from adults, and safety and tolerability data in adults support the administration of the 400 mg BID dose in adolescents who weigh ⩾35 kg and are able to swallow tablets. The expression of CYP3A4 and CYP 2C19, which are primary enzymes for maribavir metabolism in the liver, occurs during the first weeks of life (Lu and Rosenbaum, 2014). The expression of CYP1A2, which is also involved with maribavir metabolism, the last enzyme to develop, is present by 13 months of life. By 1 to 2 years of age, all the isoenzyme activities are similar to those of adults. Therefore, the bioavailability and systemic exposure of maribavir in adolescent subjects is not expected to be different from adults at the same oral dose.

2.4 Study Objectives

2.4.1 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.

2.4.2 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 tissue-invasive CMV 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).

2.4.3 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, (4 weeks post-treatment period), 16 (8 weeks post-treatment/follow-up phase), and 20 (12 weeks post-treatment).

- To assess the 2 study treatment arms for 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 (4 weeks of post treatment period), and 20 (12 weeks post treatment).
- 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.

2.4.4 Exploratory Objectives

The exploratory objectives of this study are:

[redacted]

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of maribavir treatment compared to investigator-assigned anti-CMV treatment in HSCT and 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 in the randomization. Results from the same laboratory and same sample type (whole blood or plasma) must be used for these assessments. The current CMV infection must be refractory to 1 or more of the available anti-CMV agents (ganciclovir, valganciclovir, foscarnet, or cidofovir) and the subject 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 a 14 day 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 a 14 day 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 the 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; these assessments will be based on the results from the central specialty laboratory and utilized for analysis. Subject enrollment will be monitored to achieve an approximate target of 60% of subjects who have a CMV infection with documented resistance to any of the anti-CMV agents (ganciclovir, valganciclovir, foscarnet, or cidofovir) according to the central specialty results from samples taken at baseline.

The subjects randomized to maribavir treatment arm will discontinue the 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. Addition of or switch to another anti-CMV agent will be declared as a failure for the purpose of study analysis. After randomization changes to the investigator treatment of choice could include, change in dosing, dosing regimen, but will not include an addition of or switch to another anti-CMV agent. Note that changes between 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 $\geqslant$273000 IU/mL in whole blood or $\geqslant$91000 IU/mL in plasma, intermediate viral load $\geqslant$27300 and <273000 IU/mL in whole blood or $\geqslant$9100 and <91000 IU/mL in plasma, and low viral load <27300 and $\geqslant$2730 IU/mL in whole blood or CMV DNA <9100 and $\geqslant$ 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 BID or investigator-assigned anti-CMV treatment for 8 weeks.

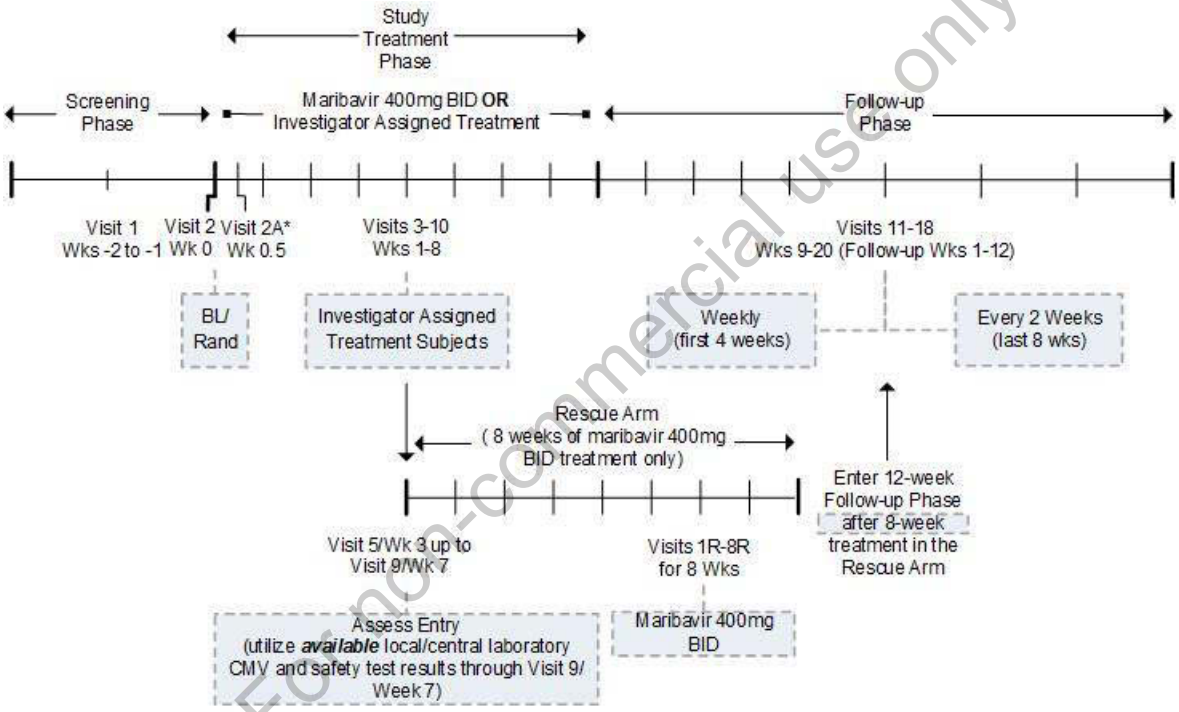
A cohort of subjects will have tissue-invasive CMV disease or CMV syndrome at baseline, as initially determined by the investigator (also referred as "***symptomatic subjects"***). Therefore, this study will also assess improvement or resolution of tissue-invasive CMV disease and CMV syndrome at the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

Figure 1: Study Design Flow Chart



*Visit 2A/A-R is only required for subjects taking tacrolimus, cyclosporine, everolimus, or sirolimus at Visit 2/2R.
BID=twice daily; BL=baseline; R=rescue; Rand=randomized; wks=weeks

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

Screening Phase

As presented in Schedule of Assessment 1, Table 1, 413 subjects will be screened for approximately 2 weeks to establish eligibility for study participation. All screening procedures will be completed within 14 days prior to initiation of study treatment, with the exception of the following:

1. Screening clinical laboratory tests (hematology, chemistry, and pregnancy) must be performed within 7 days prior to initiation of study treatment.

2. 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 or in 2 consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory quantitative polymerase chain reaction (PCR) or comparable quantitative CMV DNA results. The first sample must be available within 14 days prior to study enrollment (ie, start of study treatment) at Visit 2/Day 0. The second sample must be available within 5 days prior to the study enrollment. CMV DNA quantification may be performed by the local or central specialty laboratory. Already available results from the local laboratory (historical results) will be acceptable for screening, if taken within the time frames indicated and if from the same laboratory and same sample type (whole blood or plasma).

3. Historical results for human immunodeficiency virus (HIV) tests performed within 3 months prior to the study treatment initiation will be acceptable for screening. If no HIV test result within 3 months is available, the subject must have testing done locally during the screening period and have negative results available prior to randomization.

4. The investigator must identify the remaining treatment options available for the subject and must be willing to treat the subject with at least 1 of the available anti-CMV drugs.

All clinical laboratory results required for eligibility verification (screening) must be available prior to randomization.

Study Treatment Phase

Approximately 351 eligible subjects with refractory or resistant CMV infection will be stratified and then randomized in a 2:1 ratio at Visit 2/Day 0 to receive either maribavir or investigator-assigned anti-CMV treatment (collectively, the study treatment; 234 subjects [maribavir]: 117 subjects [investigator-assigned anti-CMV treatment]) for 8 weeks.

The screening and Visit 2/Week 0/Day 0 visits can occur on the same day if the historical laboratory results including CMV DNA quantification results, needed for evaluation of eligibility are available or results can be obtained the same day. All Visit 2/Day 0 procedures and screening laboratory results needed to confirm eligibility, including blood collection for CMV DNA quantification, hematology and chemistry analysis in the central laboratory, must be completed and documented prior to randomization and study treatment administration. Central laboratory results of CMV DNA quantification and genotyping, hematology and chemistry from samples taken at Visit 2/Day 0 will not be available for use for screening the patients. 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.

All subjects will perform study-specific evaluations weekly during the 8-week study treatment phase. Refer to Schedule of Assessment 1 (Table 1) for a complete list of the evaluations performed in the study treatment phase.

Subjects Randomized to Maribavir Treatment

Depending on the time of the first maribavir dose on Visit 2/Week 0/Day 0, a second dose should be administered on Visit 2/Day 0 provided that doses can be separated by a minimum of 8 hours; otherwise, only 1 dose should be administered on Visit 2/Day 0. Maribavir will then be administered (preferably) every 12 hours (q12h). When q12h dosing is not feasible, the doses should be separated by a minimum of 8 hours. Since 200 mg strength maribavir tablets will be utilized, subjects will be required to take 2 tablets of maribavir q12h as shown in Table 4. Subjects will take the maribavir 400 mg BID dose for the 8 weeks of the study treatment phase.

Subjects Randomized to Investigator-Assigned Anti-CMV Therapy

Investigator-assigned anti-CMV treatment strategies for the 8 weeks of the study treatment phase must only utilize up to 2 available anti-CMV agents from the following: ganciclovir, valganciclovir, foscarnet, or cidofovir. Combination therapy of cidofovir and foscarnet is prohibited due to the risk of nephrotoxicity.

If investigator's decision is to change the pre-study anti-CMV agent(s), the investigator can select up to 2 new anti-CMV drugs (ganciclovir, valganciclovir, foscarnet, cidofovir) as the study treatment.

Investigator may also decide to keep the subject on the same anti-CMV drug(s), which was/were used for treatment of subject prior to randomization/ treatment initiation.

If the treatment was continued or started as 2 anti-CMV agents, withdrawal of one agent, while continuing the second one will be possible. After randomization changes to the investigator treatment of choice could include, change in dosing, change in dosing regimen, but will not include an addition of or switch to another anti-CMV agent (other than changing between IV ganciclovir and oral valganciclovir).

Dose adjustment is allowed as deemed appropriate by the investigator. The rationale for dose adjustment will be documented; change to another anti-CMV agent during the study treatment period is not allowed. Investigational anti-CMV agents are not permitted. Additional treatment strategies can complement the use of a single anti-CMV agent, for example, reducing or modifying the immunosuppressant drug use or use of IVIg or CMV Ig.

Subjects will follow the investigator's prescribed anti-CMV treatment. Subjects will remain on their investigator-assigned anti-CMV therapy for the 8 weeks of the study treatment phase. Subjects may stop treatment at the discretion of the investigator, for lack of confirmed viremia clearance and/or intolerance to the assigned treatment. Subjects may be assessed for rescue arm eligibility at the investigator's discretion. Intolerance to assigned treatment without clear evidence of virologic and/or clinical failure will not qualify a patient for the rescue arm. Viremia clearance should be based on the results from the same laboratory used for randomization. Subjects may be assessed for entry into a rescue arm, starting at Visit 5/Week 3 (after a minimum 3 weeks of treatment), for treatment with maribavir 400 mg BID for 8 weeks. Subjects must meet 1 of the following criteria to be eligible to enter the maribavir rescue arm:

1. Subject has increased whole blood or plasma CMV viremia levels of ⩾1 $\log_{10}$ from baseline as measured by the local or central specialty laboratory qPCR assay (results from the same laboratory will be compared). Local specialty laboratory results must be documented.
2. Subjects with tissue invasive CMV disease must meet both criteria after being on treatment for at least 3 weeks:
   - Subject whole blood or plasma CMV DNA has decreased <1 log10 from baseline as measured by the local or specialty laboratory qPCR assay (results from the same laboratory will be compared). Local specialty laboratory results must be documented.
   - Symptomatic subject's presenting tissue invasive CMV disease did not improve, or worsened as assessed by the investigator OR subject who was asymptomatic at baseline developed tissue invasive CMV disease.
3. No CMV viremia clearance was achieved (results from the same laboratory will be assessed) necessitating continued anti-CMV treatment AND the subject has demonstrated intolerance to the investigator-assigned anti-CMV treatment as evidenced by 1 of the conditions:
   - Acute increase in serum creatinine, at least 50% increase from the baseline value, attributed to treatment (cidofovir, foscarnet) toxicity.
   - Development of hemorrhagic cystitis when on treatment with cidofovir or foscarnet.
   - Development of neutropenia (absolute neutrophil count ANC <500/mm^3 [0.5 x 10^9/L]) when on treatment with ganciclovir or valganciclovir.

Assessments based on local laboratory results must be documented.

The transition into the rescue arm will be allowed after the study medical monitor has reviewed the investigator's request and has approved the subject's eligibility for the rescue arm. Blood sample taken for CMV DNA test at the first visit of the maribavir rescue treatment period will be used as the 'baseline' assessment for the purpose of the analyses of the response to maribavir rescue treatment (including resistance analyses). Subjects who are unable to continue taking investigator-assigned anti-CMV treatment due to the lack of anti-viral activity and/or intolerance to the assigned treatment and do not meet the eligibility criteria to enter the maribavir rescue arm will be treated as deemed appropriate by the investigator.

The investigator may also choose to interrupt therapy for a maximum of 7 consecutive days, or up to 2 study treatment interruptions for a total of up to 7 days. This will not result in permanent study treatment discontinuation. If study drug is interrupted for any reason and subsequently resumed, the end of the study drug administration period would remain fixed at a maximum of 8 weeks after the date of the start of treatment.

All subjects will undergo study-specific evaluations weekly during the study treatment phase. Refer to Schedule of Assessment 1 (Table 1) for a complete list of the evaluations performed in

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

Subjects who prematurely discontinue study treatment and if in the investigator assigned anti-CMV treatment arm and not transferred to the maribavir rescue arm, will complete the end of treatment procedures described for Visit 10/Study Week 8 in the Schedule of Assessment 1; 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. The modified schedule of assessments through the remaining visits of study treatment phase will not include the use of the diary for study treatment compliance, dispense or use of any study treatment, and PK sample collection. The end of treatment sample for immunosuppressant drug concentration level will be collected at the next visit scheduled 1 week after the treatment discontinuation. After completing the 8-week duration specified for the study treatment phase, subjects will enter the 12-week follow-up phase.

Subjects who withdraw consent during the study treatment phase will be asked to undergo all end of treatment evaluations and procedures listed for Visit 10/Week 8; no further follow-up will be performed.

Further details regarding discontinuation of subjects are provided in Section 4.5.1.

Subjects who are transferred to maribavir rescue arm will be treated with maribavir for 8 weeks and will follow the procedures similar to subjects in the maribavir treatment arm, as indicated in the Schedule of Assessment 1 (Table 1; visits denoted with letter R). After the completion of 8 weeks of maribavir rescue treatment, subjects will enter the 12-week follow-up phase and will follow the procedures indicated in the Schedule of Assessment 2 (Table 2).

Follow-up Phase

Study-specific evaluations including central specialty laboratory CMV test and safety assessments will occur weekly for the first 4 weeks, then every 2 weeks for the final 8 weeks of the 12-week follow-up phase. Refer to Schedule of Assessment 2 (Table 2) for a complete list of evaluations. Subjects who withdraw from the study during the follow-up phase will undergo the end of study evaluations and procedures for Visit 18/Week 20 (Follow-up Week 12) as soon as possible, and whenever possible, prior to initiation of any nonstudy anti-CMV treatment (as deemed by the investigator); no further follow-up will be performed.

If the subject is unable to travel to the site for the follow-up visits, these visits may be on exceptional basis performed remotely (ie, at subjects' home) by a qualified sponsor or site designee, and only if permitted according to local regulations. Clinical laboratory assessments will be collected and all other follow-up assessments will be completed. Adverse events and SAE collection may be completed by telephone follow-up call on the day of the scheduled visit. It is recommended that the end of study visit be completed at the site if the subject is able to travel.

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 22 weeks (screening: up to 2 weeks; open-label phase: 8 weeks; follow-up phase: 12 weeks). Follow-up visits will occur weekly for the first 4 weeks (Weeks 9-12), followed by visits every 2 weeks for the last 8 weeks (Weeks 12-20) of this 12-week follow-up phase.

For subjects in the maribavir rescue arm the maximal duration of study will be 29 weeks, depending on the time of the transfer into the rescue arm.

The study will be completed in approximately 25 months. The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. This includes the follow-up visit or contact, whichever is later. The study completion date is used to ascertain timing for study results posting and reporting.

3.3 Sites and Regions

This is a multicenter study. Approximately 140 sites in North America, Europe, and Asia Pacific will participate.

4. STUDY POPULATION

Approximately 351 subjects, including adolescents ⩾12 to <18 years of age, who are transplant recipients (HSCT or SOT) with a current CMV infection that is refractory or resistant to treatment with commercially available anti-CMV agents (ie, ganciclovir, valganciclovir, foscarnet, or cidofovir) will be enrolled. Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

1. The subject must be able to provide written, personally signed, and dated informed consent to participate in the study before completing any study-related procedures. As applicable, a parent/both parents or legally authorized representative (LAR) must provide signature of informed consent and there must be documentation of assent by the subject before completing any study-related procedures.

2. The subject must be a recipient of hematopoietic stem cell or solid organ transplant.

3. The subject 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 results. Both samples should be taken within 14 days prior to randomization with second sample obtained within 5 days prior to randomization. The same laboratory and same sample type (whole blood or plasma) must be used for these assessments.

4. The subject must have a current CMV infection that is refractory to the most recently administered of the four anti-CMV treatment agents. Refractory is 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 a 14 day or longer treatment period with IV ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir.

    - Subjects with documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir must also meet the definition of refractory CMV infection.

5. The investigator must be willing to treat the subject with at least 1 of the available anti-CMV drugs (ganciclovir, valganciclovir, foscarnet, or cidofovir). Note: Combination therapy with foscarnet and cidofovir is **not permitted** in the IAT arm due to the potential for serious nephrotoxicity.

6. The subject must be ⩾12 years of age at the time of consent.

7. The subject must weigh ⩾35 kg.

8. The subject must have all of the following results as part of screening laboratory assessments (results from either the central laboratory or a local laboratory can be used for qualification):
    a. Absolute neutrophil count (ANC) ⩾1000/mm^3 [1.0 x 10^9/L]
    b. Platelet count ⩾25000/mm^3 [25 x 10^9/L]
    c. Hemoglobin ⩾8g/dL
    d. Estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2 as assessed by Modification of Diet in Renal Disease (MDRD) formula for subjects ⩾18 years of age or Schwartz formula for subjects <18 years of age (see Appendix 11 for the formulae)

9. The subject must have a negative serum β-human chorionic gonadotropin (β-HCG) pregnancy test at screening, if a female of child bearing potential. Additional urine pregnancy tests may be done per institutional requirements. Sexually active females of child bearing potential must agree to comply with any applicable contraceptive requirements of the protocol. If male, must agree to use an acceptable method of birth control, as defined in the protocol, during the study treatment administration period and for 90 days afterward if treated with maribavir, ganciclovir, valganciclovir, or cidofovir and for 180 days afterward if treated with foscarnet.

10. The subject must be able to swallow tablets, or receive tablets crushed and/or dispersed in water via a nasogastric or orogastric tube.

11. The subject must be willing and have an understanding and ability to fully comply with study procedures and restrictions defined in the protocol.

12. The subject must be willing to provide necessary samples (eg, biopsy) for the diagnosis of tissue invasive CMV disease at baseline as determined by the investigator.

13. The subject must have a life expectancy of ⩾8 weeks.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met.

Subjects must not:

1. Have a current CMV infection that is considered refractory or resistant due to inadequate adherence to prior anti-CMV treatment, to the best knowledge of the investigator

2. Require ganciclovir, valganciclovir, foscarnet, or cidofovir administration for conditions other than CMV when study treatment is initiated (example: herpes simplex virus (HSV) coinfection requiring use of any of these agents after the randomization) or would need a coadministration with maribavir for CMV infection. NOTE: A subject who is not continuing with the same anti-viral drug(s) (ganciclovir, valganciclovir, or foscarnet) for the study treatment (if randomized to the investigator assigned anti-CMV treatment arm), must

discontinue their use before the first dose of study drug. If subject is currently being treated with cidofovir and is assigned another anti-CMV therapy by the investigator, the subject must discontinue its use at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment.

3. Be receiving leflunomide, letermovir, or artesunate when study treatment is initiated. NOTE: Subjects receiving leflunomide must discontinue the use at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment. Subjects receiving letermovir must discontinue use at least 3 days prior to the first dose of study treatment. Subjects receiving artesunate must discontinue the use prior to the first dose of study treatment.

4. Have severe vomiting, diarrhea, or other severe gastrointestinal illness within 24 hours prior to the first dose of study treatment that would preclude administration of oral/enteral medication.

5. Have known hypersensitivity to the active substance or to an excipient for a study treatment.

6. Have tissue invasive CMV disease with central nervous system involvement, including the retina (eg CMV retinitis).

7. Have serum aspartate aminotransferase (AST) >5 times upper limit of normal (ULN) at screening, or serum alanine aminotransferase (ALT) >5 times ULN at screening, or total bilirubin ⩾3.0 x ULN at screening (except for documented Gilbert's syndrome), by local or central lab. Note: Subjects with biopsy confirmed CMV hepatitis will not be excluded from study participation despite AST or ALT >5 times ULN at screening.

8. Have known positive results for human immunodeficiency virus (HIV). Subjects must have a confirmed negative HIV test result within 3 months of study entry or, if unavailable, be tested by a local laboratory during the screening period.

9. Require mechanical ventilation or vasopressors for hemodynamic support at the time of enrollment.

10. Be female and pregnant or breast feeding.

11. Have previously received maribavir.

12. Have received any investigational agent with known anti-CMV activity within 30 days before initiation of study treatment or investigational CMV vaccine at any time.

13. Have received any unapproved agent or device within 30 days before initiation of study treatment.

14. Have active malignancy with the exception of nonmelanoma skin cancer. Subjects who have had a HSCT and who experience relapse or progression of the malignancy, as per investigator's opinion are not to be enrolled.

15. Be undergoing treatment for acute or chronic hepatitis C.

16. Have any clinically significant medical or surgical condition that in the investigator's opinion could interfere with the interpretation of study results, contraindicate the administration of the assigned study treatment, or compromise the safety or well-being of the subject.

4.3 Restrictions

There will be no special restrictions for subjects participating in this study. Subjects are to maintain their normal diets, medications (except those listed in Section 5.2.2), and activities of daily life as determined by the investigator.

4.4 Reproductive Potential

4.4.1 Female Contraception

There is no clinical experience with maribavir in pregnant subjects. The investigator assigned treatments (ganciclovir, valganciclovir, or cidofovir) have no clinical experience in pregnant subjects and based on the reproductive toxicity observed in animal studies should be considered a potential teratogen and carcinogen in humans (Valcyte Prescribing Information). The reproductive toxicity studies with foscarnet (Foscavir) in animals were conducted using exposures that are inadequate to define the potential of teratogenicity at levels to which women will be exposed (Foscavir Prescribing Information). All female subjects of child-bearing potential will be tested and should have negative serum β-human chorionic gonadotropin pregnancy test results prior to randomization. They must agree to abstain from sexual activity that could result in pregnancy or agree to use an acceptable method of contraception. Females of child-bearing potential must be advised to use acceptable contraceptives throughout the study period and for 90 days after the last dose of study treatment. If hormonal contraceptives are used they should be administered according to the package insert and in conjunction with another acceptable method of contraception. Females of child-bearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 90 days following the last dose of study treatment. Sexually active females of child-bearing potential should be using an acceptable form of highly effective method of contraception, as defined below.

Methods of contraception that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered ***highly effective*** birth control methods for females of child-bearing potential are presented below:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) or progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable [low user dependency]) stabilized for at least 30 days prior to the screening visit (Visit 1), plus condoms. Note: Since hormonal contraception may be susceptible to interaction with the study treatment(s) in the study, which may reduce the efficacy of the contraception method, this method must be supplemented with a barrier method (preferably male condom).

- Intrauterine devices (IUD, all types) or intrauterine hormone releasing systems (IUS) plus condoms. Note: contraception methods that in the context of the clinical trial facilitation group (CTFG) guidance are considered to have lower user dependency.
- Bilateral tubal occlusion.
- Vasectomized male partner is a highly effective birth control method provided that partner is the sole sexual partner of the female trial participant who is of child bearing potential and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Note: the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Female subjects 12 years of age and older, who are amenorrheic for reasons other than menopause (12 consecutive months of spontaneous amenorrhea in patients with previous normal menstruation), including subjects who did not yet have the menarche, would be allowed to participate provided they agree to abstinence or an acceptable form of contraception, as defined above.

Female subjects who are postmenopausal (12 consecutive months of spontaneous amenorrhea) or surgically sterile (having undergone 1 of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and are at least 6 weeks poststerilization do not need a pregnancy test performed prior to randomization and do not have to agree to the use of acceptable methods of contraception.

4.4.2 Male Contraception

Male subjects will be required to use a condom in conjunction with a highly effective method of birth control for their female partners of child-bearing age (described in Section 4.4.1). Both male participants and their female partners must use this form of birth control from the time prior to first dosing until 90 days after the last dose of study treatment (ie, maribavir, ganciclovir, valganciclovir, or cidofovir) or 180 days after the last dose, if treated with foscarnet. For male subjects, sexual intercourse with pregnant partners should also be avoided during the course of the study unless condoms are used from the time prior to the first dose until 90 days after the last dose of study treatment (ie, maribavir, ganciclovir, valganciclovir, or cidofovir) or 180 days after the last dose, if treated with foscarnet. Male subjects must not donate sperm until 90 days after the last dose of study treatment (ie, maribavir, ganciclovir, valganciclovir, or cidofovir) or 180 days after the last dose, if treated with foscarnet.

4.5 Discontinuation and/or Withdrawal of Subjects

A subject may withdraw (eg, withdraw consent) from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or the sponsor may withdraw the subject at any time (eg, in the interest of the subject's safety). The investigator is encouraged to discuss withdrawal of a subject from study treatment with the sponsor's medical monitor when possible. Subjects who withdraw consent during the study treatment phase will be asked to undergo all end of treatment evaluations and

procedures listed for Visit 10/Week 8, if they agree; subjects who withdraw from the study during the follow-up phase will undergo all end of study evaluations and procedures listed for Visit 18/Week 20 (Follow-up Week 12) as soon as possible and whenever possible, if they agree, prior to initiation of any nonstudy anti-CMV treatment (as deemed by the investigator); no further follow-up will be performed.

Subjects who prematurely discontinue study treatment and if in the investigator-assigned treatment and not transferred to the maribavir rescue arm, will complete the end of treatment procedures described for Visit 10/Study Week 8 in the Schedule of Assessment 1 (Table 1); 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. The modified schedule will exclude the use of the diary for study treatment compliance, dispense or use of any study treatment, and PK sample collection. The end of treatment sample for immunosuppressant drug concentration level will be collected at the next visit scheduled 1 week after the treatment discontinuation. During the period after the study treatment discontinuation and until the end of the study, subjects might be administered an anti-CMV treatment for lack of efficacy, recurrence of CMV viremia, or for worsening or new onset of CMV disease as deemed necessary by the investigator.

Subjects in the investigator-assigned anti-CMV treatment who cannot continue the treatment they have been randomized to and meet the criteria (see Section 3.1) to be transferred to maribavir rescue arm will complete the end of treatment evaluations listed for Visit 10/Week 8 prior to being transferred. Overlapping study procedures for Visit 2R/Week 0R do not need to be repeated when the end-of-treatment visit is performed on the same day as rescue arm entry. They will be treated with maribavir for 8 weeks and will follow the procedures in the manner similar to that followed by subjects in the maribavir treatment arm, as indicated in the Schedule of Assessment 1 (Table 1) (visits denoted with letter R). After the completion of 8 weeks of maribavir rescue treatment, subjects will enter the 12-week follow-up phase and will follow the procedures indicated in the Schedule of Assessment 2 (Table 2).

Subjects who withdraw consent during the study treatment phase will be asked to undergo all end of treatment evaluations and procedures listed for Visit 10/Week 8 as soon as possible, if they agree, prior to initiation of any nonstudy anti-CMV treatment for lack of efficacy, recurrence of CMV viremia, or for worsening or new onset of CMV disease (as deemed by the investigator). Subjects who withdraw consent during the follow-up phase will be asked to undergo all end of study evaluations and procedures listed for Visit 18/Week 20 as soon as possible, if they agree, prior to initiation of any nonstudy anti-CMV treatment (as deemed by the investigator). No further follow-up will be performed.

The reason for treatment discontinuation, study termination, date of stopping study treatment (maribavir or investigator-assigned anti-CMV treatment), and the total amount of study treatment taken will be recorded in the electronic diary, case report form (CRF), and source documents as appropriate.

Subjects who discontinue will not be replaced.

4.5.1 Reasons for Discontinuation and/or Withdrawal

The reason for study treatment discontinuation (maribavir or investigator-assigned anti-CMV treatment) and/or withdrawal from the study must be determined by the investigator and recorded in the subject's medical record and in the CRF. If a subject discontinues treatment or is withdrawn from the study for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered in the CRF.

Reasons for discontinuation include but are not limited to:

- Withdrawal of consent (by subject or by a parent or both parents/legal guardian for pediatric subjects)
- Adverse event (must specify on the CRF)
- CMV central nervous system (CNS) infection
  - Maribavir does not cross the blood-brain barrier. If a subject in the study develops CMV CNS infection (eg, meningo-encephalitis), then the subject will discontinue study treatment in order to be treated for this condition.
- Protocol deviation (eg, lack of compliance, use of experimental drug)
- Pregnancy
- Sponsor decision (must specify on the CRF)
- Death
- Lost to follow-up
- Lack of efficacy

Other (must specify on the CRF)

The end of study treatment and the end of study date for each subject (ie, the date of completion of the study or premature withdrawal from the study) will be recorded in the CRF.

4.5.2 Subjects 'Lost to Follow-up' Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT MEDICATIONS, THERAPIES, AND PROCEDURES

5.1 Prior Medications, Therapies, and Procedures

Prior treatment information must be recorded on the appropriate CRF page, and will include the following presented in Table 3.

Table 3: Prior Medications, Therapies, and Procedures

Time Period (Prior to Visit 2/Day 0)	***Category***	***Prior Medications, Therapies, and Procedures***
Medications/procedures administered/performed for transplant related reason from their start or **date of transplant** (whichever is first) to the first dose of study treatment on **Visit 2/Day 0**	*Induction Therapy for Transplant**	Including but not limited to: • Pre-transplant irradiation • Chemotherapy agents • Lymphocyte depleting and nondepleting therapies, including monoclonal, polyclonal, and anti-thymocyte globulin preparations
	*Anti-CMV Prophylaxis and Treatment**	Including, but not limited to: • Ganciclovir • Valganciclovir • Foscarnet • Cidofovir • CMV immune globulin (CCMV-GIV, Cytogam®) • Leflunomide • IVIG • Artesunate • CMV specific T-cell transfer (considered investigational) • Letermovir
All medications **within 3 months** prior to the first dose of study treatment on **Visit 2**/Week 0/**Day 0**	*Transplant maintenance, rejection treatment, and other adjuvant/related therapy*	Including, but not limited to: • Systemic steroids • Cyclosporine, tacrolimus, sirolimus, everolimus, mycophenolate • GVHD prophylaxis and treatment • Antirejection medications including T-cell depleting therapies • Photopheresis
	Hematopoietic Growth Factors	
	Blood or Blood Product Transfusions	
	Other Anti-Infective Agents	• Prophylaxis and/or treatment of viral, bacterial and fungal infections
Within **30 days or 5 half-lives** (whichever is longer)	*All Other*	• All other prescription medications • All other over-the-counter medications (OTC) • All herbal supplements**

Table 3: Prior Medications, Therapies, and Procedures

Time Period (Prior to Visit 2/Day 0)	*Category*	*Prior Medications, Therapies, and Procedures*
Any therapeutic or diagnostic intervention performed **within 30 days** prior to the first dose of study treatment on **Visit 2/Week 0/Day 0**		Including, but not limited to: • Biopsies (along with the results obtained) • Dialysis • X-rays, CT scans, MRI, ultrasound imaging (along with significant findings)

CMV=cytomegalovirus; GVHD=graft-versus-host-disease; HSV=herpes simplex virus; IVIg=intravenous immunoglobulin; VZV=varicella zoster virus; OTC=over-the-counter medications

*Subjects for whom transplant was performed >3 months from the time of screening limited (no dose data) information for induction therapy will be collected. Similarly for anti-CMV treatment data older than >3 month prior to screening will be recorded in more limited manner (dose prescribed, major interruptions, overall treatment duration).

****If half-life is unknown, report use within 30 days prior to study.**

5.2 Concomitant Medications, Treatments and Procedures

Concomitant treatment refers to all treatment (including medications) taken between the dates of the first dose of study treatment and the end of the follow-up phase, inclusive. A 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.

5.2.1 Permitted Treatment during the Study Drug Treatment

All concomitant treatment information must be recorded on the appropriate CRF page. Additional treatment strategies may complement the use of the study specified anti-CMV agents, eg, reducing or modifying the immunosuppressant drug use, or use of hemopoietic growth factors as needed for neutropenia.

Of note, changes in the net state of immunosuppression can influence response to treatment of CMV infection, so the reason for the change in immunosuppression with the date of change must be provided on the CRF. Note that the sample for the assessment of immunosuppressant agent concentration is included in the schedule of assessments as maribavir was found to impact the metabolism of some immunosuppressive agents. Any changes in immunosuppression regimens due to the concomitant administration with maribavir or other reasons must be recorded in the CRF.

Maribavir is specifically intended to treat human CMV infections. Maribavir is not active in vitro against most non CMV herpesvirus infections, including herpes simplex virus (HSV type 1 and type 2) and VZV. At baseline, investigators will assess subjects to determine whether prophylaxis for these viruses is appropriate according to institutional guidelines or standard practices. If considered appropriate, permitted medications to use for this purpose include systemic acyclovir, valacyclovir, or famciclovir. Choice of medication, dose, and duration of such therapy is at the discretion of the investigator based on a given subject's clinical condition

(eg, net state of immunosuppression, risk factors, and other medications). These medications (acyclovir, valacyclovir, or famciclovir) also can be used to treat any HSV or VZV infection that may occur during the study. Antifungal and antibacterial prophylactic medications will be allowed. Although potent inhibitors of CYP 3A4 (such as ketoconazole) could increase blood levels of maribavir, they are likely to be associated with minimal increased risk given the safety profile of maribavir demonstrated at up to 1200mg BID in Phase 2 studies.

The following concomitant medications should be taken with caution:

Maribavir has the potential to inhibit CYP2C19 and P-gp and therefore, may increase the concentration of drugs that are substrates of CYP2C19 and P-gp. For drugs with narrow therapeutic window, the increase in drug concentration may lead to toxicity. A drug interaction study showed that maribavir (400 mg BID) increased blood concentrations of tacrolimus (a substrate of CYP3A and P-gp) with C_{max} and AUC increased by 38% and 51%, respectively. Therefore monitoring tacrolimus (and other narrow therapeutic index immunosuppressants) blood concentration and tacrolimus-associated adverse events, and the appropriate dose adjustment of tacrolimus is recommended when maribavir and tacrolimus are used concomitantly. Conversely, after a period of coadministration, discontinuation of maribavir could lead to reduced blood levels of tacrolimus and potentially reduced therapeutic effect. Similarly, for drugs that are substrates of CYP2C19 or P-gp and have narrow therapeutic window, careful monitoring is recommended both after initiation of maribavir (when substrate levels may increase) and after discontinuation of maribavir (when substrate levels may decrease).

Although maribavir does not affect the activity of CYP3A enzyme nor other CYP enzymes other than CYP2C19 (including CYP1A2, CYP2B6, CYP 2C9, CYP2C8, CYP2D6, and CYP2E1), additional caution is needed when a patient receives other concomitant medications that affect cytochrome P450. For patients who receive concomitant medications that are inhibitors/inducers of CYP3A while on maribavir treatment, additional monitoring of immunosuppressant blood concentrations and immunosuppressant-associated adverse events may be needed within a few days after the start of concomitant medications or maribavir.

5.2.2 Prohibited Treatment

Concomitant use of the following medications/treatments is prohibited for all subjects *during the study*:

- Any unapproved agent or device.
- Any investigational anti-CMV agent, including receipt of CMV vaccine at any time prior to study.
- Infusion of T-cells specific for CMV or regulatory T-cells (Tregs) for the control of transplant tolerance, which is an experimental treatment.

Maribavir

Concomitant use of any of the following medications is prohibited while the subject is receiving ***maribavir***:

- Strong CYP 3A inducers: avasimibe, carbamazepine, phenytoin, rifampin, rifabutin, St. John's wort (*Hypericum perforatum)*
- Herbal medications known to have potential toxicities or drug interactions, eg, Ginkgo biloba or *Piper methysticum* (kava)
- Any of the following systemic anti-CMV therapies (except unintentional administration for no longer than 1 day):
    - Ganciclovir
    - Valganciclovir
    - Foscarnet
    - Cidofovir
    - Leflunomide
    - Artesunate
    - Letermovir

Except for ganciclovir/valganciclovir, maribavir does not antagonize the effects of other anti-viral (anti-CMV) agents. Maribavir inhibits the CMV UL97 serine/threonine kinase by competitively inhibiting the binding of adenosine triphosphate (ATP) to the kinase ATP-binding site. Since ganciclovir/valganciclovir is dependent on its initial phosphorylation by the viral UL97 kinase, maribavir may antagonize its clinical efficacy. Therefore, concomitant treatment with maribavir and ganciclovir/valganciclovir is not allowed.

Potent inducers of CYP 3A4 and/or P-gp (such as rifampin, rifabutin, or phenobarbital) could reduce blood levels of maribavir, potentially reducing its antiviral activity. Use of alternate agents with less enzyme induction potential should be considered during administration of maribavir.

In vivo drug interaction studies with Valcyte have not been performed. Since valganciclovir is extensively and rapidly metabolized to ganciclovir; drug interactions associated with ganciclovir will be expected for valganciclovir (Valcyte SmPC).

Maribavir does not cross the blood-brain barrier. If a subject in the maribavir treatment arm develops CMV central nervous system (CNS) infection (eg, meningo-encephalitis) then the subject will discontinue maribavir treatment in order to be treated for this condition. Subjects who develop new CMV retinitis while in the maribavir treatment arm may continue on therapy if the investigator does not intend to add another systemic or intraocular anti-CMV agent to treat the retinitis.

Administration of any of the prohibited treatments (except coadministration of foscarnet or cidofovir for indications other than CMV infection) will require discontinuation of maribavir (including the subjects in the maribavir rescue arm).

Investigator-assigned anti-CMV treatment strategies for the 8 weeks of the study treatment phase must only utilize available 1 or 2 anti-CMV agent from the following: ganciclovir, valganciclovir, foscarnet, or cidofovir. Dual agent therapy is allowed only if 1) the subject is on dual therapy prior to enrollment and this is continued as IAT during the treatment period or 2) if

dual therapy is initiated at the time of randomization. Addition of a second agent after randomization is not allowed. If on dual therapy, withdrawal of one of the two agents during the treatment phase is allowed. Dose adjustment for safety or efficacy will be allowed as deemed appropriate by the investigator. The rationale for dose adjustment will be documented; change to another anti-CMV agent during the study treatment period is not allowed (except for change from valganciclovir to ganciclovir, or vice versa).

Investigational anti-CMV agents are not permitted. Additional treatment strategies can complement the use of a single anti-CMV agent, for example, reducing or modifying the use of immunosuppressant drug or use of IVIg or CMV Ig.

Concomitant use of any of the following medications is prohibited while the subject is receiving ***investigator-assigned anti-CMV treatment*** (except unintentional administration for no longer than one day):

- Leflunomide
- Artesunate
- Letermovir

Investigator should refer to the Prescribing Information for ganciclovir, valganciclovir, foscarnet, and cidofovir for details on contraindication and precaution to ensure the appropriate use and monitoring of these drugs and concurrent medications. Addition of any of these treatments to the single investigator-assigned anti-CMV treatment strategy is not allowed during study treatment.

5.2.3 Treatments Taken During the Follow-up Phase

All permitted (Section 5.2.1) and prohibited medications (Section 5.2.2) specified for the study treatment phase are applicable to the follow-up phase; however, in case of no viremia clearance, presence of tissue invasive CMV disease, a CMV recurrence, appropriate medications required for CMV treatment may be administered in the follow-up phase as deemed necessary by the investigator. The secondary prophylaxis for subjects with viral clearance is not recommended in the follow-up phase. All medications will be recorded on the CRF.

6. IDENTITY OF STUDY TREATMENTS

The investigational product is maribavir (SHP620), which will be provided by the sponsor in 200 mg strength tablet form. Additional information is provided in the current maribavir investigator's brochure.

Investigator-assigned anti-CMV treatment will not be considered an investigational product in the context of this study. Study investigators will 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 investigator-assigned anti-CMV treatment arm may utilize 1 or 2 (only if the subject's current dual therapy at enrollment is continued after randomization or started at randomization) of the following 4 anti-CMV agents: (change from ganciclovir to valganciclovir or vice versa will be allowed):

- Ganciclovir
- Valganciclovir
- Foscarnet
- Cidofovir

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.

6.1 Blinding the Treatment Assignment

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

6.2 Administration of Investigational Product(s)

6.2.1 Interactive Response Technology for Investigational Product Management

An IRT (interactive response technology) will be employed in this study to manage the tracking and confirmation of shipment, supply, inventory, ordering, expiration, randomization, site-assignments of the investigational product, and accountability. The IRT provider will provide a user manual and training to each site, with detailed instruction on the use of the IRT.

6.2.2 Allocation of Subjects to Treatment

This is a randomized, open-label, active-controlled study. Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

All eligible subjects will first be stratified based on 2 factors:

1. By transplant type (HSCT or SOT)

2. By the most recent screening whole blood or plasma CMV DNA concentration categorized in to 3 CMV DNA concentration level groups based on local or central specialty laboratory qPCR results:

    - High viral load with CMV DNA ⩾273,000 IU/mL in whole blood or ⩾ 91,000 IU/mL in plasma, or
    - Intermediate viral load with CMV DNA ⩾27,300 and <273,000 IU/mL in whole blood or ⩾9,100 and <91,000 IU/mL in plasma, or
    - Low viral load with CMV DNA <27,300 and ⩾2,730 IU/mL in whole blood or <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 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.

Investigational product packaging identification numbers, separate from randomization numbers/unique identifiers, may also be assigned to subjects for specific treatment assignment as dictated by the study. In these cases, the same investigational product packing identification number may not be assigned to more than 1 subject.

6.2.3 Dosing

Initiation of study treatment, ie, the first dose administration, will occur at Visit 2/Week 0 on Day 0 after completion of all required assessments for that visit. The first dose should be administered under supervision of investigator site personnel, and be initiated as soon as possible after randomization. In cases where IV anti-CMV agents cannot be ordered, prepared, and administered immediately after randomization, the first dose of drug must be given within 24 hours of randomization.

Subjects Randomized to Maribavir Treatment

Depending on the time of the first maribavir dose on Visit 2/Day 0, a second dose should be administered on Visit 2/Day 0 provided that doses can be separated by a minimum of 8 hours; otherwise, only 1 dose should be administered on Visit 2/Day 0. Maribavir will then be administered (preferably) every 12 hours (q12h). When q12h dosing is not feasible, the doses should be separated by a minimum of 8 hours. Since 200 mg strength maribavir tablets will be utilized, subjects will be required to take 2 tablets of maribavir q12h as shown in Table 4.

Maribavir may be administered with or without food. Maribavir tablets may be administered crushed and/or dispersed in water via orogastric or nasogastric tube for a short period of time during the study treatment phase to avoid interruption or discontinuation of treatment. Consult the maribavir pharmacy manual for additional information.

Table 4: Maribavir Dosing Regimen

Regimen	AM	PM
400 mg BID	200 mg ×2 tablets	200 mg × 2 tablets

Duration of Dosing: Subjects will take the maribavir 400 mg BID dose for the 8 weeks of the study treatment phase.

The investigator may also choose to interrupt therapy for a maximum of 7 consecutive days, or up to 2 study treatment interruptions for a total of up to 7 days. This will not result in permanent study treatment discontinuation. If study drug is interrupted for any reason and subsequently resumed, the end of the study drug administration period would remain fixed at a maximum of 8 weeks after the date of the start of treatment. Subjects can be on the investigational studies of approved products, such as different prophylactic regimens for GVHD or other anti-infective agents. However, the use of investigational treatment is prohibited.

Subjects Randomized to Investigator-Assigned anti-CMV Treatment

Investigator-assigned anti-CMV treatment strategies for the 8 weeks of the study treatment phase must only utilize 1 or 2 of the available anti-CMV agent from the following: ganciclovir, valganciclovir, foscarnet, or cidofovir. The subject receiving 1 or 2 anti–CMV agents at the time of enrollment, may either change therapy at the time of randomization/treatment initiation or 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, 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 adjustment is allowed as deemed appropriate by the investigator. The rationale for dose adjustment will be documented; change of treatment to another anti-CMV agent or addition of another anti-CMV agent during the study treatment will be declared as treatment failure.

Subjects will follow the investigator's prescribed dosing regimen for their investigator's choice of anti-CMV treatment.

Investigational anti-CMV agents are not permitted. Subjects will remain on their assigned treatment for the 8 weeks of the study treatment phase. Subjects may be assessed, based on the eligibility criteria specified in Section 3.1, for entry into a rescue arm for treatment with maribavir 400 mg BID for up to 8 weeks.

The investigator may also choose to interrupt therapy for a maximum of 7 consecutive days, or up to 2 study treatment interruptions for a total of up to 7 days. This will not result in permanent study treatment discontinuation. If study drug is interrupted for any reason and subsequently resumed, the end of the study drug administration period would remain fixed at a maximum of 8 weeks after the date of the start of treatment.

Subjects who would require the treatment with 1 of the 4 available anti-CMV drugs in the dosages comparable or higher than used in the study for longer than 1 day, for indications other than CMV treatment (eg, foscarnet for other viral infections), would continue with assigned study treatment for 8 weeks per protocol. Concomitant treatment of ganciclovir/valganciclovir with maribavir is not allowed (see Section 5.2.2).

Additional treatment strategies can complement the use of maribavir treatment and the study specified anti-CMV agents, for example, reducing or modifying the immunosuppressant drug use if possible or use of IVIg or CMV Ig.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification are applied to the maribavir container. Study drug kits and individual bottles will be affixed with a label containing minimally the protocol number, study drug kit number, dosage form, storage conditions, the statements 'For clinical trial use only', and/or 'CAUTION: New Drug - Limited by Federal (US) Law to Investigational Use', and other information that may be required by the local laws.

Maribavir will be supplied as blue, film-coated, oval shaped convex tablets intended for oral administration. The tablet cores are composed of common compendial ingredients (Microcrystalline Cellulose, NF; Sodium Starch Glycolate, NF; and Magnesium Stearate, NF). The core tablet contains 200 mg maribavir and is coated with a blue standard Opadry II pharmaceutical coating.

Investigator-assigned anti-CMV treatment (ganciclovir, valganciclovir, foscarnet or cidofovir) will be prescribed by the investigator and either administered at the hospital or other facility used to administer IV products as per local site standard practice, or will be prescribed by the investigator and typically purchased by the study subject at the commercial pharmacy. This study protocol does not modify the treatment that the subject normally would have received regardless of his/her participation in the study. For feasibility reasons and because there is no modification to the treatment plan that the investigator would otherwise follow, if the patient was not enrolled

in the study, labeling of the investigator treatment of choice is not planned, unless required by country-specific regulations. The investigator assigned anti-CMV treatment will be chosen and prescribed by the investigator and typically purchased by the study subject at the commercial or hospital pharmacy, or will be administered at the hospital (in case of drugs that require IV administration, per local guidelines).

6.3.2 Packaging

The investigational product, maribavir, is packaged in 40-count white 60cc square HDPE bottles with child-resistant cap and foil induction seal.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Maribavir tablets will be stored at room temperature (15-30°C or 59-86°F). Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product (maribavir) to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section. An interactive response technology (IRT) will be used to manage subject randomization and the investigational product.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will dispense the investigational product (maribavir) only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given (if assigned to maribavir) or prescribed (if assigned to the investigator-assigned anti-CMV treatment) only the study treatment carrying his/her treatment assignment. The principal investigator must maintain accurate records of investigational products received, including dates of receipt, expiry, dispensing, and lot numbers. All dispensed or prescribed medication will be documented on the CRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all investigational product supplies from subjects. 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. Compliance will be collected in the subject's e-diary. The disposition of the unused supply of the dispensed investigational product and the prescribed investigator-assigned anti-CMV medication will be documented in the accountability log.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

With the written agreement of the sponsor, at the end of the study, or as instructed by the sponsor, all unused investigational product stock, subject-returned investigational product, and empty/used investigational product packaging will be returned to a sponsor specified designation. Should local, state or national laws prohibit the return of unused stock, subject returned investigational product, or empty/used investigational product packaging to the sponsor designated locations, it may be destroyed at the site or local facility once the sponsor has reviewed and approved the site's SOP. In this case, Certificates of Destruction (CoD) identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor.

Destruction of investigational products must be in accordance with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

For drug administration at the site, hospital staff or study personnel will administer all doses of study drug. Missed/incorrect doses will be recorded in the subject's electronic diary (e-diary) and CRF, as appropriate.

Investigator assigned anti-CMV treatments will be chosen and prescribed by the investigator, and will be either administered at the hospital or other facilities used to administer IV products, as per local site standard practice, or will be prescribed by the investigator and typically purchased by the study subject at the commercial or hospital pharmacy. For drug administration as outpatients, a study diary for tracking adherence to study drug dosing and an adequate supply of study drug will be dispensed for home use. Subjects must be instructed to bring their unused study drug, empty/used study treatment packaging, and the study diary to every visit. Drug accountability must be assessed at the container/packaging level for unused study drug that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging. Unused investigational product will not be redispensed. The pharmacist/nominated person will record details on the drug accountability form. Instructions will be provided in the pharmacy manual.

7. STUDY PROCEDURES

7.1 Study Schedule

See Table 1 for study procedures for the study treatment phase and Table 2 for study procedures for the follow-up phase.

7.1.1 Screening Period

Screening Visit (Visit 1/ Day -14 to Day 0/Week -2 to Week 0)

As specified in Table 1, the screening procedures will include:

- Informed consent
- Inclusion/Exclusion criteria (see Sections 4.1 and 4.2)
- Height and body weight (Section 7.2.3.2)
- Vital signs (Section 7.2.3.3)
- Medical history, including transplant history and CMV history
- Prior medication, including any prior anti-CMV medication used to treat the current CMV infection, therapies, and procedures (Section 5.1)
- HIV status: Historical results for human immunodeficiency virus (HIV) tests performed within 3 months prior to the study treatment initiation will be acceptable for screening. If no HIV test result within 3 months is available, the subject must have testing done locally during the screening period and have the results available prior to randomization (Exclusion Criterion 8)
- Hematology/Chemistry (Section 7.2.3.5)
- Serum pregnancy test for all females of child bearing potential (Inclusion Criterion 9; see Section 7.2.3.5). Additional urine pregnancy tests may be done per institutional requirements. Urine pregnancy test results are not sufficient for eligibility determination.
- Interactive response technology (IRT [IV/WRS]; Section 6.2.1)
- CMV DNA test (quantitation): Documentation of CMV infection in whole blood or plasma (with a screening value of ⩾910 IU/mL, in 2 consecutive samples separated by at least 1 day as determined by local or central specialty laboratory qPCR or comparable quantitative CMV DNA results with the first sample available within 14 days prior to randomization at Visit 2/Week 0/Day 0. The second sample must be taken within 5 days prior to randomization. Results from the same laboratory are to be used to assess subject eligibility criteria. The laboratory used for DNA quantification could be either local specialty laboratory or central specialty laboratory.

Available local specialty laboratory genotyping results from the plasma samples obtained within the screening period will be collected.

Informed consent must be obtained before any study specific procedures are performed. All screening procedures will be completed within 14 days prior to randomization, with the exception of following:

- At screening, either central or local laboratory results for CMV DNA quantification hematology/chemistry/pregnancy testing can be used for qualification.

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been randomized or administered study treatment. Screen failures due to low platelet count, hemoglobin, and low neutrophil counts or liver and renal parameters can be rescreened once within the 14 day screening period at the investigator's discretion when other inclusion criteria are fulfilled. Other screen failures may be rescreened in the future (with new informed consent and screening period) if their clinical course results in a change that deems them eligible for the trial.

The screening visit (Visit 1) and Visit 2/Week 0/Day 0 visits can occur on the same day.

7.1.2 Study Drug Administration Period

Visit 2/Week 0 (Baseline; Day 0) to Visit 10/Week 8 (End of Treatment)

Permissible assessment windows during the 8-week study treatment phase are: Study Visit 2A (Day 4) ± 1 day; Study Visit 3 (Day 7) +2 days; Study Weeks 2 to 4 ± 2 days; Study Weeks 5 to 8 ± 3 days.

As specified in Table 1 the following assessments will be performed during the study treatment phase:

- Randomization on Visit 2/Week 0 (Day 0; baseline)
- Physical examination (including weight) at Visit 2/Week 0, Visit 6/Week 4, and Visit 10/Week 8 (Section 7.2.3.2)
- Review of medical history and prior medication at Visit 2/Week 0 (Section 5.1)
- Weight at Visit 4/Week 2 and Visit 8/Week 6 (Section 7.2.3.2)
- Vital signs at Visit 2/Week 0, Visit 4/Week 2, Visit 6/Week 4, Visit 8/Week 6, and Visit 10/Week 8 (Section 7.2.3.3)
- 12-lead electrocardiogram (ECG) at Visit 2/Week 0, Visit 10/Week 8 (Section 7.2.3.4)
- Hematology/Chemistry at Visit 2/Week 0, Visit 4/Week 2, Visit 6/Week 4, Visit 8/Week 6, and Visit 10/Week 8; Potassium and magnesium at Visit 2A (Section 7.2.3.5)
- Urinalysis at Visit 2/Week 0, Visit 4/Week 2, Visit 6/Week 4, Visit 8/Week 6, and Visit 10/Week 8 (Section 7.2.3.5)
- Pregnancy test at Visit 2/Week 0, Visit 6/Week 4, Visit 10/Week 8 (Section 7.2.3.5)
- HBV and HCV test at Visit 2/Week 0
- CMV DNA test: Cytomegalovirus quantification in the plasma samples taken at each visit of

study treatment phase will be conducted at central specialty laboratory. Cytomegalovirus genotyping to assess for mutations in the UL97, UL27, and UL54 genes will be conducted only on the following samples: at baseline; from subjects with failure to attain CMV viremia clearance AND viral load above the predefined cut off (presented in the CMV resistance plan) taken at Study Weeks 4 and 8; and collected during recurrence or rebound of viremia at any time during the study treatment.

- Tissue invasive CMV disease and CMV syndrome assessment (see Appendix 3) at all visits through the study treatment phase.
- [redacted]
- Immunosuppressant drug concentration levels measured at Visit 2/Week 0, Visit 2A/Day 4, Visit 3/Week 1, and Visit 10/Week 8 (see Section 7.2.3.5). If maribavir is discontinued early during the treatment phase, Immunosuppressant drug concentration should also be measured one week after discontinuation.
- Pharmacokinetic sample collection for adult subjects ⩾18 years of age, randomized to maribavir will be as follows: at Visit 3/Day 7/Week 1 (premorning maribavir dose and between 2-4 hour postmorning maribavir dose); at Visit 6/Week 4 (only one premorning maribavir dose); and at Visit 10/Week 8 (one premorning dose and one between 2-4 hour postmorning maribavir dose). Pharmacokinetic sample collection for adolescent subjects ⩾ 12 to <18 years of age, 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 premorning dose PK sample); at Visit 10/Week 8 (one premorning dose and one between 2-4 hour post morning dose PK samples).
- Maribavir rescue arm eligibility assessed at Visit 5/Week 3 up to Visit 9/Week 7 (Section 7.1.2).
- IRT at all visits through the study treatment phase, except Visit 10/Week 8.
- Study drug dispensed at every visit except Visit 10/Week 8; study drug administration through 8 weeks of study treatment phase (Study Week 0 through Study Week 7).
- Study diary dispensed at baseline and collected at the last follow-up visit; will be used for tracking compliance throughout the study treatment phase and for tracking completion of [redacted]. Note: 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.
- Invasive bacterial, viral and fungal infections/transplant relevant infection assessed at baseline, Visit 2/Week 0, and at all visits throughout the study treatment phase.
- Transplant status at baseline, Visit 2/Week 0, and at all visits throughout the study treatment phase.
- Hepatic function grading according to the Child-Pugh classification (see Appendix 2 and Section 7.2.3.1) at Visit 2/Week 0.

- GVHD assessment (for HSCT subjects only) at all visits through the study treatment phase.
- Comorbidity status evaluation: Karnofsky Performance Status (KPS) scale for subjects ⩾ 16 years of age and Lansky performance status scale for subjects ⩾12 to <16 years of age; at baseline, Visit 2/Week 0, Visit 6/Week 4, and Visit 10/Week 8.

[redacted]

- Concomitant medications, therapies, and procedures through the study treatment phase.
- AE/SAE monitoring throughout the study treatment phase.

7.1.3 Follow-up Phase

Visit 11/Week 9/Follow-up Week 1 to Visit 18/Week 20/Follow-up Week 12 (End of Study)

The follow-up period for this protocol is 84 days or 12 weeks (post-treatment Visits 11-18). The permissible assessment windows for the visits are: Study Weeks 9-12 (Follow-up Weeks 1-4) ± 2 days; Study Weeks 14-20 (Follow-up Weeks 6-12) ± 3 days.

As specified in Table 2 study evaluations include:

- Physical examination (including weight) at Visit18/Week 20
- Vital signs at Visit18/Week 20
- 12-Lead ECG at Visit 18/Week 20
- Hematology/Chemistry at Visit 12/Week 10, Visit 14/Week 12, Visit 16/Week 16, Visit 18/Week 20
- Urinalysis at Visit 18/Week 20
- Immunosuppressant drug concentration level at Visit 11/Week 9, if treatment continued until Week 8 (drug concentration level to be measured 1 week after the end of the study treatment)
- Invasive bacterial, viral and fungal infection assessment at all visits during the follow-up phase; Visit 11/Week 9, Visit 12/Week 10, Visit 13/Week 11, Visit 14/Week 12, Visit 15/Week 14, Visit 16/Week 16, Visit 17/Week 18, and Visit 18/Week 20
- CMV DNA test: Cytomegalovirus DNA quantification in the plasma samples taken at each visit of study follow-up phase (Visit 11/Week 9, Visit 12/Week 10, Visit 13/Week 11, Visit 14/Week 12, Visit 15/Week 14, Visit 16/Week 16, Visit 17/Week 18, and Visit 18/Week 20) will be conducted at central specialty laboratory. Cytomegalovirus genotyping will be conducted only on the samples: from subjects who fail to attain CMV viremia clearance AND have viral load above the predefined cut off (presented in the CMV resistance plan), taken at Visit 16/Week 16 and Visit 18/Week 20; from cases of recurrence of viremia at any visit in the follow-up phase.

- Tissue invasive CMV disease and CMV syndrome assessment (see Appendix 3) at all visits through the study follow up phase
- Transplant status at all visits throughout the follow-up phase
- GVHD assessment (for HSCT subjects only) at all visits through the follow-up phase
- Comorbidity status evaluation: KPS scale for subjects ⩾16 years of age and Lansky performance status scale for ⩾12 to <16 years of age; at Visit 14/Week 12, Visit 16/Week 16, and Visit 18/Week 20

[redacted]

- [redacted]
- AE/SAE monitoring through the follow-up phase according to Section 7.2.3.6
- Concomitant medications and procedures collected throughout the follow-up phase

All SAEs not resolved at the time of end of study visit (Visit 18/Week 12 or Follow-up Week 12) will be followed to closure or stabilization (see Section 8.1). If a subject is withdrawn from the study, all Follow-up Week 12/end of study procedures must be performed as soon as possible after discontinuation.

7.1.4 Maribavir Rescue Arm

All procedures presented in Table 1 (Schedule of Assessment 1), beginning at Visit 2/Week 0, will be performed for the subjects who discontinue the investigator-assigned anti-CMV treatment, meet the eligibility criteria to enter the rescue arm where maribavir 400 mg BID will be administered for a duration of 8 weeks, and complete the end-of-treatment evaluations listed for Visit 10/Week 8 prior to being transferred to the maribavir rescue arm. Subjects will enter the 12-week follow-up phase after completing 8 weeks of maribavir treatment in the rescue arm.

7.1.5 Additional Care of Subjects after the Study

No after care is planned for this study.

7.2 Study Evaluations and Procedures

All study evaluations and procedures are specified in Schedule of Assessment 1, Table 1, and Schedule of Assessment 2, Table 2.

7.2.1 Demographic and Other Baseline Characteristics

Age and/or year of birth, sex, race, and ethnicity will be recorded for all subjects.

7.2.2 Efficacy

7.2.2.1 CMV DNA Quantitation (CMV Infection)

Blood samples collected will be assessed at a central specialty laboratory for the quantification of CMV DNA in plasma using the COBAS® AmpliPrep/COBAS® TaqMan® CMV Test. Central specialty laboratory plasma CMV DNA results will be reported to the investigator site as available. Additional CMV DNA tests at local specialty laboratories may be performed and collected at more frequent intervals or use additional assay methods at the discretion of the investigator utilizing local specialty laboratory. These results will also be collected when available.

Confirmed CMV viremia clearance will be 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 postbaseline samples, separated by at least 5 days.

Recurrence or the recurrence of CMV viremia will be 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. Every attempt should be made by study investigators to collect the 2 consecutive plasma samples and monitor results to confirm recurrence prior to initiating alternative available therapy.

7.2.2.2 CMV Genotyping and Phenotyping

Plasma samples collected at Visit 2/Week 0 for protocol-specified CMV DNA testing at the central specialty laboratory will be genotyped for the final determination of mutations in the viral UL97 and UL54 genes known to confer resistance to commercially available anti-CMV agents. In addition, viral UL27 gene will be tested. During the study, CMV genotyping will be conducted at prespecified time points when the CMV DNA viral load is above a predefined cut off level (validated for this type of analysis) in cases of failure to clear CMV viremia, in cases of recurrence of viremia on and off treatment, and in cases of viremia rebound if >1 $\log_{10}$ above nadir while on treatment (***Rebound*** is defined as increase in viral DNA load for >1 $\log_{10}$ above nadir without prior clearance of viremia) at any time during the study. The entire UL97, UL27, and UL54 CMV genes will be sequenced in every sample that meets the criteria for genotyping, including the baseline samples. Additionally, virus susceptibility testing will be performed on selected de novo CMV sequence variants of maribavir treated subjects by recombinant resistance phenotyping. Details of the analysis will be specified in the resistance analysis plan. The list of CMV mutations conferring resistance to ganciclovir, valganciclovir, foscarnet, or cidofovir is presented in Appendix 4.

7.2.2.3 Tissue Invasive CMV Disease and CMV Syndrome Assessments

Tissue-invasive CMV disease will be defined as described by Ljungman et al., 2002 and Ljungman et al., 2017 (see Appendix 3). The gold standard for diagnosing CMV tissue invasive disease is the identification of CMV inclusions in the infected cells of the tissues OR identification of CMV in biopsy tissue samples. However, in some cases both diagnostic

methods are required, for example when tissue samples have a high chance of being contaminated by body fluids that shed virus (bronchoalveolar lavage [BAL], urine or stool). In some subjects, when it is not possible to obtain a tissue biopsy, a culture of body fluids or DNA quantification (for selected cases) may be used to confirm diagnosis, with a lower level of confidence. In cases of CMV retinitis, the retinal images taken by the ophthalmologist may be used as the evidence supporting the diagnosis.-CMV syndrome (in SOT subjects only) will also be defined as described by Ljungman et al., 2017, and requires at least 2 of 6 signs and symptoms to be present (see Appendix 3 for full description of criteria).

All subjects will be monitored for the occurrence of tissue invasive CMV disease and CMV syndrome throughout the study. For *symptomatic* subjects who present with tissue invasive CMV disease or CMV syndrome at baseline, the investigator will document the initial diagnosis of CMV disease at Visit 2/Day 0 (ie, absence or presence at baseline) and all serial assessments of infection status (ie, no change, improvement, worsening, or resolution) at all subsequent visits in the study. In subjects asymptomatic at baseline, the occurrence of new tissue invasive CMV disease or CMV syndrome after start of study treatment will be initially assessed by the investigator at the study visit when the diagnosis is made, and serial assessments of infection status (ie, no change, improvement, worsening, or resolution) at all subsequent visits in the study. Case charts documenting the infection diagnosis (baseline or new symptomatic infection) and follow-up status at study visits will be provided for adjudication to an independent Endpoint Adjudication Committee. The definitions and requirements for the diagnosis of different CMV diseases and CMV syndrome will be the basis for the data collection charts that are required to support the diagnosis of the each tissue invasive CMV disease type or CMV syndrome. Sites are encouraged to take tissue biopsies to support the diagnosis of the disease as per Ljungman et al., 2002 and Ljungman et al., 2017. The roles, responsibilities, and rules governing operation of the independent Endpoint Adjudication Committee will be fully documented in an Endpoint Adjudication Committee charter.

During the medical monitoring, additional cases not identified by the investigator with symptomatology similar to tissue invasive disease (eg, GVHD with GI symptoms, transplanted organ rejection) may be identified as requiring adjudication by the EAC for confirmation or exclusion of the tissue invasive CMV disease.

The ***recurrence of the symptomatic CMV infection*** will be 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., 2002 and Ljungman et al., 2017 after the period of resolution of symptomatic CMV infection in subjects symptomatic at baseline.

CMV antigen (pp65) producing lymphokines, interferon gamma (IFNγ), tumor necrosis factor alpha (TNFα) or interleukin-2 (IL-2) will be assessed using flow cytometry.

7.2.2.5 Graft Status

History of the current transplant and its status at screening and baseline will be collected for all transplant types, including dates of transplant, graft complications, and use of antirejection therapies for prophylaxis or treatment of graft rejection.

Assessment of the transplant throughout the study will include the status of the graft function, the presence of the episode(s) of acute rejection, or development of other relevant complications (eg, new onset diabetes). The outcome of graft failure is a clinical determination that the graft irreversibly and irrevocably ceases functioning (eg, in case of renal transplant, with the subject returning to permanent dialysis if dialysis-dependent prior to transplant or return to insulin dependency in the case of pancreas transplant) as determined by the investigator.

Detailed information will be collected in separate CRF forms for SOT (by organ) or HSCT, as specified in the study manual.

7.2.2.6 Graft-versus-host-disease (GVHD) Assessments

GVHD is a well-recognized complication of transplantation, much more frequently in HSCT transplants. GVHD occurs when the donor cells (the "graft") recognize the patient being transplanted (the "host") as being foreign, ie, when donor T lymphocytes respond to mismatched protein antigens expressed in host T-cells. It presents in an acute and chronic form.

The most influential protein mismatches are human leukocyte antigens (HLAs) and the incidence of acute GVHD is directly related to the degree of mismatch between HLA proteins expressed by the HCT donor and recipient (Loiseau et al., 2007). Even in patients that receive HLA-matched (HLA-A/B/C/DRB1) grafts, however, GVHD arises in approximately 40% of patients due to differences in minor histocompatibility antigens, and requires systemic therapy. Acute GVHD that typically occurs in first 100 days after transplant includes: erythema, maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus or cholestatic liver disease.

Chronic GVHD typically occurs later (>100 days after transplant) and is manifested on skin, appendages, mouth, eyes, lungs, genitalia, esophagus and connective tissues. Chronic GVHD diagnosis is supported by histologic evidence of GVHD from any affected site. The diagnosis might be difficult as negative histological findings do not exclude the existence of chronic GVHD, and similarity to other conditions that often occur in HSCT patients (such as mycophenolate mofetil (MMF) toxicity or the presence of GI tissue invasive CMV disease.

Investigators are expected to consider recommendations for diagnosis provided in guidance in Appendix 9 and Appendix 10 (Jagasia et al., 2015; Shulman et al., 2015). Detailed information on GVHD and its grading, at baseline and during the study will be collected in separate CRF forms.

Assessment of absence or presence of acute GVHD will be done at baseline, and if present, grading will be performed according to published guidelines provided in Appendix 8 (Harris et

al., 2016); acute or chronic GVHD present at baseline will also be followed throughout the study treatment phase, at every study visit, utilizing the same diagnosis until resolution (during the duration of the study) as indicated in Table 1 and Table 2. New onset of acute or chronic GVHD will be reported as the event of special interest.

7.2.2.7 Comorbidity Status

Transplant patients often have multiple other comorbidities, resulting from their immunosuppressed status (co-infections, graft versus host disease, transplant malfunctioning due to rejection), toxicities from therapies for maintenance of the transplant or reactivation of the baseline disease for which they had been transplanted (malignancy for example), and other concomitant diseases resulting in very diverse population that might be enrolled into the study. The comorbidity assessment will be conducted to allow for the comparison of the population enrolled into 2 treatment arms and to account for the subjects' health status when assessing overall and individual subject response.

Comorbidity assessment as evaluated by the Karnofsky Performance Sstatus or Lansky performance status scale will be performed at time points indicated in Table 1 and Table 2. Given the possible difference in confounding comorbidities in the HSCT and SOT recipients, assessment of comorbidity at baseline and over time in the study will be performed. The difference between treatment arms in terms of baseline comorbidities might be controlled for in the analyses if determined to be substantial.

Comorbidity assessment for both HSCT and SOT recipients will utilize KPS scale for subjects ⩾16 years of age (Peus et al., 2013; Schag et al., 1984) and Lansky performance status scale for ⩾12 to <16 years of age (Lansky et al., 1987).

Karnofsky Performance Status is a valuable tool for measurement of and comparison between the functional statuses of individual patients. It is increasingly utilized as the prognostic factor in renal transplant patients (prior to transplantation).

Refer to Appendix 5 and Appendix 6, respectively, for the KPS and Lansky performance status scale forms.

7.2.2.8 Subject Survival

Subject survival (yes/no) will be determined at all visits during the study. The date and cause of death will be recorded in the CRF, and will be reported as a serious adverse event according to Section 8.2.

7.2.3 Safety

7.2.3.1 Medical History

A medical history will be taken during the screening period and updated on Visit 2/Day 0/Week 0 as specified in Table 1. All medical history findings that have been present/active within the 2 years prior to enrollment at Visit 2/Day 0 will be recorded regardless of clinical relevance or presence at study start. Medical history finding that have not been present/active within the 2 years prior to enrollment will be recorded if deemed clinically

relevant by the investigator to the conduct of the study. Medical history related to the transplant (including the disease/diseases leading to transplant) and CMV infection will be recorded without a time limit. The medical history should include any history of allergic reactions to drugs. Refer to Section 5.1 for prior medication history.

Specific information regarding the subject's transplant history that will be collected, including but not limited to, are: the number of past transplants prior to the current transplant; the type of transplant and details for each, such as cell source and type for HSCT or organ for SOT; the human leukocyte antigen (HLA) matching level; the date and the history of the current transplant including complications; transplant related infections; induction and maintenance therapy received for transplant; history of relevant viral serology; history of anti-viral prophylaxis; and status of the transplant at baseline.

Specific information regarding the subject's CMV infection will be collected in separate CRFs. The collected information will include, but will not be limited to: CMV serology of donor and recipient; CMV infection episodes with viral loads and/or treatment; CMV resistance information (sequencing data); prophylactic treatment, if utilized. More details will be specified in the study manual.

Subjects will be classified into 1 of the following categories with respect to hepatic function, based on baseline clinical and laboratory assessments (see Appendix 2). This information will primarily be utilized in the interpretation of the PK data for which the samples will be collected at the specified visits in the study:

- No chronic liver disease
- Chronic liver disease - Child-Pugh Class A
- Chronic liver disease - Child-Pugh Class B
- Chronic liver disease - Child-Pugh Class C

7.2.3.2 Physical Examination (Including Weight)

Abnormalities identified at the screening visit (Visit 1) will be documented in the subject's source documents and on the medical history CRF. Changes after the screening visit (Visit 1) will be captured as AEs on the AE CRF page, as deemed clinically relevant by the investigator.

The investigator or designee will perform physical examinations at time points specified in Table 1 and Table 2. Physical examinations will be performed in accordance with standard practices at the investigational site. Body weight and height will be measured at time points specified in the schedule of assessments.

7.2.3.3 Vital Signs

Vital signs (body temperature, arterial blood pressure, and pulse) will be collected in a standard manner at the time points specified in Table 1 and Table 2. Any clinically significant deviations from baseline (Visit 2/Day 0/Week 0) vital signs which are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

7.2.3.4 Electrocardiogram

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

7.2.3.5 Clinical Laboratory Evaluations

Laboratory Assessments

Clinical laboratory tests (hematology, chemistry, urinalysis, HBV, HCV, pregnancy) will be performed by a central laboratory at the time points specified in Table 1 and Table 2. During screening, clinical laboratory tests will be performed by the central laboratory, however local laboratory results if available might be utilized for the assessment of the eligibility. If no result of HIV testing within 3 months prior to screening is available, an HIV test will be performed at a local laboratory during the screening period for eligibility assessment. If local laboratory results are used for the assessment of the eligibility, the reference ranges must be provided. This also applies to CMV DNA quantitation results. At baseline (Visit 2/Week 0) blood samples will be taken for CMV DNA quantitation and genotyping, hematology and chemistry and tested in the central specialty laboratory. All clinical laboratory assays will be performed according to the central laboratory's standard procedures. Reference ranges will be supplied by the central laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Clinically significant finding should be reported as an AE unless signs of already reported conditions exist. Abnormal clinical laboratory values that are unexpected or not explained by the subject's clinical condition may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following clinical laboratory assessments will be performed:

Chemistry

Serum sodium, potassium, chloride, bicarbonate/carbon dioxide, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, uric acid, total protein, albumin, creatine phosphokinase, total bilirubin, direct bilirubin, ALT, AST, gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), cholesterol (total and HDL/LDL ratio), triglycerides, and immunoglobulins. The samples for chemistry are preferred to be taken under fasting conditions, although this is not mandatory. The information whether samples were taken under fasting conditions will be collected.

Potassium and magnesium levels will be performed at a local laboratory at Visit 2A/2AR (Day 4 ±1 day) if on tacrolimus, cyclosporine, everolimus or sirolimus at Visit 2/2R, and at four days ±1 day after initiation of tacrolimus, cyclosporine, everolimus, or sirolimus (if the

subject is not taking the agent at baseline).

Hematology

White blood cell (WBC) and differential counts (with absolute neutrophil count [ANC]), hemoglobin, hematocrit, red blood cell (RBC) count, reticulocytes, and platelet count.

International normalized ratio (INR) and prothrombin time at baseline only.

Urinalysis

pH, specific gravity, protein, glucose, ketones, hemoglobin, leukocyte esterase, protein/creatinine ratio and microscopic evaluation (RBC, WBC, crystals, casts, bacteria).

Virology

- Hepatitis (hepatitis B Surface Antigen and/or viral DNA, hepatitis C antibody and/or viral RNA). Historical results within 3 months of randomization are acceptable. If historical results are unavailable, blood will be drawn at Visit 2/Week 0 for hepatitis B surface antigen and hepatitis C antibody testing at the central lab. Central lab results do not need to be available prior to randomization.
- Human immunodeficiency virus (HIV) test. Historical results within 3 months prior to the study treatment initiation will be acceptable for screening. If no result of HIV testing within the prior 3 months is available, the subject must have testing done locally during the screening period, and must have the results available prior to randomization.

<u>Local Laboratory Test to Monitor Immunosuppressant Drug Concentration Levels</u>

For subjects who are receiving tacrolimus, cyclosporine, sirolimus, or everolimus, testing of the blood concentration levels of these drugs will be performed at each site's local laboratory, using each site's standard assay and standard therapeutic drug monitoring practice (eg, time of sample collection relative to dosing). The testing will be performed at the time points outlined below, provided the subject is still receiving tacrolimus, cyclosporine, or everolimus on these study days.

If the subject is receiving tacrolimus, cyclosporine, sirolimus or everolimus on Study Visit 2/Day 0/Week 0, obtain a tacrolimus, cyclosporine, sirolimus or everolimus blood level:

- On Visit 2/Day 0/Week 0 prior to initiation of study treatment
- At the Visit 2A/Day 4 (± 1 day) study visit
- At the Visit 3/Day 7 (+2 day)/Week 1 study visit
- At Visit 10/Week 8 (± 2 day) or on end of treatment visit (if earlier than Week 8)
- At the Week 1 post-treatment follow-up visit (ie, 1 week [± 2 days] after discontinuation of study treatment)

If the subject is not receiving tacrolimus, cyclosporine, sirolimus or everolimus on Study Day 0, but starts any of these drugs after Day 0 while still receiving study treatment, obtain a tacrolimus, cyclosporine, sirolimus or everolimus blood level:

- Four days (± 1 day) after the first dose of tacrolimus, cyclosporine, sirolimus, or everolimus
- At the next scheduled study visit after first starting the tacrolimus, cyclosporine, sirolimus or everolimus, while still receiving study treatment
- At Visit 10/Week 8 (± 2 day) or on end of treatment visit (if earlier than Week 8)
- At the Week 1 post-treatment follow-up visit (ie, 1 week [± 2 days] after discontinuation of study treatment

For the subjects transferred to the maribavir rescue arm, obtain a tacrolimus, cyclosporine, sirolimus or everolimus blood level prior to initiation of maribavir, at Visit 2AR/Day 4R (± 1 day) at Visit 3R/Week 1R, at Visit 10R/Week 8R or at the end of rescue treatment, and at Week 1 post-treatment follow-up visit after the end of the rescue treatment.

Pregnancy Test

A serum β-HCG pregnancy test will be performed on all females of child-bearing potential at the screening visit (Visit 1), baseline (Visit 2/Week 0), Visit 6/Week 4, and at the end of study treatment visit (Visit 10/Week 8), or if pregnancy is suspected, or on withdrawal of the subject from the study. A pregnancy test performed within 7 days prior to randomization will not be repeated at baseline (if central laboratory is utilized). Local or central laboratory analysis performed on samples taken between Day -7 and Day -14 will be repeated on Day 0 before randomization. Local laboratory test results can be used for the assessment of pregnancy on Day 0/Week 0.

7.2.3.6 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). All AEs will be recorded from the time informed consent is signed through 30 days after the last dose of investigational product. Following the 30-day capture period for all AEs, only those AEs deemed related to investigational product or other protocol-mandated procedures and all SAEs (regardless of causality assessment) will be collected through the end of the study (Visit 18/Week 20 [Follow-up Week 12]). Refer to Section 8 for detailed AE reporting requirements.

7.2.4 Others

7.2.4.1 Clinical Pharmacology Assessments

For subjects ⩾18 years of age, randomized to maribavir, 1 or 2 PK samples will be collected on each of the study days specified in Table 1. The premorning dose PK sample will be obtained at all 3 PK visits. The postmorning dose PK samples at Visit 3/Week 1 and at Visit 10/Week 8 will be obtained any time between 2-4 hours after the morning dose. Any episode of vomiting

occurring within 2 to 4 hours after the morning dose and before the postmorning dose PK sample collection must be documented. Subjects will record the date and time of the previous maribavir dose taken before a PK visit in their electronic diary. The instructions will be provided in the study manual.

Subjects ≥18 years Sparse PK Schedule		
Week 1, Day 7 (±1d)	**Week 4, Day 28 (±2d)**	**Week 8, Day 56 (±2d)**
Study Treatment Period		
• Pre-morning dose • 2-4 hours post morning dose	• One pre-morning dose	• Pre-morning dose • 2-4 hours post morning dose

For subjects ⩾12 to <18 years of age, an intensive PK sampling will be performed at Visit 3/Week 1. Subjects will be asked to complete the 12 hour post morning dose PK sample prior to taking their evening dose of maribavir. Sparse PK sampling similar to adults (⩾18 years) will be performed at Week 4 and Week 8.

Subjects ≥12 to < 18, Including Intensive PK (Week 1) Schedule		
Week 1, Day 7 (±1d) (Intensive PK)	**Week 4, Day 28 (±2d)**	**Week 8, Day 56 (±2d)**
Study Treatment Period		
• Premorning dose, 1, 2, 3, 4, 6, 8 (all ±5 min), and 12 hours (±15 min) post morning dose	• One premorning dose	• Premorning dose and • 2-4 hours post morning dose

The following will be recorded in the CRF:

- Date and time of the last dose of maribavir before the predose PK sample was taken
- Date and time that the predose PK sample was taken
- Date and time of the last dose of maribavir before the postdose PK sample was taken
- Date and time that the 2-4 hour postdose PK sample was taken
- Date and time of vomiting within 2-4 hours after the morning dose and before the postmorning dose PK sample collection

If a subject has maribavir dose interrupted for 2 consecutive days prior to the morning maribavir dose on a PK visit, no PK sample will be collected. If a subject has completed the premorning dose PK sample collection, but has missed the morning dose of maribavir on the day of the PK visit, then no postdose PK sample will be collected.

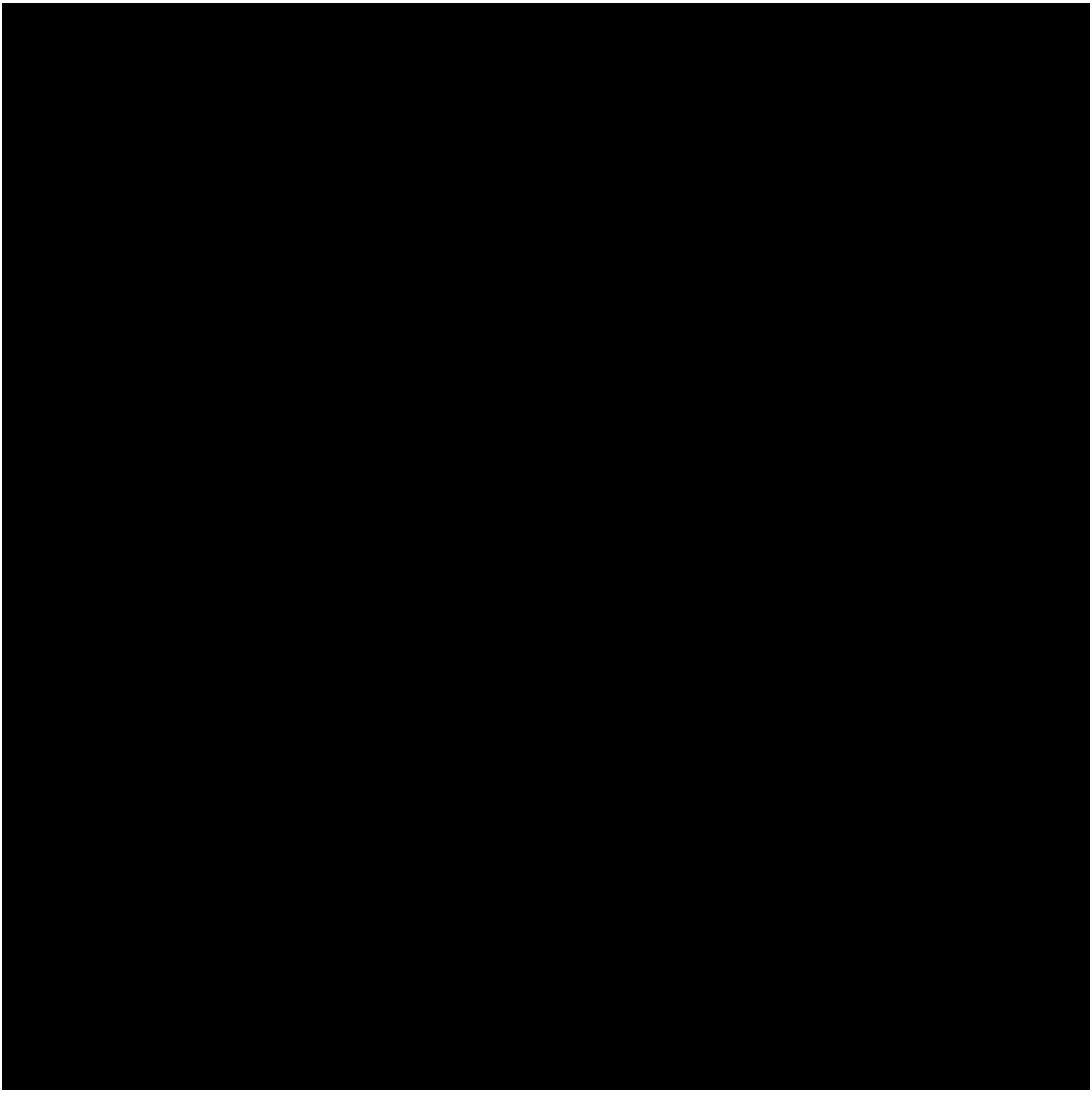
Unscheduled PK sample collection

For purposes of special PK sampling, gastrointestinal (GI) GVHD is defined as any of the following (Boeckh et al., 1998):

- Biopsy-proven GVHD of the GI tract plus diarrhea (>300 mL/day)
- Biopsy proven GVHD of the GI tract and nausea

- Documented acute GVHD of the liver (stage II, total bilirubin >3 mg/dL or biopsy-proven) plus diarrhea (>500 mL/day) with no other explanation or
- Biopsy-proven acute GVHD of the skin plus diarrhea (>500 mL/day) with no other explanation

If a subject on maribavir treatment is diagnosed with GI GVHD during the study treatment phase and therapy with study drug remained permissible, study drug will be continued and blood samples for the determination of maribavir plasma concentrations will be collected. This unscheduled PK sampling will occur at the next visit after the first occurrence of a GI GVHD diagnosis, and will follow the schedule of sampling and recording of information as described in Table 1 (Schedule of Assessment 1).



[redacted]

7.2.5 Volume of Blood to be Drawn from Each Subject Per Visit

The volume of blood drawn from each subject per visit is shown in Table 5.

Table 5: Volume of Blood Drawn Per Study Visit

Study Visit / Rescue Arm Visit	Blood Volume per Visit (mL)
Visit 1/NA Rescue Arm Visit (Screening)	33[a]
Visit 2/2R	48
Visit 2A/2A-R	11
Visit 3/3R	26
Visit 4/4R	23
Visit 5/5R	15
Visit 6/6R	29
Visit 7/7R	35
Visit 8/8R	23
Visit 9/9R	15
Visit 10/10R (End of Treatment)	60
Visit 11/11R	20
Visit 12/12R	23
Visit 13/13R	15
Visit 14/14R	23
Visit 15/15R	15
Visit 16/16R	23
Visit 17/17R	15
Visit 18/18R (End of Study)	43
Additional PK	**PK Blood Volume per Visit (mL)**
See Section 7.2.4.1	4

[a] Includes an additional 4 mL sample for local HIV testing to be drawn from subjects lacking result of an HIV test within 3 months prior to Screening.
Note: Refer to Schedule of Assessments 1 (Table 1) and 2 (Table 2)
PK=pharmacokinetics

During this study, it is expected that approximately 491 mL of blood will be drawn from each subject, regardless of sex. In addition, subjects between the ages of 12 and 18 years will have up to 24 mL of blood drawn for intensive PK visits.

Note: The amount of blood to be drawn for each assessment at any visit is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is

to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational/investigator assigned anti-CMV treatment) product, whether or not related to the medicinal (investigational/investigator assigned anti-CMV treatment) product (International Conference on Harmonisation [ICH] Guidance E2A 1995).

All AEs will be recorded from the time the informed consent is signed through 30 days after the last dose of investigational product. 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 investigational product or other protocol-mandated procedures and all SAEs (regardless of causality assessment) will be collected until the defined follow-up period stated in Section 7.1.3. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

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. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates. The highest level of severity will be recorded for an event. Worsening of pretreatment events, after initiation of study treatment, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Besides the above mentioned standard categories of severity grading for tissue invasive CMV disease and a few selected events of special interest (see Section 8.1.4), the severity (intensity) of AEs will also be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to study treatment for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study treatment. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the study treatment and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the study treatment is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the study treatment and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Adverse Events of Special Interest

In addition, the following adverse events of special interest will be closely monitored and reported throughout the study regardless of seriousness or of relationship to study treatment. Medical assessment of severity will be determined using standard grading category (mild, moderate, and severe), and by using other specific severity grading for each AESI as mentioned below:

Adverse Events of Special Interest (severity grading based on CTCAE Version 4.03)

1. Tissue invasive CMV disease and CMV syndrome. It is expected that certain number of subjects will also have tissue invasive CMV disease or CMV syndrome at baseline and its clinical course will be monitored throughout the study; the effect of the study treatment on this event will be assessed. At each visit the investigator will provide the evaluation of the tissue invasive CMV disease or CMV syndrome until resolution, which will be collected on the CRF. The investigator will have the final discretion in determining whether or not the CMV DNA test results and other clinical data represent a new tissue invasive CMV disease or CMV syndrome for a given subject. When these events are entered into the CRF, they should be recorded using the terminology shown in Appendix 3 (eg, 'CMV pneumonitis', 'CMV colitis', etc.). For details on how the disease under study will be reported see Section 8.1.5.
2. Taste disturbance (dysgeusia): If a subject reports an AE of taste disturbance, the investigator will record the subject's description of the taste disturbance (when available) as part of the event verbatim in the CRF.
4. Events of nausea, vomiting, and diarrhea will be recorded. Additional information for each case of diarrhea will be collected, including the information whether condition such as GVHD, GI-CMV or enteric infection confirmed by culture/PCR or other method is present.
5. Neutropenia.

Adverse Events of Special Interest (grading based on standard severity categorization to mild, moderate, and severe)

1. Immunosuppressant drug concentration level increased: Immunosuppressant drug levels will be monitored as specified Section 7.2.3.5. High to toxic levels will be recorded as AEs.
2. Graft rejection (acute, chronic, or failure): Transplant status will be captured at every visit as shown in the Schedule of Assessments (Table 1 and Table 2), and graft rejections will be captured.
3. Invasive fungal (aspergillus, candida, *Pneumocystis jiroveci*, etc.) or bacterial infections (*Staphylococcus aureus*, *Streptococcus pneumonia*, enterococcus, pseudomonas, etc.). Baseline conditions will be captured as part of medical history, while new events will be captured as AEs. The additional information such as diagnostic method used for the pathogen and the source of the sample used for the diagnosis will be collected. Additionally the presence of viral infections frequently occurring in transplant population will also be collected.

4. Graft-versus-host-disease (HSCT subjects): GVHD will be diagnosed based on the investigator's judgment (see Section 7.2.2.6). Severity of Acute GVHD (Grading I-IV) will be assessed using grading scale provided in Appendix 8 as in published guidelines (Harris et al., 2016) and for chronic GVHD using severity grading into mild, moderate and severe according to the scoring provided in Appendix 9, as in the published guidelines (Jagasia et al., 2015). Harris et al (2016) provides the confidence levels of the diagnosis (see Confidence Level Criteria Table in Appendix 9). For the purpose of this study the disease considered 'confirmed' or 'probable' should be reported as GVHD. Acute or chronic GVHD present at baseline will also be followed utilizing the same diagnosis and severity assessments at every study visit until resolution (during the duration of the study). The baseline presence of the acute or chronic GVHD will be reported on the Transplant History page.

8.1.5 Disease Under Study

Subjects will be enrolled in study after fulfilling the criteria for CMV viremia (≥910 IU/mL) and their viral load will be monitored throughout the study. Viremia clearance, persistence, or recurrence will be reported as the part of efficacy assessment based on central laboratory result.

It is expected that certain number of subjects will also have tissue invasive CMV disease or CMV syndrome (SOT subjects only) at baseline and its clinical course will be monitored throughout the study and will be reported as part of the secondary efficacy assessment.

Since new tissue invasive CMV disease or CMV syndrome constitutes a medically important event, independent of hospitalization or prolongation of hospitalization required for this event, it will qualify to be reported as an SAE.

In the event of worsening of tissue invasive CMV disease or CMV syndrome present at baseline, an SAE reporting will be determined based on that event fulfilling the seriousness criteria (definition in Section 8.2.3).

The investigator has the final discretion in determining whether or not CMV test results and other clinical data represent a new CMV event for a given subject.

If a CMV event crosses into different categories over time, the category of greatest severity should be recorded.

If a subject is initially diagnosed with an asymptomatic CMV infection, but this event evolves into CMV organ disease (eg, colitis), the event would be recorded as CMV colitis and reported as SAE.

The terminology used for reporting should be:

- Asymptomatic CMV infection
- CMV syndrome (applicable only in SOT subjects)
- Tissue invasive CMV disease, specify organ for example CMV pneumonitis, CMV colitis

Table 6 presents the criteria for reporting CMV infection as an AE or as an SAE during its clinical course during the study.

Table 6: Criteria for reporting CMV infection as an AE or as an SAE

	Course during the study (based on the investigator's assessment)	Reportable as AE	Reportable as SAE
Tissue invasive CMV disease at baseline	No change	No	No
	Improving	No	No
	Worsening, but does not meet criteria for SAE as determined by the investigator	Yes	No
	Worsening and meeting criteria for SAE (see definition in Section 8.2.3)	No	Yes
New onset of tissue invasive CMV disease		No	Yes
	Improving	No	No
	Worsening	No	Yes but same event with upgraded severity
CMV syndrome at baseline	Improving	No	No
	Worsening but does not meet criteria for SAE	Yes	No
	Worsening and meeting criteria for SAE (see definition Section 8.2.3)	No	Yes
	Worsening to tissue-invasive CMV disease	No	Yes
Asymptomatic CMV infection at baseline	Improving	No	No
	Worsening CMV viremia (or CMV viremia recurrence or rebound after clearance)	Determined by the investigator based on the assessment of clinical significance; either local or central laboratory results to be used at investigator's discretion.	Yes, if fulfilling seriousness criteria. If the only reason for hospital admission or prolongation of hospitalization is the need for IV treatment in the hospital setting, then this will not qualify as an SAE
	Worsening to tissue invasive CMV disease	No	Yes
	Worsening to CMV syndrome	No	Yes

Table 6: Criteria for reporting CMV infection as an AE or as an SAE

	Course during the study (based on the investigator's assessment)	Reportable as AE	Reportable as SAE

CMV=cytomegalovirus; AE=adverse event; SAE=serious adverse event

8.1.6 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during study, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the study treatment phase or at the end of the follow-up phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at baseline, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.7 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.3.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Shire Global Drug Safety Department using the Shire investigational and marketed products pregnancy report form. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days and 1 year postpartum. An ethics committee (EC) and Institutional Review Board (IRB) approved informed consent form must be signed by a pregnant partner of a study participant prior to obtaining pregnancy outcome information from the nonstudy participant.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire clinical study serious adverse event and nonserious AEs required by the protocol form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire clinical study serious adverse event and nonserious AEs required by the protocol form as well as the Shire investigational and marketed products pregnancy report form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

8.1.8 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse**–Persistent or sporadic intentional intake of study treatment when used for a nonmedical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.
- **Misuse**–Intentional use of study treatment other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).
- **Overdose**–Intentional or unintentional intake of a dose of maribavir exceeding a total daily dose of 400 mg BID, or a prespecified dose of the investigator-assigned anti-CMV treatment. The highest dose of maribavir studied in Phase 2 treatment studies (SHP620-202 and SHP620-203) was 1200 mg BID. There was no significant difference in safety across all 3 doses (400 mg BID, 800 mg BID, and 1200 mg BID) studied.
- **Medication Error**–An error made in prescribing, dispensing, administration, and/or use of the study treatment. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the study treatment are not considered reportable as medication errors. Medication errors should be reported for all products under investigation. The administration and/or use of an expired investigational product or an investigator-assigned anti-CMV treatment should be considered as a reportable medication error.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference safety information to assess the expectedness of an AE for this study is as follows:

- The maribavir investigator's brochure which the sponsor has provided under separate cover to all investigators
- The respective summary of product characteristics (SmPC) for each investigator-assigned anti-CMV treatment (valganciclovir [Valcyte®, 11 March 2015], ganciclovir [Cymevene®, 27 October 2016], and foscarnet [Foscavir®, 28 February 2014]) or country-specific product package insert for

cidofovir (eg, Tillomed Laboratories, Ltd; 12 September 2017 [UK], 23 February 2017 [EU])

8.2.2 Reporting Procedures

-All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.8) unless they result in an SAE.

The investigator must complete, sign, and date the Shire clinical study serious adverse event and nonserious AEs required by the protocol form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to the Shire Global Drug Safety Department. .

In the event of an SAE, the investigator must fax or e-mail the Shire clinical trial serious adverse event form within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and an e-mail address can be found on the form (sent under separate cover) and are provided below:

Fax: [redacted]
E-mail: [redacted]

8.2.3 Serious Adverse Event Definition

A **serious adverse event (SAE)** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death.
- Is life-threatening. Note: The term ‘life-threatening’ in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.

- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

For this protocol the following events will not be collected as SAE(s).

- Pre-existing conditions that have not worsened during study participation:
  - Preplanned (planned prior to the initiation of the study) hospitalizations
  - Preplanned treatments or surgeries
- Hospitalization for the administration of foscarnet when it is the investigator's choice of therapy for the subjects randomized to 'control' treatment arm, or hospitalization for ganciclovir or cidofovir administration if this is a required practice at a local site.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the end of defined follow-up period stated in Section 7.1.3, and must be reported to the Shire Global Drug SafetyDepartment within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject’s death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject’s death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another study treatment action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the study treatment should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The study treatment action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor and/or the clinical CRO is responsible for notifying the relevant regulatory authorities US central IRBs/European Union (EU) central ECs of related, unexpected SAEs.

The study population is HSCT or SOT recipients with cytomegalovirus infections. The following SAEs are common in this study population and are anticipated to occur, **hence these SAEs (including fatal outcomes) will not be considered unexpected and will not be individually reported to the regulatory agencies, IRBs, Ethics Committees, and investigators, provided there is no increased frequency of these events*:**

- Any CMV infection, including CMV reactivation/recurrence, CMV syndrome, and tissue invasive CMV disease
- Any other bacterial, viral infection, or fungal infection
- Acute and chronic graft versus host disease, graft rejection, and graft failure
- Reactivation of the malignancy under treatment in HSCT recipients

This includes fatal outcomes for the aforementioned SAEs.

*Maribavir Phase 2 (studies 1263-202 and 1263-203) data will be used as reference.

However, these are AESI and will be closely monitored and recorded on the CRF**.** Refer to Section 8.1.4 for more information on AESI.

In addition, if the event is serious (fulfilling seriousness criteria) it will be reported on SAE report form per Section 8.2.2. An independent DMC will be established per Section 9.4.

In addition sponsor or the sponsor's delegate is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the maribavir program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent. All statistical analyses will be performed using SAS® Version 9.1 2 or higher (SAS Institute, Cary, NC 27513).

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics, and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed and plan for subgroup analysis. In addition, the SAP will include statistical method to summarize the maribavir pharmacokinetics data and explore the relationship between maribavir C_{min} (predose concentration) and efficacy and safety measures of interest. To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock. Maribavir PK concentrations will be analyzed by a population PK analysis approach. A separate SAP will be prepared for this analysis and a separate report will present the pharmacokinetic analysis results in addition to the primary clinical study report.

9.4 Data Monitoring Committee

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.

Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of study treatment.

9.5 Endpoint Adjudication Committee

An independent Endpoint Adjudication Committee has been established to confirm the diagnosis of CMV tissue invasive disease and CMV syndrome for *symptomatic* subjects at baseline and to confirm the change over time (no change, improvement, worsening, or resolution), or diagnosis of new tissue invasive CMV disease and CMV syndrome.

The roles, responsibilities, and rules governing operation of the Endpoint Adjudication Committee are discussed in full in the Endpoint Adjudication Committee charter, which will be available prior to the administration of investigational product.

9.6 Sample Size Calculation and Power Considerations

In the Phase 2 Study SHP620-202, the proportion of subjects with undetectable plasma CMV DNA was 70%, 63%, and 68% for the 400 mg, 800 mg, and 1200 mg BID dose groups, respectively, within 6 weeks. The proportion of subjects with undetectable plasma CMV DNA was 70%, 65%, and 75% for the 400 mg, 800 mg, and 1200 mg BID dose groups, respectively, within 12 weeks. 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.

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 the investigator assigned treatment group when calculating the sample size. It is believed that the treatment difference of 20% higher in maribavir group compared to the control group is larger than a clinically meaningful difference.

For the proposed trial, 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.

9.7 Study Analysis Population

- The **enrolled set** will consist of all subjects who have signed an informed consent and have begun some study procedures.
- The **randomized set** will consist of all subjects in the enrolled set who have been randomized to the study. Subjects will be analyzed in the treatment group to which they are randomized.
- The **safety set** will consist of all subjects who have taken any dose of study treatment. Subjects will be analyzed according to the treatment actually received.
- The **per-protocol** (PP) **set** will consist of all subjects in the randomized set who do not have predefined major protocol deviations that may affect the primary efficacy assessment.
- The **pharmacokinetic set** will consist of all subjects in the safety set who had plasma samples drawn and tested for maribavir concentrations.
    - The adolescent pharmacokinetic set will consist of all subjects ⩾12 to <18 years of age in the safety set who had plasma samples drawn and tested for maribavir concentrations.

The randomized set and the 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.

9.8 Efficacy Analyses

The following definitions will be used for study analyses:

Confirmed 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.

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

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 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 lack of 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. Subjects who take rescue medication will be considered as failures for primary efficacy analyses. 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. The same is applicable for patients who might be discontinued from maribavir treatment due to intolerance. Subjects who discontinue due to intolerance and without viremia clearance at Study Week 8 will be considered failures in both treatment arms.

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint (a binary response) for the study is confirmed clearance of plasma CMV DNA (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 (Visit10) 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 examples in Table 7 below).

Table 7: 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, prior to the start 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 (CMV viremia clearance) = 2 consecutive postbaseline assessments of CMV DNA target <LLOQ, separated by at least 5 days.

Statistical Methodology for Primary Efficacy Endpoint:

The difference in proportion of subjects with confirmed CMV viremia clearance, at the end of Study Week 8, between treatment groups (maribavir and investigator's choice of anti-CMV treatment) will be obtained using Cochran-Mantel-Haenszel (CMH) weighted average across all strata, and analyzed using CMH test with transplant type and baseline plasma CMV DNA concentration as 2 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 the high viral load group is less than 5, the high and intermediate viral load groups will be collapsed into 1 stratum level. The baseline plasma CMV DNA levels will be the last central laboratory assessment before the first dose of study treatment. If the p-value from the CMH test is $\leqslant 0.0505$ and the proportion of response from maribavir is higher, it will be concluded that maribavir is more efficacious compared to the control group.

Subjects who are unable to continue taking investigator's assigned anti-CMV treatment due to the lack of 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. Subjects who take rescue medication will be considered as failures for primary efficacy analyses. The data collected postmaribavir 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. Since intolerance to the assigned treatment alone will not qualify a subject for the rescue arm, such subjects will not be considered nonresponders for the purpose of the primary efficacy analysis. The same is applicable for subjects that might be discontinued from maribavir treatment due to intolerance. Subjects that do not achieve confirmed CMV viremia clearance will be considered failures in both treatment arms. Subjects who discontinue without confirmed CMV viremia clearance at Study Week 8 will be considered failures in both treatment arms.

Sensitivity and supportive analyses of the primary endpoint of CMV viremia clearance at Week 8 will be conducted to evaluate the robustness of the result from the primary method. This will be specified in the SAP. Two examples are given below:

- Subjects who discontinue study treatment early without CMV DNA measurement available for evaluation of study drug effect at Week 8 (see Table 7). 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 study discontinuation will be included as responders.
- Multivariate regression analysis to evaluate treatment difference after controlling for important demographic and baseline clinical characteristics. The list of demographic and baseline clinical characteristics to be considered will include but will not be limited to transplant type (HSCT versus SOT), CMV viral load resistant versus refractory, CMV serostatus, immune function status, presence of GVHD, high dose steroids use at baseline, prior use of CMV prophylaxis.

The analysis of primary efficacy endpoint and the key secondary efficacy endpoint will be conducted using both the randomized set and PP set.

9.8.2 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 (resolution or improvement of tissue invasive disease or CMV syndrome for symptomatic subjects at baseline, or no new symptoms for subjects asymptomatic at baseline) 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.

The investigator will perform the initial diagnosis of tissue-invasive CMV disease or CMV syndrome (absence or presence) 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 through the study. All investigator-assessed cases of tissue invasive CMV disease and CMV syndrome will be reviewed and adjudicated by an independent 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).

All investigator-assessed cases of tissue invasive CMV disease and CMV syndrome will be reviewed and adjudicated by an independent EAC both for the confirmation of the diagnosis at baseline and new tissue invasive CMV disease or CMV syndrome and for the outcome (ie, no change, improvement, worsening, or resolution). An adjudicated baseline disease diagnosis of "confirmed" or "probable" will be accepted (only "probable" for CMV syndrome). An adjudicated outcome of "improved" or "absent" will constitute improvement of tissue invasive CMV disease or CMV syndrome. New cases of tissue invasive CMV disease or CMV syndrome identified by the investigator will also be adjudicated. Endpoint Adjudication Committee 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 (criteria for the CMV viremia clearance are presented in Table 8).

Table 8: 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 "+" in FU by week 16
Yes	+/-	+/-	+/-	+/-	+/-	-	+/-/NA	Yes	Week16 is "-" and no 2 consecutive "+" during FU
Yes	+/-	+/-	+/-	+/-	+/-	+	+/-/NA	No	Week 16 is "+" and week 18 is "+" or NA, criteria of 2 consecutive "+" is 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 is 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 only if Week 16 data are unavailable or missing.

*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.

Notes: Scenarios in the table above are provided as examples and may not be all-inclusive of all possibilities.
Only CMV viremia data prior to receiving nonstudy CMV treatment or rescue treatment will be included in the assessment.

Statistical Methodology for Key Secondary Endpoint

The key secondary endpoint will be analyzed using the same approach as the primary endpoint.

The analysis of primary efficacy endpoint and the key secondary efficacy endpoint will be conducted using both the randomized set and PP set.

9.8.3 Multiplicity Adjustment

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. The statistical test will be performed sequentially in the order of primary

efficacy endpoint, and the key secondary endpoint. First, the primary endpoint analysis (CMV viremia clearance at Week 8) will be assessed at α=0.05. If and only after the primary efficacy endpoint is statistically significant, the key secondary endpoint will be assessed at α=0.05.

9.8.4 Subgroup Analyses

The primary and key secondary endpoints will be examined for the following subgroups (inclusive, but not limited to):

- Subjects symptomatic at baseline
- SOT/HSCT recipients
- CMV DNA viral load (high, intermediate, low)
- Resistant (yes/no)
- Adolescents ⩾12 to <18 years of age (exploratory analysis: may be conducted if sample size is adequate)

The proportion of subjects achieving the primary efficacy endpoint and the key secondary efficacy endpoint, and the corresponding 95% CIs will be calculated for each group separately. In addition, the difference in each respective proportion between treatment group and the associated 95% CI will be presented.

9.8.5 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are as follows:

- The achievement of the confirmed CMV viremia clearance after 8 weeks of receiving study-assigned treatment.
    - The proportion of subjects achieving the confirmed CMV viremia clearance after receiving 8 weeks of study-assigned treatment, and the corresponding 95% CIs will be calculated for each treatment group separately. The difference in each respective proportion between treatment groups and the associated 95% CI will be calculated using the same approach as the primary efficacy endpoint, and will be assessed using CMH test with transplant type and baseline CMV DNA concentration as 2 stratification factors.

- The achievement of the confirmed CMV viremia clearance and CMV infection symptom control after receiving 8 weeks of study-assigned treatment, followed by maintenance of this treatment effect through Study Weeks 12 (4 weeks post treatment period), 16 (8 weeks post treatment/follow-up phase), and 20 (12 weeks post treatment).
    - The proportion of subjects who achieved confirmed CMV viremia clearance and CMV infection symptom control after 8 weeks of receiving study-assigned treatment and maintaining the effect through Study Weeks 12, 16, and 20, and the corresponding 95% CIs will be calculated for each treatment group separately. The difference in each respective proportion between treatment groups and the associated 95% CI will be calculated using the same approach as the primary

efficacy endpoint, and will be assessed using CMH test with transplant type and baseline CMV DNA concentration as 2 stratification factors.

- The maintenance of the CMV viremia clearance, and CMV infection symptom control, at the end of Study Week 8, through weeks 12 and 20, regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy.
    - The proportion of subjects who maintained confirmed CMV viremia clearance and CMV infection symptom control at end of Study Week 8 and maintained the effect through Study Week 12 and 20, and the corresponding 95% CIs will be calculated for each treatment group separately. The difference in each respective proportion between treatment groups and the associated 95% CI will be calculated using the same approach as the primary efficacy endpoint, and will be assessed using CMH test with transplant type and baseline CMV DNA concentration as 2 stratification factors.

- The recurrence of CMV viremia during the first 8 weeks of the study, in the follow-up period of 12 weeks, and at any time during the 20 weeks of the study, regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy.
    - The proportion of subjects with recurrence of CMV viremia during the first 8 weeks of the study, and the corresponding 95% Cl will be calculated.
    - The proportion of subjects with recurrence of CMV viremia, in the 12 weeks of the follow-up phase and the corresponding 95% Cl will be calculated.
    - The proportion of subjects with recurrence of CMV viremia any time on study and the corresponding 95% Cl will be calculated.

  Additional subgroup analysis will be done for the subjects who completed 8 weeks of study-assigned treatment with the same type of endpoints:
    - The proportion of subjects with recurrence of CMV viremia during the 8 weeks of study treatment, and the corresponding 95% Cl will be calculated.
    - The proportion of subjects with recurrence of CMV viremia, in the 12 weeks of the follow-up phase and the corresponding 95% Cl will be calculated.
    - The proportion of subjects with recurrence of CMV viremia at any time on the study and the corresponding 95% Cl will be calculated.

- The recurrence of CMV viremia during study-assigned treatment and in the follow-up period after the subject is discontinued from study-assigned treatment.
    - The proportion of subjects with recurrence of CMV viremia while on study treatment, and the corresponding 95% Cl will be calculated.
    - The proportion of subjects with recurrence of CMV viremia, in the period from the termination of study treatment to the end of the study, and the corresponding 95% Cl will be calculated.

- The maribavir CMV resistance profile
    - The proportion of maribavir subjects who developed maribavir CMV resistance on study and the corresponding 95% CI will be calculated.

- All causes mortality by the end of the study (Visit 18/Week 20[Follow-up Week 12])
    - The proportion of subjects who died at the end of the study and the corresponding 95% CIs will be calculated for each group separately. In addition, the difference in each respective proportion between treatment group and the associated 95% CI will be presented.
      The time to all causes mortality will also be summarized using the Kaplan-Meier method.

The secondary efficacy endpoints assessed for the ***maribavir rescue arm*** are as follows:

- The confirmed clearance of plasma CMV DNA at the end of 8 weeks after starting maribavir rescue treatment
    - The proportion of subjects receiving maribavir rescue treatment who achieved the CMV viremia clearance at the end of 8 weeks after starting maribavir rescue treatment and the corresponding 95% CI will be calculated.

- Achievement of viremia clearance at the end of 8 weeks after starting maribavir rescue treatment and resolution or improvement of tissue invasive CMV disease or CMV syndrome for subjects who are symptomatic at the start of maribavir treatment or subjects who are asymptomatic at the start of maribavir treatment remain symptom free, followed by maintenance of the treatment effect for an additional 8 weeks when off maribavir rescue treatment (as evidenced by sustained clearance of viremia and improvement or resolution of symptomatic infection and no new tissue invasive CMV disease or CMV syndrome development between end of treatment and up to Week 16)
    - The proportion of subjects receiving maribavir rescue treatment who achieved the confirmed CMV viremia clearance and tissue invasive disease or CMV syndrome control at the end of 8 weeks after starting maribavir rescue treatment and maintain the effect through Week 16 and the corresponding 95% CI will be calculated.

The analysis of the secondary efficacy endpoints will be conducted using the Randomized 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.

9.8.6 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

[redacted]

[redacted]

The randomized set will be used for the analysis of the exploratory efficacy endpoints. Descriptive statistics will be used to summarize the data. Summary statistics will include the number of subjects (N), mean, standard deviation, median, minimum and maximum (range) values for continuous variables, and incidences and percentages for categorical variables. The denominator for the percentages will be based on the number of patients with nonmissing information in the randomized set. Time-to-event endpoints will be summarized using Kaplan-Meier estimation. Ninety-five percent (95%) confidence intervals for the estimated 25%, 50%, and 75% times will be presented.

9.9 Safety Analyses

The safety analyses will include evaluation and procedures to meet the secondary objective of assessing the safety and tolerability of maribavir.

Safety evaluation will be made during the periods as illustrated in Figure 1, ie, screening phase, treatment phase, and follow-up phase.

Two observation periods are defined for the purpose of analyses:

1) 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 if cidofovir is used. For subjects who transfer from the study treatment to either maribavir rescue or to a nonstudy CMV treatment, the on treatment observation period starts at the time of the study treatment initiation through 7 days after the last dose of study treatment (or through 21 days if cidofovir is used), or until the maribavir rescue treatment initiation or until the nonstudy CMV treatment initiation, whichever is earlier. This will serve as the primary analysis of safety.

2) The overall-study observation period minus the period on rescue arm starts at the time study treatment start through the end of the study. For subjects who receive maribavir rescue therapy, the overall-study observation period minus the period on rescue arm starts at the time study treatment start through the time before receiving maribavir rescue therapy.

Similar observation periods are defined for the safety analysis of the maribavir rescue arm. The events 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.

An AE (classified by preferred term) that has a start date on or after the first dose of study treatment or that has a start date before the date of first dose of study treatment, but increases in

severity after the first dose of study treatment will be considered a treatment-emergent AE (TEAE).

Safety endpoints will be summarized descriptively for the on treatment period, and overall-study period, as appropriate. Baseline assessments will be the last assessment before the first dose of study treatment. The safety set population will be used to analyze the safety data. Summary of all safety analyses will be provided separately for the maribavir rescue arm.

The safety endpoints include the following:

- TEAEs 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.

The number of events, incidence, and percentage of TEAEs and overall-study AEs will be displayed for each treatment group by system organ class (SOC) and by Preferred Terms using the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries in terms of severity and relationship to study medication will also be provided. Treatment-emergent SAEs will be summarized separately in a similar fashion. Summaries of AEs causing discontinuation of study medication, withdrawals, AEs leading to death, SAEs and adverse of events special interest (AESI) will be provided.

Adverse events of special interest, eg, tissue invasive CMV disease, dysgeusia, GI events (nausea, vomiting and diarrhea), neutropenia, increased immunosuppressant drug concentration levels, graft rejection, opportunistic infections, and GVHD will be analyzed according to primary System Organ Classes (SOCs) and Preferred Terms (PTs). MedDRA queries (SMQs) may be used, as applicable. Additional grading of events of special interest will be applicable. Summary tables with SOCs and PTs will be generated presenting the number and percentage of subjects by AE, severity, seriousness, and relationship to study medication.

Usage of concomitant medications and procedures will be summarized descriptively for each of the treatment groups and the maribavir rescue treatment group for the on treatment period and overall-study period. Treatment of hemopoietic growth factors, blood and blood transfusion products will be summarized separately

Change from baseline in vital signs and clinical laboratory tests will be summarized for each treatment group with descriptive statistics at each assessment visit. Summary and shift tables will be produced for selected laboratory parameters based on National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE v4.0).

Abnormal physical examination findings will be listed.

Summary of ECG findings will be provided by treatment groups.

An independent data monitoring committee (DMC) will be established to assess the data for safety and to ensure the validity and scientific merit of the trial. Detailed plans for the DMC's

purpose and responsibilities will be described in the DMC charter and the statistical analysis plan.

9.10 Other Analyses

[redacted]

9.10.3 Pharmacokinetic Analyses

The Pharmacokinetic Set will be used to analyze the pharmacokinetic endpoints. The adolescent pharmacokinetic set will consist of all subjects ≥12 to <18 years of age in the safety set who had plasma samples drawn and tested for maribavir concentrations.

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

Secondary endpoint

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

Exploratory endpoints:

[redacted]

Blood samples at predose (C_{min}) and 2-4 hour postdose administration will be assessed for plasma maribavir concentration levels. Maribavir PK will be analyzed for all subjects with maribavir plasma concentration results. Maribavir PK concentrations will be summarized by visit and planned sampling time. A scatter plot of all reportable maribavir concentration vs actual sampling time will be generated. A listing of subjects with maribavir concentration below the quantitation limit will be provided along with the Week 8 efficacy response. Analysis on the relationship between C_{min} (predose maribavir concentration) and efficacy endpoints of interest will be conducted by graphical exploration and by statistical models.

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. 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 maybe conducted by combining maribavir PK data from other Phase 2 and Phase 3 studies.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates/revisions, and local ethical and legal requirements.

The name and address of each third party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6, EU Directive 2001/20/EC, Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2) Current Step 4 version dated 9 November 2016, and updates/revisions, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO/investigator as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for nonpediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The sponsor will make an end of study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC and its updates/revisions.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6, EU Directive 2001/20/EC, Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2) Current Step 4 version dated 9 November 2016, and updates/revisions, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and subinvestigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator will, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC and its updates/revisions as amended by Directive 2003/63/EC and ICH Guidance E3.

The investigator is responsible for supervising any individual or party to whom the investigator delegates study tasks conducted at the trial site. If the investigator/institution retains the services of any party to perform study tasks they should ensure this party is qualified to perform those study tasks and should implement procedures to ensure the integrity of the study tasks performed and any data generated.

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any coinvestigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms are supplied by the sponsor/CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data sent to the sponsor must be endorsed by the investigator.

The CRA/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diary, original clinical laboratory reports, and histology and pathology reports.

The investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be

attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary (eg, via an audit trail).

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor, the respective national, local, or foreign regulatory authorities, the IRB/EC, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC, or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc.). Nonstudy site personnel will not disclose any personal information or personal medical information (applicable in the UK).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US Food and Drug Administration (FDA), EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.2.4 Compliance to all Local, State, and National Controlled-substance Biohazard and Infectious Disease Regulations and Legislation

When using controlled substances, biohazardous material, or substances for infectious diseases, the investigator must at all times comply with all local, state, and national laws pertaining to

registration and reporting with the appropriate regulatory body and control and handling of such substances.

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent and assent, where applicable from all study subjects prior to any study-related procedures including screening assessments; parents will sign the assent form, as applicable. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally-authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent and assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally-authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

Within the source documents, site personnel should document instruction of and understanding by a parent or both parents/legally-authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information, and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

For sites within the EU, the applicant for an EC opinion can be the sponsor, the investigator, or for multicenter studies the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor/CRO has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for sites within the EU, this can be done by the sponsor, the investigator or for multicenter

studies the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with Health Insurance Portability and Accountability Act (HIPAA). A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO/sponsor.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representative reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP620; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique number for identification. The results of studies containing subjects' unique identifying number and relevant medical records will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a noncommercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy. A description of this clinical study may also be available on other externally facing public websites and registries. A summary of the study results may be potentially disclosed as per local and country specific requirements.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the

copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12. APPENDICES

Appendix 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	25 April 2016	Global
Amendment 1	08 July 2016	Global
Amendment 2	01 December 2016	Global
Amendment 2.1[a]	18 May 2017	Germany
Amendment 3	01 March 2017	Global (except Germany)
Amendment 3.1[a]	10 October 2017	Germany, Singapore
Amendment 4	26 March 2018	Global (except Germany and Singapore)
Amendment 5	11 July 2018	Global (except Germany and Singapore)
Amendment 5.1[a,b]	20 August 2018	Germany, Singapore, Switzerland
Amendment 6	07 December 2018	Global (except Germany, Singapore, Switzerland)
Amendment 6.1	07 December 2018	Germany, Singapore, Switzerland

[a] Summary of changes for country-specific amendments are included in the respective documents.
[b] Amendment 5.1 replaces Amendment 3.1 (no intervening protocol version).

Amendment 5 to protocol SHP620-303 incorporated the following changes:

- Added a study visit at Study Day 4 (+/-1) for subjects taking a narrow therapeutic index immunosuppressive agent (ie, tacrolimus, cyclosporine, everolimus, sirolimus) at baseline to align the protocol with a recent recommendation from the data monitoring committee (DMC).

- Added a visit for subjects not taking a narrow therapeutic index immunosuppressive agent at baseline who begin therapy during the course of the treatment period (4 days after starting the immunosuppressive agent), and subjects in the investigator-assigned therapy arm who enter the maribavir rescue arm (4 days after starting maribavir) to align the protocol with a recent recommendation from the DMC.

- Updated definition of symptomatic CMV infection to include both tissue invasive CMV disease and CMV syndrome throughout the protocol.

Noteworthy changes to the protocol are captured in the table below. Other minor editorial revisions (including changes for consistency and clarity) are not described in this table.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **5**	**Amendment Date** **11 Jul 2018**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated the definition for "Refractory": Documented failure to achieve >1 $\log_{10}$ (common logarithm to base 10) decrease in CMV DNA level in whole blood or plasma after a 14 day 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.		Definitions, Synopsis, Section 3.1
Updated the definition for "Resistant": Documented failure to achieve >1 $\log_{10}$ (common logarithm to base 10) decrease in CMV DNA level in whole blood or plasma after a 14 day 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.		Definitions, Synopsis, Section 3.1
Updated inclusion criterion 4 to clarify that the subject must have a current CMV infection that is refractory to the most recently administered of the four anti-CMV treatment agents; that refractory is 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 a 14 day or longer treatment period with IV ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir; and that subjects with documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir must also meet the definition of refractory CMV infection.		Synopsis, Section 4.1
Removed the statement that prospectively, the study may enroll an additional cohort of 150 subjects with tissue-invasive CMV disease, in a 2:1 ratio (maribavir: investigator-assigned anti-CMV therapy) to subsequently confirm the clinical benefit of maribavir in improvement or resolution of tissue-invasive CMV disease in a total of 210 subjects (inclusive of 60 subjects enrolled initially); and that feasibility of this approach will be confirmed during the study conduct.		Synopsis, Section 2.2, Section 3.1
Clarified EAC review procedure.		Synopsis, Section 3.1
Updated number of site visits to 19 times.		Synopsis, Section 3.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **5**	**Amendment Date** **11 Jul 2018**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Added Visit 2A/2A-R to the Study design Flow Chart.		Synopsis, Section 3.1
Clarified the screening CMV DNA concentration limits (in whole blood or plasma) used for stratification of eligible subjects and specified that the most recent qPCR results should be used.		Synopsis, Section 3.1, Section 6.2.2
Clarified that, for subjects randomized to investigator-assigned anti-CMV treatment, switching between valganciclovir and ganciclovir is allowed, while switching to another CMV agent is not.		Synopsis, Section 6.2.3
Clarified that, in the randomized set, subjects will be analyzed in the treatment group to which they are randomized.		Synopsis, Section 9.7
Clarified that the safety set will consist of all subjects who have taken any dose of study treatment and that subjects will be analyzed according to the treatment actually received.		Synopsis, Section 9.7
Removed the following statement: "Since intolerance alone will not qualify the patient for the rescue, such patients will not be considered nonresponders for the purpose of the primary analysis."		Synopsis, Section 9.8
Removed the following statement: "It is expected that 60 subjects with tissue invasive disease (symptomatic subjects) will be enrolled in this study.		Synopsis, Section 9.8.2
Clarified that the on treatment observation period will serve as the primary analysis of safety.		Synopsis, Section 9.9
Clarified the overall study observation period as follows: "The overall-study observation period minus the period on rescue arm starts at the time of the start of the study treatment through the end of the study or through the time before receiving maribavir rescue therapy for subjects who receive maribavir rescue therapy."		Synopsis, Section 9.9
Clarified that similar observation periods are defined for the safety analysis of the maribavir rescue arm.		Synopsis, Section 9.9
Updated the definition of treatment emergent adverse events.		Synopsis, Section 9.9
Clarified exploratory endpoint to be [redacted]		Synopsis, Section 9.10.3

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **5**	**Amendment Date** **11 Jul 2018**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Added a column for additional visit 2A/2A-R to collect the following assessments: Hematology/Chemistry, Immunosuppressant drug concentration levels, Study diary; Concomitant medications, therapies, and procedures, as well as Adverse events.		Table 1, Section 7.1.2
Added Visit 2A/2AR (Day 4) ± 1 day and Study Visit 3/3R (Day 7) +2 days to the definition of the permissible assessment window.		Table 1, Footnotes, Section 7.1.2
Clarified that 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.		Table 1, Footnotes, Section 7.2.3.5
Clarified when a blood sample to measure immunosuppressant drug concentration level will be obtained for subject receiving immunosuppressant drugs and for subjects not receiving immunosuppressant drugs at Day 0, but who started any time after Day 0.		Table 1, Footnotes, Section 7.2.3.5
Added new footnote to clarify that Visit 2A/2AR is only required for subjects taking tacrolimus, cyclosporine, everolimus, or sirolimus at Visit 2/2R.		Table 1, Footnotes
Updated timeframe for collection of medical history data from 5 years to 2 years.		Section 7.2.3.1
Updated for consistencies with changes in Table 1.		Section 7.2.5, Table 5
Updated the blood volume expected to be drawn from each subject regardless of age or sex.		Section 7.2.5
Clarified criteria for reporting CMV infection as an AE or as an SAE.		Section 8.1.5, Table 6

Amendment 4 to Protocol SHP620-303 incorporates the following major changes:

- Modified adverse event collection period to indicate that collection of nonserious adverse events that are not related to study treatment will be restricted to 30 days after the last dose of study drug.

- Amended exclusion criterion 6 regarding patients who have tissue invasive CMV disease with central nervous system involvement to indicate that such central nervous system involvement includes the retina (eg CMV retinitis).

- Modified the reporting requirements for prior therapeutic or diagnostic interventions performed prior to study enrollment.

- Clarified procedure requirements for subjects moving from investigator-assigned treatment to rescue arm to indicate that procedures do not need to be repeated when the end-of-treatment visit is performed on the same day as rescue arm entry.

- Clarified that study treatment may be interrupted for up to 7 consecutive days, or up to 2 study treatment interruptions for a total of up to 7 days.

- Clarified language regarding sample size calculation, removing anticipated treatment discontinuation rate for foscarnet-treated subjects.

- Clarified restrictions regarding re-screening of subjects who have previously screen-failed.

- Limited hepatitis testing requirements at screening to antibody testing.

- Added GVHD assessment criteria forms from cited publications in the appendices.

- Added letermovir to list of prohibited medications during study, and washout instructions for letermovir use prior to study entry

Noteworthy changes to the protocol are captured in the table below. Other minor editorial revisions (including changes for consistency and clarity) are not described in this table.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **26 Mar 2018**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated signatory to [redacted], MD		Protocol Signature Page
Updated Emergency Contact Information to provide more extensive information on the reporting of serious adverse events (SAEs).		Emergency Contact Information
Replaced "Pharmacovigilance" with "Drug Safety" to reflect the department name change		Emergency Contact Information, Section 8.1.7, Section 8.2.2, Section 8.2.4
Updated PDD medical monitor to [redacted], MD, PhD, MBA, [redacted], PPD, Drug Safety		Emergency Contact Information
Clarified the definition for "Refractory": requires 2 weeks of <u>continuous</u> treatment, and applies to the current infection and the most recently administered anti-CMV agent. The definition for "Resistant" is inclusive of the definition for "Refractory" and has been amended accordingly.		Definitions, Synopsis, Section 3.1, Section 4.1
Updated number of sites to approximately 140 sites worldwide.		Synopsis, Section 3.3
Updated planned study period to 2016 –2019.		Synopsis
Clarified changes to the investigator treatment of choice after randomization to include note that changes between IV ganciclovir and oral valganciclovir are allowed and that combination therapy with cidofovir and foscarnet is prohibited due to risk of nephrotoxicity.		Synopsis, Section 3.1, Section 6, Section 6.2.3
Updated permitted duration of treatment interruption from originally 4 to 7 consecutive days, or up to 2 study treatment interruptions for a total of up to 7 days.		Synopsis, Section 3.1, Section 6.2.3
Changed exclusion criterion 3 to include the recently-approved anti-CMV agent letermovir.		Synopsis, Section 4.2
Changed exclusion criterion 6 to exclude subjects with CMV retinitis present at baseline.		Synopsis, Section 4.2
Clarified language regarding sample size calculation, removing mention of anticipated treatment discontinuation rate for foscarnet-treated subjects.		Synopsis, Section 9.6
Clarified that the end of the on-treatment period is 7 days after the last dose of study drug or 21 days if cidofovir is used.		Synopsis, Section 9.9
Removed paragraph on the reporting of disease under study from Synopsis to avoid redundancy with Section 8.1.5.		Synopsis
Clarified several footnotes in the Schedules of Assessment to provide		Table 1, Footnotes

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **26 Mar 2018**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
additional details regarding the timing and requirements of several study assessments.		
Clarified procedure requirements for subjects moving from IAT to Rescue Arm.		Study Schedules, Section 4.5
Clarified procedure for tissue invasive CMV disease assessment in symptomatic and asymptomatic subjects.		Study Schedules, Section 7.2.2.3
Added new in vitro data on the effects of maribavir on drug metabolism enzymes.		Section 1.2.1
Included letermovir in the list of prior medications to be recorded on the CRF.		Section 5.1
Updated medical history to be recorded from "any therapeutic or diagnostic intervention performed **within 3 months** prior to the first dose of study treatment on Visit 2/Week0/Day 0" to "any therapeutic or diagnostic intervention performed **within 30 days** prior to the first dose of study treatment on Visit 2/Week0/Day 0"		Section 5.1
Added additional precaution with concomitant medication.		Section 5.2.1
Added procedure to be followed for subjects developing new CMV retinitis while in the maribavir treatment arm.		Section 5.2.2
Added letermovir to the list of systemic anti-CMV therapies prohibited for concomitant use in subjects receiving maribavir (except unintentional administration for no longer than 1 day).		Section 5.2.2
Added letermovir to the list of concomitant medications prohibited while the subject is receiving investigator-assigned anti-CMV treatment.		Section 5.2.2
Clarified that in cases where IV anti-CMV agents cannot be ordered, prepared, and administered immediately after randomization, the first dose of drug must be given within 24 hours of randomization.		Section 6.2.3
Clarified restrictions regarding rescreening of subjects who have previously screen-failed.		Section 7.1.1
Clarified clinical laboratory assessments for hepatitis.		Section 7.2.3.5
Amended adverse event collection period to specify that following the 30 day capture period for all adverse events, only those adverse events deemed related to investigational product or other protocol-mandated procedures and all SAEs (regardless of causality assessment) will be collected		Section 7.2.3.6, Section 8.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **26 Mar 2018**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
through the end of the study (Visit 18/Week 20 [Follow-up Week 12]).		
Updated e-mail contact address for the Shire Global Drug Safety Department		Section 8.2.2
Updated tabular presentation of assessments of responders for key secondary efficacy endpoint to provide clearer rationales.		Section 9.8.2
Added additional descriptive summary to the study secondary efficacy endpoint of all causes mortality by the end of the study.		Section 9.8.5
Clarified safety endpoints for analysis.		Section 9.9
Clarified the shift analysis of laboratory results.		Section 9.9
Reproduced GVHD assessment criteria forms (from cited publications).		Appendix 10, Appendix 11
Updated wording and added two additional references: Ascioglu, S., Rex, J. H., De Pauw, B., Bennett, J. E., Bille, J., Crokaert, F., Denning, D. W., Donnelly, J. P., Edwards, J. E., Erjavec, Z., Fiere, D., Lortholary, O., Maertens, J., Meis, J. F., Patterson, T. F. & R 2002. Defining Opportunistic Invasive Fungal Infections in Immunocompromised Patients with Cancer and Hematopoietic Stem Cell Transplants: An International Consensus. Clinical Infectious Diseases, 34, 7-14. De Pauw, B., Walsh, T. J., Donnelly, J. P., Stevens, D. A., Edwards, J. E., Calandra, T., Pappas, P. G., Maertens, J., Lortholary, O., Kauffman, C. A., Denning, D. W. & Patterso 2008. Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clinical Infectious Diseases, 46, 1813-1821.		References, Appendix 13

Amendment 3 to Protocol SHP620-303 incorporated the following major changes:

- Modified primary, key secondary, and secondary objectives and corresponding endpoints to include subjects who discontinue study treatment early and meet the criteria of confirmed CMV viremia clearance as responders in the primary efficacy analysis.
- Added an intensive pharmacokinetic sampling schedule at Visit 3/Week 1 for adolescent subjects (≥12 to <18 years of age).

- Modified Inclusion Criterion 5 to indicate that the investigator is willing to treat the subject with at least 1 of the available anti-CMV drugs. Note: Combination therapy with foscarnet and cidofovir is not permitted in the IAT arm due to the potential for serious nephrotoxicity.

- Clarified Inclusion Criterion 9 to indicate that urine-based pregnancy tests may be performed per institutional requirements (in addition to protocol-required serum β-hCG testing); however they are not sufficient for eligibility determination.

- Modified Inclusion Criterion 10 to allow subjects the option to receive tablets crushed and/or dispersed in water via a nasogastric or orogastric tube.

- Clarified in Exclusion Criterion 13 that subjects who have received an unapproved agent or device within 30 days before initiation of study treatment will not be eligible.

- Added recommendations related to male contraception in clinical trials, per the clinical trial facilitation group (CTFG). Male subjects will be required to use a condom in conjunction with highly effective method of birth control for their female partners of child-bearing age. Both male participants and their female partners must use this form of birth control from the time prior to the first dosing until 90 days after the last dose of study treatment.

Noteworthy changes to the protocol are captured in the table below. Other minor editorial revisions (including changes for consistency and clarity) are not described in this table.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **01 Mar 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated signatory to [redacted], MD, MSc.		Protocol Signature Page
Added investigator-assigned anti-CMV treatment (IAT) to the abbreviations list.		Abbreviations
Added clarifying text to indicate that 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.		Synopsis, Table 1(footnote "c"), Section 3.1
Modified Exclusion Criterion 8 to indicate that historical results for human immunodeficiency virus (HIV) will be accepted to assess eligibility and no additional study testing will be required. "Have known (previously documented) positive results for human immunodeficiency virus (HIV)." ~~Subjects must have a confirmed negative result within 3 months of study entry or be willing to be tested at screening. Local laboratory results are acceptable~~."		Synopsis, Table 1 (footnote "i"), Section 3.1, Section 4.2, Section 7.1.1, Section 7.2.3.5
Added the rationale for the inclusion of adolescent subjects ⩾12 to <18 years of age in the study.		Synopsis, Section 2.1, Section 2.3
Modified primary objective and corresponding endpoint and analysis to clarify that subjects who discontinue study treatment early and meet the criteria of confirmed CMV viremia clearance at Study Week 8 will be considered as responders in the primary efficacy analysis.		Synopsis, Section 2.4.1, Section 9.8.1.
Modified key secondary objective and corresponding endpoints and analyses to clarify that subjects who discontinue study treatment early and meet the criteria of confirmed CMV viremia clearance will be considered for responder evaluation in the efficacy analysis.		Synopsis, Section 2.4.2, Section 9.8.2
Modified secondary objectives and corresponding endpoints and analyses to include subjects who discontinue study treatment early and meet the criteria of confirmed CMV viremia clearance as responders in the efficacy analysis. Added the former primary and key secondary objectives as secondary objectives: • "To compare the efficacy of maribavir to anti-CMV therapy (IAT) 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 improvement or resolution after completion of 8 weeks of treatment and maintenance of this treatment effect through Study Weeks 12 (4 weeks of post		Synopsis, Section 2.4.3, Section 9.8.5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **01 Mar 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
treatment period),16 (8 weeks post treatment/follow-up phase), and 20 (12 weeks of post treatment)." Added the following secondary objectives and corresponding endpoints: • "To assess the 2 study treatment arms for maintenance of CMV viremia clearance and resolution or improvement of tissue invasive CMV disease, 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 8 weeks of study, during the 12 weeks of the follow-up phase, and at any time during the study." • "To evaluate the incidence of recurrence of CMV viremia in the 2 study treatment arms, when on treatment and off treatment." Deleted the following secondary objective and the corresponding endpoint since it is redundant with the modified primary objective: "~~To assess the 2 study treatment arms for maintenance of CMV viremia clearance achieved while on study treatment, irrespective of its duration, at 8 weeks of study.~~"		
Deleted the following exploratory objectives and corresponding endpoints that are redundant with the modified secondary objective. [redacted]		Synopsis, Section 2.4.4, Section 9.8.6
Modified the following for clarity: "The CMV infection must be refractory to 1 or more of the anti-CMV agents (ganciclovir, valganciclovir, foscarnet, or cidofovir) ~~currently administered to the subject,~~ and the subjects must meet the remaining specified eligibility criteria."		Synopsis, Section 3.1
Modified Inclusion Criterion 5: ~~Per "~~The investigator is willing to treat the subject ~~'s judgment, be eligible for treatment~~ with at least 1 of the available anti-CMV drugs (ganciclovir, valganciclovir, foscarnet, or cidofovir)". ~~The treatment for which a subject would be eligible, if randomized to investigator assigned treatment, must be documented prior to randomization.~~ Note: Combination therapy with foscarnet and cidofovir is not permitted in the IAT arm due to the potential for serious nephrotoxicity.		Synopsis, Section 3.1, Section 4.1
Updated Inclusion Criterion 10 to allow subjects the option to receive tablets crushed and/or dispersed in water:		Synopsis, Section 4.1, Section 6.2.3

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **01 Mar 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
• Be able to swallow tablets, or receive tablets crushed and/or dispersed in water via a nasogastric or orogastric tube		
Added to Inclusion Criterion 9 that additional urine pregnancy tests may be performed per institutional requirements.		Synopsis, Section 4.1, Section 7.1.1
Clarified in Exclusion Criterion 13 that subjects who have received an unapproved agent or device within 30 days before initiation of study treatment will not be eligible.		Synopsis, Section 4.2, Section 5.2.2
Clarified that the randomized set rather than the FAS will be used for efficacy analysis along with the per-protocol set and that the randomized set would be used for the primary analysis and the per-protocol set would be used as the supportive analysis.		Synopsis, Section 9.7
Added the definition of adolescent pharmacokinetic set.		Synopsis, Section 9.7
Updated Tables 7 and 8 to include additional scenarios for responder determination.		Synopsis, Section 9.8.1, Section 9.8.2
Updated the primary, key secondary, secondary, and exploratory endpoints to align with updates made to the objectives.		Synopsis, Section 9.8.1, Section 9.8.2, Section 9.8.5, Section 9.8.6
Added an additional subgroup analysis for adolescents: • Adolescents ⩾12 to <18 years of age (exploratory analysis: may be conducted if sample size is adequate)		Synopsis, Section 9.8.4
Added PK parameters assessed as secondary endpoints for adolescent subjects who provided intensive PK sample at Visit 3/Week 1. The secondary PK endpoint for all subjects who received maribavir will be maribavir C_{min} (predose maribavir concentration).		Synopsis, Section 9.10.3
Clarified that urine test results are not sufficient for eligibility determination.		Table 1 (footnote “h”), Section 7.1.1
[redacted]		Table 1 (footnote “m”) , Section 7.1.2, Section 7.2.2.4
Added an intensive PK sampling schedule (at Visit 3/Week 1) for adolescent subjects participating in the study.		Table 1 (footnote “o”), Section 7.1.2, Section 7.2.4.1
Clarified that female subjects 12 years of age and older, who are amenorrheic for reasons other than menopause (12 consecutive months of spontaneous amenorrhea in patients with previous normal menstruation), including subjects who did not yet have the menarche, would be		Section 4.4.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **01 Mar 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
allowed to participate provided they agree to abstinence or an acceptable form of contraception defined in the protocol.		
Added recommendations related to male contraception in clinical trials, per the clinical trial facilitation group (CTFG): Male subjects will be required to use a condom in conjunction with highly effective method of birth control for their female partners of child-bearing age. Both male participants and their female partners must use this form of birth control from the time prior to the first dosing until 90 days after the last dose of study treatment.		Section 4.4.2
Removed text requiring retinal images to be collected and provided to support diagnosis and mention of EAC analysis of individual histopathology slides: "In cases of CMV retinitis, the retinal images taken by the ophthalmologist may be ~~collected and provided~~ **used** as the evidence supporting the diagnosis." "~~EAC might request the individual histopathology slides to be read by an independent pathologist.~~"		Section 7.2.2.3
Added the additional blood draw volume required for intensive PK sampling for adolescents: "Subjects between the ages of 12 and 18 years will have an additional 24 mL of blood drawn for intensive PK visits."		Section 7.2.5, Table 5
Updated the reference safety information section to indicate that the country-specific product package inserts for cidofovir should be checked to assess the expectedness of an AE for this study. • The respective summary of product characteristics (SmPC) for a comparator anti-CMV treatment (valganciclovir, ganciclovir, and foscarnet) or ~~US~~ **country-specific** product package insert for cidofovir.		Section 8.2.1
Amended reference safety information to include fatal outcomes: The study population is HSCT or SOT recipients with cytomegalovirus infections. The following SAEs are common in this study population and are anticipated to occur, hence these SAEs (including fatal outcomes) will not be considered unexpected and will not be individually reported to the regulatory agencies, IRBs, Ethics Committees, and investigators**, provided there is no increased frequency of these events***: • Any CMV infection, including CMV reactivation/recurrence, CMV syndrome, and tissue invasive CMV disease • Any other bacterial, viral infection, or fungal infection • Acute and chronic graft versus host disease and graft rejection and loss • Reactivation of the malignancy under treatment in HSCT recipients		Section 8.2.7

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **01 Mar 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
This includes fatal outcomes for the aforementioned SAEs. ***Maribavir phase 2 (studies 1263-202 and 1263-203) data will be used as reference.**		
Added new text to clarify subject entry into the study rescue arm: "Subjects in the investigator-assigned treatment arm who are unable to continue taking investigator-assigned anti-CMV treatment due to the lack of 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. Subjects who take rescue medication will be considered as failures for primary efficacy analyses. 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. Since intolerance alone will not qualify the patient for the rescue, such patients will not be considered nonresponders for the purpose of the primary analysis. The same is applicable for patients who might be discontinued from maribavir treatment due to intolerance. Subjects who discontinue due to intolerance and without viremia clearance at Study Week 8 will be considered failures in both treatment arms."		Section 9.8
Added additional reference to an updated industry regulation: Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2) Current Step 4 version dated 9 November 2016.		Section 10.1.1, Section 10.2.1
Updated the table in Appendix 4 with the following pUL97 substitutions: D456N, M460L, C480R, P521L, C592F, L595T, N597D/I, G598D/V, and C603Y and the following pUL54 substitutions: L862F, D879G, and A972V.		Section 12
Applied editorial changes throughout the document for clarity.		Synopsis and throughout document, as needed

Amendment 2 to Protocol SHP620-303 incorporated the following major changes:

- An additional pregnancy test at Visit 6/Week 4 performed at monthly interval.
- Addition of highly effective method of female and male contraception per the recommendations related to contraception and pregnancy testing in clinical trials by clinical trial facilitation group (CTFG).

- Modification of Inclusion Criterion 10 to *only* allow enrollment of subjects who will be able to swallow tablets.
- Inclusion of cut off levels for CMV DNA concentration in whole blood for evaluating eligibility at screening.
- Emphasis on potent inducers of Cytochrome P450 (CYP) 3A4 and/or P-glycoprotein (P-gp) and caution for concomitant use of potent inhibitors of CYP 3A4, in alignment with the guidance to the investigators provided in the maribavir investigator's brochure.
- Caution and recommendation for careful monitoring of concentration levels of concomitant medications that are substrates of CYP 2C19 and P-gp both after initiation of maribavir (when substrate levels may increase) and after discontinuation of maribavir (when substrate levels may decrease), in alignment with the guidance to the investigators provided in the maribavir investigator's brochure.
- Specified that since intolerance to assigned treatment alone does not qualify a subject for the rescue arm, such subjects will not be considered nonresponders for the purpose of primary analysis. The same is applicable for subjects that might be discontinued from maribavir treatment due to intolerance.
- Creation of a list of definitions relevant for analyses for easy access and convenience.

Noteworthy changes to the protocol are captured in the table below. Other minor editorial revisions (including changes for consistency and clarity) are not described in this table.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **01 Dec 2016**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Created a list of definitions pertaining to evaluations/analyses for the study for easy access and convenience, and for consistency throughout the document.		The list of definitions follows the list of abbreviations in the "Table of Content", also in Section 9.8
Added screening value for CMV DNA concentration in whole blood along with that in plasma to Inclusion Criterion 3: "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…"		Synopsis, Section 3.1, Section 4.1
Specified CMV DNA concentration in whole blood for stratification based on baseline 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 IU/mL in whole blood or** ⩾9100 IU/mL **in plasma,** and low viral load **<27300 IU/mL in whole blood** or <9100 IU/mL **in plasma** as determined by the local or central specialty laboratory qPCR results…."		Synopsis, Section 3.1, Section 6.2.2
Amended Inclusion Criterion 10 to *only* allow enrollment of subjects who will be able to swallow tablets. Subjects who have the condition at baseline that requires orogastric or nasogastric administration of study treatment will not be enrolled until the results of additional in vitro recovery study, with 200mg maribavir tablets are available. Emphasized in "dosing" section that if subjects develop the condition requiring nasogastric or orogastric tube administration while on study treatment, maribavir tablets may be administered via this method to avoid interruption or discontinuation of treatment.		Synopsis, Section 4.1, Section 6.2.3
Added that there is no clinical experience with investigator assigned treatments (ganciclovir, valganciclovir, or cidofovir) in pregnant subjects and based on the reproductive toxicity observed in animal studies these should be considered a potential teratogen and carcinogen in humans (Valcyte and Vistide Prescribing Information). The reproductive toxicity studies with foscarnet (Foscavir) in animals were conducted using exposures that are inadequate to define the potential of teratogenicity at levels to which women will be exposed (Foscavir Prescribing Information).		Section 4.4.1
Added recommendations related to contraception in clinical trials, per the clinical trial facilitation group (CTFG). Elaborated on highly effective method of contraception for sexually active females of child bearing potential participating in the study. Added that vasectomized male partner is a highly effective birth control method provided that		Section 4.4.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **01 Dec 2016**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
partner is the sole sexual partner of the female trial participant who is of child bearing potential and that the vasectomized partner has received medical assessment of the surgical success.		
Added caution and recommendation for careful monitoring of concentration levels of concomitant medications that are substrates of CYP 2C19 and P-gp both after initiation of maribavir (when substrate levels may increase) and after discontinuation of maribavir (when substrate levels may decrease), in alignment with the guidance to the investigators provided in the maribavir investigator's brochure.		Section 5.2.1
Added caution for concomitant use of potent inhibitors of CYP 3A4 and emphasized prohibition of potent inducers of Cytochrome P450 (CYP) 3A4 and/or P-glycoprotein (P-gp), in alignment with the guidance to the investigators provided in the maribavir investigator's brochure.		Section 5.2.1, Section 5.2.2
Added an additional pregnancy test at Visit 6/ Week 4 so that these test are performed at monthly interval since the female subjects included in the study could potentially receive drugs with known teratogenic effect.		Schedule of Assessment 1, Section 7.1.2, Section 7.2.3.5
[redacted]		[redacted]
Specified that since intolerance to assigned treatment alone does not qualify a subject for the rescue arm, such subjects will not be considered non responders for the purpose of the primary efficacy analysis. Also added that this is applicable to subjects that might discontinue for maribavir treatment due to intolerance. Subjects who do not achieve confirmed viremia clearance will be considered failures in both treatment arms.		Section 9.8.1

Amendment 1 to Protocol SHP620-303 incorporated the following major changes:

- Removal of the restriction to utilize only a single commercially available anti-CMV treatment for 8 weeks of the study for the subjects in the Investigator-assigned anti-CMV treatment arm. Subjects may also continue on prior therapy if this is the best treatment option selected by the investigator.
- Addition of assessment of "**invasive bacterial and fungal infection**" to the list of safety endpoints since it is one of the adverse events of special interest in the study population.

- Update to the table for prior medications/procedures/diagnostic interventions.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **08 Jul 2016**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
In order to facilitate recruitment and optimal inclusion of broader patient population, hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients, whose CMV infections are refractory to available anti-CMV treatment (ie, ganciclovir, valganciclovir, foscarnet, or cidofovir), the restriction to utilize only a single commercially available anti-CMV treatment for 8 weeks of the study was removed for the subjects in the Investigator-assigned anti-CMV treatment arm. Subjects may also continue on prior therapy if this is the best treatment option selected by the investigator. Added text in Section 2.2 Investigator assigned anti-CMV treatment with 1 **or 2** of the 4 anti-CMV drugs (ganciclovir, valganciclovir, foscarnet, or cidofovir) with additional strategies when deemed necessary by investigator (eg, change in the dose of the anti-CMV drug, reduction of immunosuppressant, addition of IVIG or CMV Ig) is the active control group for this study. **The subject on single or dual therapy with anti –CMV agents at the time of enrollment, may either change therapy at the time of randomization/treatment initiation or remain on the same therapy as the investigator assigned anti-CMV treatment, if randomized to this study arm. If the treatment was continued or started as 2 anti-CMV agents, withdrawal of 1 agent, while continuing the second one will be possible.** Added text in Section 3.1 **The subjects randomized to maribavir treatment arm will discontinue the 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. If the treatment was continued or started as 2 anti-CMV agents, withdrawal of 1 agent, while continuing the second one will be possible. Addition of another anti-CMV agent will be declared as failure for the purpose of study analysis. After randomization, changes to the investigator treatment of choice could include, change in dosing, dosing regimen, but will not include an addition of another anti-CMV agent.** Modified text in Synopsis and Section 3.1 "Subjects Randomized to Investigator-Assigned Anti-CMV **Investigator-assigned anti-CMV treatment strategies for the 8 weeks of**		Synopsis, Section 2.2, Section 3.1 (Study design-Study Treatment Phase), Section 5.2.2 (Prohibited treatment during study drug treatment), and Section 6 (Identity of study treatments) and 6.2.3 (Dosing)

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the study treatment phase must only utilize up to 2 available anti-CMV agents from the following: ganciclovir, valganciclovir, foscarnet, or cidofovir. **If investigator's decision is to change the pre-study anti-CMV agent(s), the investigator can select up to 2 new anti-CMV drugs as the study treatment.** **Investigator may also decide to keep the subject on the same anti-CMV drug(s), which was/were used for treatment of subject prior to randomization/ treatment initiation.** **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, change in dosing, change in dosing regimen, but** will not include an addition of another anti-CMV agent. **Dose adjustment is allowed as deemed appropriate by the investigator. The rationale for dose adjustment will be documented; change to another anti-CMV agent during the study treatment period is not allowed. Investigational anti-CMV agents are not permitted. Additional treatment strategies can complement the use of a single anti-CMV agent, for example, reducing or modifying the immunosuppressant drug use, use of IVIg or CMV Ig."** Subjects will follow the investigator's prescribed anti-CMV treatment. Subjects will remain on their investigator-assigned anti-CMV therapy for the 8 weeks of the study treatment phase. **The subject may stop treatment due to intolerance based on investigator judgment, however if the interruption is longer than protocol specified and/or subject is not able to continue with 8 weeks of treatment it may result in classifying the subject as a failure for analysis purposes.** Subjects may be assessed for entry into a rescue arm, starting at Visit 5/Week 3 (after a minimum 3 weeks of treatment), for treatment with maribavir 400 mg BID for 8 weeks. Subjects must meet 1 of the following criteria to be eligible to enter the maribavir rescue arm: <u>Modified text in Section 6:</u> Study investigators will 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 investigator-assigned anti-CMV treatment arm **may** ~~only~~ utilize 1 **or 2 (only if subject's current dual therapy at enrollment is continued after randomization or started at randomization)** of the following 4 ~~noninvestigational~~ anti-CMV agents:	

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(change from ganciclovir to valganciclovir or vice versa will be allowed): Modified text in Section 6.2.3 Investigator-assigned anti-CMV treatment strategies **for the 8 weeks of the study treatment phase** must only utilize ~~a single~~ **1 or 2** of the available anti-CMV agent **from the following:** ganciclovir, valganciclovir, foscarnet, or cidofovir. **The subject receiving 1 or 2 anti –CMV agents at the time of enrollment, may either change therapy at the time of randomization/treatment initiation or 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, change in dosing regimen, but will not include an addition of another anti-CMV agent. 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.** Dose adjustment **is** allowed as deemed appropriate by the investigator. The rationale for dose adjustment will be documented; change **of treatment** to another anti-CMV agent or addition of another anti-CMV agent during the study treatment will be ~~considered~~ **declared** as treatment failure~~except for change of therapy from ganciclovir to valganciclovir and vice versa.~~		
Clarified that the investigator-assigned anti-CMV agents to which the CMV infection is refractory is currently administered to an eligible subject.		Synopsis, Section 3.1 (Study Design and Flow Chart)
Clarified the definition for "Refractory" that the documented failure to achieve >1 $\log_{10}$ decrease in CMV DNA level in whole blood or plasma could be after 2 or more weeks of treatment with IV ganciclovir, oral valganciclovir, IV foscarnet, or IV cidofovir or could be after treatment with any combination of this anti-CMV agents.		Synopsis, Section 3.1 (Study Design and Flow Chart)
Removed a redundant statement not necessary for the definition of and clarified that "***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 2 or more weeks of treatment with IV ganciclovir, oral valganciclovir, IV foscarnet, or IV cidofovir **(or any combination thereof).** ~~Results from the same laboratory and the same sample type (blood or plasma) are to be used to determine the refractoriness~~"		Synopsis, Section 3.1 (Study Design and Flow Chart)
Specified for clarity this study will also assess improvement or resolution of tissue-invasive CMV disease at the end of the 8-week study treatment phase and during the follow-up phase **for subjects with disease present** at baseline.		Synopsis, Section 3.1 (Study Design and Flow Chart)
To be consistent with other sections in the protocol, it was clarified that subject enrollment will be monitored to achieve an approximate target of 60% of subjects who have a CMV infection with documented resistance to any of the		Synopsis, Section 3.1 (Study design)

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anti-CMV agents (ganciclovir, valganciclovir, foscarnet, or cidofovir) ~~proven by~~ **according to the central specialty results** from samples taken at baseline.		
To facilitate study conduct and to be consistent with other sections in the protocol, the following details were added in the synopsis for the Screening Phase: "Historical laboratory results (local laboratory) for tests specified in the Schedule of Assessment 1 may be used during screening for the assessment of the eligibility, including local CMV DNA quantification test results. If local laboratory results are not available, the central laboratory assessments may be conducted. All clinical laboratory results required for eligibility verification must be available prior to randomization" It was added that the historical laboratory results from local laboratory for CMV DNA quantification test may be used for assessment of eligibility at screening.		Synopsis, Section 3.1 (Screening Phase)
Added information that the blood sample taken for CMV DNA test at the first visit of the maribavir rescue treatment period will be used as the 'baseline' assessment for the purpose of the analyses of the response to maribavir rescue treatment (including resistance analyses).		Synopsis, Section 3.1
The following statements were added for clarity: "**CMV DNA quantification may be performed in the local or central specialty laboratory. Already available results from the local laboratory (historical results) will be acceptable for screening, if taken within the time frames indicated and if from the same laboratory**." "**All clinical laboratory results required for eligibility verification must be available prior to randomization.**"		Section 3.1 (Screening Phase)
Since not all required tests at baseline will be performed at screening for assessing eligibility, the text was modified to state that samples for all hematology/chemistry tests, and for the CMV DNA quantification test specified at baseline will be collected even if these tests were performed within 7 days prior to the first dose, and central laboratory results were available. <u>Modified text in the Synopsis</u> "The screening and Visit 2/Week 0/Day 0 visits can occur on the same day in the case when **historical local laboratory results are available for determination of eligibility. All Visit 2/Day 0 procedures must be completed prior to study treatment administration. The whole blood/plasma samples for CMV DNA quantification, hematology, and chemistry testing must be taken for all subjects at**		Synopsis, Section 3.1 (Study design-Study Treatment Phase), Section 7.1.1 (Screening Period), Schedule of assessment (Table 1),

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Visit 2/Week 0/Day 0. The test results of these assays will not be available prior to the start of treatment." Modified text in Section 3.1 "The screening and Visit 2/Week 0/Day 0 visits can occur on the same day **if the historical laboratory results, including CMV DNA quantification results, needed for evaluation of eligibility are available, or results can be obtained the same day. All Visit 2/Day 0 procedures, including blood collection for CMV DNA quantification, hematology and chemistry analysis in the central laboratory, must be completed prior to study treatment administration. Central laboratory results of CMV DNA quantification and genotyping, hematology, and chemistry from samples taken at Visit 2/Day 0 will not be available to for the screening of subjects.**" Modified text in Section 7.1.1 • At screening, either central or local laboratory results for **CMV DNA quantification** hematology/chemistry/pregnancy testing can be used for qualification. Schedule of Assessment 1 Footnotes "c" and "g" were modified to reflect that all required tests at baseline will performed prior to study treatment initiation and these central specialty laboratory results will not be available for screening purpose. Footnote "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 must be completed prior to initiation of study treatment. **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 screening."** Footnote "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/pregnancy testing can be used for eligibility and their results must be available prior to randomization. Local laboratory β-human chorionic gonadotropin test results can be used for the assessment of pregnancy on Day 0/Week 0. ~~Only Central lab results for hematology/chemistry/pregnancy testing obtained within 7 days prior to initiation of study treatment will be acceptable for randomization (test will not be repeated~~ on Day 0). ~~Local or central laboratory analysis performed on samples taken between Day -7 and Day -14 will be repeated on Day 0 before randomization."~~	
The sentences within the Inclusion Criterion 4 were modified: • to remove "requiring the change of current therapy" to align with the		Inclusion Criterion 4 in the Synopsis and Section 4.1

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fact that subjects on the anti-CMV agent ganciclovir, valganciclovir, foscarnet, or cidofovir immediately prior to randomization may continue on the same if randomized to the investigator-assigned treatment arm, and • to indicate that the subject could be refractory or resistant after 2 or more weeks of treatment with IV ganciclovir, oral valganciclovir, IV foscarnet, or IV cidofovir or after treatment with any combination of these anti-CMV agents Modified Inclusion Criterion 4 is as follows: "Have a current CMV infection refractory or resistant to treatment ~~and requiring the change of current therapy~~. Refractory is defined as documented failure to achieve >1 $\log_{10}$ decrease in CMV DNA level in whole blood or plasma after 2 or more weeks of treatment with IV ganciclovir, oral valganciclovir, IV foscarnet, or IV cidofovir (**or any combination thereof**). Resistant is 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 an interval of 2 or more weeks of treatment with IV ganciclovir, oral valganciclovir, IV foscarnet, or IV cidofovir **(or any combination thereof)** AND documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir, valganciclovir, foscarnet, or cidofovir.		
A statement within Exclusion Criterion 2 was modified for clarity and to align with the study design: "A subject who is **not continuing with the same anti-viral drug(s)** (ganciclovir, valganciclovir, or foscarnet) **for the study treatment (if randomized to the investigator assigned anti-CMV treatment arm)**, must discontinue **their** use before the first dose of study drug. **If** subject is **currently being treated with cidofovir and is assigned another anti-CMV agent by the investigator, the subject** must discontinue its use at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment.		Exclusion Criterion 2 in the Synopsis and Section 4.2
A statement within the Exclusion Criterion 3 was modified to: "Subjects receiving artesunate must discontinue the use ~~at least 1 day~~ prior to ~~randomization at Visit 2/Day 0 and~~ the first dose of study treatment"		Exclusion Criterion 3 in the Synopsis and 4.2.
Added a note for subjects with biopsy in Exclusion Criterion #7: "Serum aspartate aminotransferase (AST) >5 times upper limit of normal (ULN) at screening, or serum alanine aminotransferase (ALT) >5 times ULN at screening, or total bilirubin ≥3.0 x ULN at screening (except for documented Gilbert's syndrome), by local or central lab. **NOTE: Subjects with biopsy confirmed CMV hepatitis will not be excluded from study participation despite AST or ALT >5 times ULN at screening**.		Exclusion Criterion 7 in Synopsis and Section 4.2
It was clarified in Exclusion Criterion 10 that breast feeding females will be		Exclusion Criterion 10 in the

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excluded from the study. Be female and pregnant or ~~nursing~~ **breast feeding**		Synopsis and Section 4.2
Replaced "reactivation" of the malignancy under treatment with "relapse or progression" of the malignancy under treatment and modified the rest of the text for clarity in Exclusion Criterion 13: "Have active malignancy with the exception of nonmelanoma skin cancer. Subjects **who have had a HSCT and who experience relapse or progression** of the malignancy ~~under treatment with HSCT~~, **as per investigator's opinion** are **not** to be **enrolled."**		Exclusion Criterion 13 in the Synopsis and Section 4.2
"Disease symptomatology" was replaced with "disease status", wherever applicable.		Synopsis and other sections of the protocol.
Transplant status will not be collected at screening.		Schedule of Assessment 1 (Table 1), Section 7.1.1 (Study Schedule-Screening Period)
Liver function assessment by Child-Pugh classification will be performed at baseline, ie, Visit 2/Week 0. It will not be performed at screening.		Schedule of Assessment 1 (Table 1), Section 7.1.1 (Study Schedule-Screening Period), Section 7.1.2, and Section 7.2.3.1
It was added that the e-diary will only be utilized for study treatments that are given orally. The IV administration will be tracked in the source documents and CRF.		Footnote "s" in Schedule of Assessment 1 (Table 1), Section 7.1.2 (Study Schedule-Study Drug Administration)
For subjects who may withdraw consent during the study treatment phase or the follow-up phase, it was clarified that during the period after the study treatment discontinuation, and until the end of the study, subjects might be administered an anti-CMV treatment **for lack of efficacy, recurrence of CMV viremia, or for worsening or new onset of CMV disease** as deemed necessary by the investigator.		Synopsis, Section 4.5 (Discontinuation and/or withdrawal)
Added for clarification that **subjects who enter the rescue arm will be classified as failure for the purpose of analysis of the primary endpoint.**		Synopsis and Section 3.1, and Section 6
Specified that study treatment interruption of up to 4 consecutive days at 2 separate occurrences during the 8 weeks of study treatment is allowed in both treatment arms (maribavir or Investigator-assigned commercially available anti-CMV treatment).		Synopsis. Section 3.1, Section 6.2.3
Added "**In addition, viral UL27 gene will be tested**" to reemphasize that besides genotyping viral UL97 and UL54 CMV genes isolated from Visit 2/Day 0 plasma samples, viral UL27 gene will be genotyped too to identify mutations conferring resistance to commercially available anti-CMV agents.		Synopsis and Section 7.2.2.2
Added new text to Section for Tissue Invasive Disease Assessment to		Section 7.2.2.3

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provide more information about this assessment. • In cases of CMV retinitis, the retinal images taken by the ophthalmologist may be collected and provided as the evidence supporting the diagnosis. • EAC might request the individual histopathology slides to be read by an independent pathologist. • Presence and presentation of CMV syndrome in SOT subjects at baseline or a new onset should be reported as the event of special interest per definition provided in the Appendix 3.		
Added assessment of "**invasive bacterial and fungal infection**" to the list of safety endpoints since it is one of the adverse events of special interest in the study population. Added AEs of GI events (nausea, vomiting, and diarrhea) to be consistent with other sections. Added that additional grading of events of special interest will be applicable. Added that incidence of invasive bacterial and fungal infections for each treatment group for on treatment period and overall-study period will be provided. Added new text to state that additional shift tables may be produced for selected laboratory parameters using severity grades based on National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE v4.0) or using normal/above normal/below normal range.		Synopsis, Schedule of Assessments, Section 7.1, and Section 9.9
Following prior medications/procedures/diagnostic interventions were added to Table 3. Any therapeutic or diagnostic intervention performed within 3 months prior to the first dose of study treatment on Visit 2/Week 0/Day 0: • **Dialysis** • **X-rays, CT scans, MRI, ultrasound imaging (along with significant findings)** Anti-Rejection Therapies, **Adjuvant Therapies and Other Related Therapies** • **Anti-rejection medications ~~(for example belatacept)~~ including T-cell depleting therapies** • **Photopheresis** Induction therapies • **Pre-transplant irradiation** • **Chemotherapy agents**		Section 5.1 (Table 3)

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It was clarified that CMV specific T-cell transfer is considered investigational A footnote note was added to Table 3: ***Subjects for whom transplant was performed >3 months from the time of screening limited (no dose data) information for induction therapy will be collected. Similarly for anti-CMV treatment data older than >3 month prior to screening will be recorded in more limited manner (dose prescribed, major interruptions, overall treatment duration)**		
Added diagnostic assessment imaging, **such as X-ray, CT scans**		Section 5.2
Based on the summary of product characteristic (SmPC) for valganciclovir, it was added that ***In vivo* drug interaction studies with Valcyte have not been performed. Since valganciclovir is extensively and rapidly metabolized to ganciclovir; drug interactions associated with ganciclovir should be expected for valganciclovir (Valcyte SmPC).**		Section 5.2.2
It was added that regulatory T-cells (Tregs), which is an experimental treatment, is not allowed for the control of transplant tolerance.		Section 5.2.2
It was added that presence of CMV syndrome in SOT patients at baseline or a new onset should be reported as adverse event of special interest		Footnote "f" in Schedule of Assessment 2 (Table 2) Section 7.2.2.3 (Tissue Invasive CMV Disease Assessments)
[redacted]		[redacted]
Added a separate subsection under "Study Evaluations and Procedures-Efficacy" (now Section 7.2.2.6) for graft-versus-host-disease (GVHD) assessment for HSCT recipients only. Rearranged and relocated the text relevant to this assessment in Section 8.1.4 for emphasis and clarity.		Section 7.2.2.6 (GVHD assessment) Section 8.1.4 (Adverse events of special interest [AESI])
Added a new citation Loiseau et al. 2007 in the section for GVHD assessments Loiseau P, Busson M, Balere ML et al. 2007. HLA association with hematopoietic stem cell transplantation outcome: the number of mismatches at HLA-A, -B, -C, -DRB1, or -DQB1 is strongly associated with overall survival. Biol Blood Marrow Transplant, 13(8), 965-74.		Section 7.2.2.6 and Section 11 (References)

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Added a new citation, Harris et al 2016 as the guidance for acute GVHD staging and grading and for the confidence levels of the diagnosis: Harris AC, Young R, Devine S, Hogan WJ, Ayuk F, Bunworasate U, Chanswangphuuwana C, Efebra Y, Holler E, Litzow M, Ordemann R, Qayed M, Renteria AS, Reshef R, Wolfi M, Chen Y-B, Goldstein S, Jagasia M Locatelli F, Mielke S, Porter D, Schechter T, Shekhovtsova Z, Ferrara JLM and Levine JE, 2016. International, multicenter Standardization of Acute Graft-versus-host Disease Clinical Data collection: A report from the Mount Sinai Acute GVHD international Consortium. Biol Blood Marrow Transplant, 22, 4-10 Added Table 1 and Table 2 in Appendix 9 from this citation.		Section 7.2.2.6, Section 8.1.4, Section 11, and Appendix 9 in Section 12
Elaborated the reason for comorbidity assessment by the following addition: "**Transplant patients often have multiple other comorbidities, resulting from their immunosuppressed status (co-infections, graft versus host disease, transplant malfunctioning due to rejection), toxicities from therapies for maintenance of the transplant or reactivation of the baseline disease for which they had been transplanted (malignancy for example), and other concomitant diseases resulting in a very diverse population that might be enrolled into the study. The comorbidity assessment will be conducted to allow for the comparison of the population enrolled into 2 treatment arms and to account for the subjects' health status when assessing overall and individual subject response."** ~~Comorbidities are a physiological burden of disease and its interaction with ongoing treatment could impact the response to therapy.~~"		Section 7.2.2.7 (Comorbidity Status)
To be consistent with the schedule of assessment 1 (Table 1), a correction was made in Section 7.2.3.4 that electrocardiogram (ECG) will be performed at baseline (Visit2/Day0) and not at screening.		Section 7.2.3.4 (Electrocardiogram)
Modified text for clarity and consistency with regards to local laboratory data and reference range. "**During** screening, clinical laboratory tests will be performed by the central laboratory, however local laboratory results if available **might be utilized for the assessment of** the eligibility. **If local laboratory results are used for assessment of the eligibility, the reference ranges must be provided. This also applies to CMV DNA quantification results. At baseline (Visit 2/Week 0) blood samples will be taken for CMV DNA quantification**"		Section 7.2.3.5 (Clinical laboratory evaluation)
Added that the samples for chemistry are preferred to be taken under fasting conditions, although this is not mandatory. The information whether samples were taken under fasting conditions will be collected.		Section 7.2.3.5 (Clinical laboratory evaluation)
Added a note that only the levels of immunosuppressant drugs that are routinely conducted at the site will be collected since sites		Section 7.2.3.5 (Clinical laboratory

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differ in the immunosuppressant drug levels they routinely monitor.		evaluation)
International normalized ratio (INR) and prothrombin time will be performed at **baseline** only. It was stated in the original version that this assessment will performed only at screening visit only.		Section 7.2.3.5
Replaced an incorrect citation Boeckh et al 2003 with Boeckh et 1998: Boeckh M, Zaia JA, Jung D, Skettino S, Chauncey TR and Bowden RA 1998. A study of the pharmacokinetics, antiviral activity, and tolerability of oral ganciclovir for (MV prophylaxis in marrow transplantation. *Biol Blood Marrow Transplant, 4:13-19.*		Footnote" o" in Schedule of Assessment 1 (Table 1), Section 7.2.4.1, and Section 11 (References)
Volume of blood to be drawn from each subject per visit (Table 5) was updated to reflect reduction in number of samples collected for [redacted]		Section 7.2.5 (Volume of blood to be drawn from each subject per visit), Table 5
Removed the following text to align with the case report form for the study: "~~The CTCAE identifies 5 distinct severity grades, including Grade 5=death related to AE. In this study, investigators will be instructed to utilize only severity Grades 1–4 for each event. Should any death occur during the study, this will be recorded in the CRF as the outcome of an AE rather than as a severity grade. Other detailed instructions will be provided in the study manual.~~"		Section 8.1.1 (Severity Categorization)
Added that CMV syndrome (applicable only in SOT patients) and details of the presentation will be collected as an adverse event of special interest.		Section 8.1.4
For the events of diarrhea recorded, it was further clarified that additional information for each case of diarrhea will be collected, including the information whether additional condition such as GVHD, GI-CMV or enteric infection confirmed by culture/PCR or other method is present.		Section 8.1.4
Modified the infections of interest to add more details for monitoring and reporting invasive fungal and bacterial infections. New text: "Invasive fungal (eg, aspergillus, candida, *Pneumocystis jiroveci*, etc.) or bacterial infections (eg, S*taphylococcus aureus*, S*treptococcus pneumonia*, enterococcus, pseudomonas); see Appendix 13. Baseline conditions will be captured as part of medical history, while new events will be captured as AEs. The additional information such as diagnostic method used for the pathogen and the source of the sample used for the diagnosis will be collected. Additionally the presence of viral infections frequently occurring in transplant population will also be collected."		Section 8.1.4
Added the following: CMV syndrome (applicable in SOT patients only)		Section 8.1.4 and Section 8.1.5

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"New onset of CMV syndrome (applicable only in SOT patients) and details of the presentation will be reported as the event of special interest".		
Modified make sentence concise and indicate the time point, ie, "baseline" "If, at the end of the study treatment phase or at the end of the follow-up phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present ~~at the pretreatment value observed closest to the start of study treatment~~ **baseline,** further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values."		Section 8.1.6
Removed the collection of subjects' initials and dates of birth in Section 10.4 (Privacy and Confidentiality) since these information should not be used for identifying purposes. The unique number in itself is sufficient for that purpose.		Section 10.4 (Privacy and Confidentiality)
Added a page after the protocol signature page for the summary of changes for Amendment 1, per the sponsor's approved protocol template.		
Added an appendix (Appendix 1) for protocol history and a table for summary of changes for the current and future amendments, per the sponsor's approved protocol template. With the addition of this new appendix, all other appendices were renumbered throughout the document.		Section 12 (Appendices)
Modified Appendix 3 (Definition of Tissue Invasive CMV Disease and CMV Syndrome) to remove probable and proven methods of tissue invasive CMV disease diagnosis. Added CMV syndrome definition and the details of the assay performed for diagnosis.		Section 12 (Appendices)
Removed illegible snapshots from renumbered Appendices 10 (Recommendations For Chronic GVHD Diagnosis and Grading; previously 9a) and 11(Diagnostic Criteria for Chronic GVHD; previously 9b) and indicated source figures and tables within the articles cited in those appendices for reference.		Section 12 (Appendices)
Added a new Appendix 13 with details for invasive bacterial and fungal assessments. Following new journal articles cited in this new appendix were added to the list of references: Klumpp 1993; Dykewicz 2001; Majhail et al. 2012; Salzberger et al. 1997; Marr et al. 2002; Freifeld et al. 2011		Section 11 (References) and Section 12 (Appendices)
Applied editorial changes throughout the document for clarity		Synopsis and Sections, as needed

Appendix 2 CHILD-PUGH CLASSIFICATION OF CHRONIC LIVER DISEASE

Score	Bilirubin (mg/dL)	Albumin (mg/dL)	INR	Hepatic Encephalopathy (grade)	Ascites (grade)
1	<2	>3.5	<1.7	None	None
2	2-3	2.8-3.5	1.7-2.2	Mild (controlled medically)	Mild (controlled medically)
3	>3	<2.8	>2.2	Marked (poor control)	Marked (poor control)

Child-Pugh Class: A Score of 5-6
B Score of 7-9
C Score >9

Appendix 3 DEFINITIONS OF TISSUE INVASIVE CMV DISEASE AND CMV SYNDROME

TISSUE INVASIVE DISEASE

The following definitions of CMV disease are based on a commonly cited reference that was intended for application to transplant recipients (Ljungman et al., 2002; Ljungman et al., 2017). Definitions often require clinical judgment regarding compatible symptoms or other factors. The investigator should utilize his/her best clinical judgment for this categorization, and apply these definitions whenever possible for consistency. When reporting CMV disease, the presence of any co-pathogens that may be contributing to the organ disease must be reported as well.

Pneumonia: "CMV pneumonia" is defined by the presence of signs and/or symptoms of pulmonary disease combined with the detection of CMV in bronchoalveolar lavage fluid or lung tissue samples. Detection of CMV should be performed by virus isolation, histopathologic testing, immunohistochemical analysis, or in situ hybridization. Detection of CMV by PCR alone may be too sensitive for the diagnosis of CMV pneumonia and is therefore insufficient for this purpose. The presence of fungal copathogens, such as *Aspergillus* species, together with radiologic signs typical of *Aspergillus* pneumonia (eg, a halo sign or a crescent sign) indicates fungal pneumonia rather than CMV pneumonia. CMV documented by culture from BAL might be used as the evidence in the absence of other preferred assays.

Gastrointestinal disease: "CMV gastrointestinal disease" is defined by the identification of a combination of clinical symptoms from the upper or lower gastrointestinal tract, findings of macroscopic mucosal lesions on endoscopy, and demonstration of CMV infection (by culture, histopathologic testing, immunohistochemical analysis, or in situ hybridization) in a gastrointestinal tract biopsy specimen. Detection of CMV by PCR alone is insufficient for the diagnosis of CMV gastrointestinal disease. Patients with CMV disease that involves the intestinal tract usually have mucosal abnormalities that can be seen by the endoscopist, but the appearance of some of these lesions is subtle. The spectrum of endoscopic lesions is variable and ranges from patchy erythema, exudates, and microerosions to diffusely edematous mucosa, to multiple mucosal erosions, to deep ulcers and pseudotumors. The diagnostic yield for CMV is higher when mucosal abnormalities are targeted for study. If CMV is detected in normal mucosa near a lesion consistent with those typical of CMV infection, this can be accepted as CMV gastrointestinal disease.

Cytomegalovirus documented in blood by PCR or antigenemia or CMV documented by PCR from tissue biopsies might be used in the absence of other preferred methods of diagnosis.

Hepatitis: "CMV hepatitis" is defined by the findings of elevated bilirubin and/or enzyme levels during liver function testing, absence of any other documented cause of hepatitis, and detection of CMV infection (by culture, histopathologic testing, immunohistochemical analysis, or in situ hybridization) in a liver biopsy specimen. Detection of CMV by PCR alone is insufficient for the diagnosis of CMV hepatitis because it can imply the presence of transient viremia. Documentation of CMV (ie, by immunohistochemical analysis) within the liver tissue is needed. Other pathogens, such as hepatitis C virus, may be present without excluding the diagnosis of CMV hepatitis.

Central Nervous System (CNS) disease: Cytomegalovirus "CNS disease" is defined by the identification of CNS symptoms together with the detection of CMV in cerebrospinal fluid samples, by culture or PCR, or in brain biopsy specimens, by culture, histopathologic testing, immunohistochemical analysis, or in situ hybridization.

Retinitis: The diagnosis of disease requires typical ophthalmological signs judged by an ophthalmologist experienced with the diagnosis of CMV retinitis. If the presentation is atypical or an experienced ophthalmologist is not available, it is recommended that the diagnosis is supported by CMV documented in vitreous fluid by PCR. The images of retina taken during ophthalmological exam should be provided.

Nephritis: Cytomegalovirus nephritis can be defined by the detection of CMV infection (by culture, immunohistochemical analysis, or in situ hybridization) together with the identification of histologic features of CMV infection in a kidney biopsy specimen obtained from a patient with renal dysfunction.

Cystitis: Cystitis is defined by the detection of CMV infection (by culture, immunohistochemical analysis, or in situ hybridization) together with the identification of conventional histologic features of CMV infection in a bladder biopsy specimen obtained from a patient with cystitis.

Myocarditis: Myocarditis is defined by the detection of CMV infection (by culture, immunohistochemical analysis, or in situ hybridization) together with the identification of conventional histologic features of CMV infection in a heart biopsy specimen obtained from a patient with myocarditis.

Pancreatitis: The definition of CMV pancreatitis requires the detection of CMV infection (by culture, immunohistochemical analysis, or in situ hybridization) together with the identification of conventional histologic features of CMV infection in a pancreatic biopsy specimen obtained from a patient with pancreatitis.

Other CMV disease categories: Cytomegalovirus can also cause disease in other organs, and the definitions of these additional disease categories include the presence of compatible symptoms and signs, and documentation of CMV by biopsy (detection of CMV by PCR alone is insufficient), with other relevant causes excluded.

CMV SYNDROME (only diagnosed in SOT recipients):

The definition requires detection of CMV in blood by viral culture, antigenemia or a DNA/RNA-based assay together with **at least 2 of the following**:

a. Fever ⩾38° C for at least 2 days
b. New or increased malaise (toxicity grade ⩾2) or new or increased fatigue (toxicity grade ⩾3) (National Cancer Institute: Common Terminology Criteria for Adverse Events, version 4.0)

c. Leukopenia or neutropenia on 2 separate measurements at least 24 hours apart defined as: a WBC count of <3,500 cells/μL, if the WBC count prior to the

development of clinical symptoms was ⩾4,000 cells/ µ L **or** a WBC decrease of >20%, if the WBC count prior to the development of clinical symptoms was <4,000 cells/µL. The corresponding neutrophil counts are <1,500 cells/µL or a decrease of >20% if the neutrophil count before the onset of symptoms was <1,500 cells/µL.

d. ⩾5% atypical lymphocytes
e. Thrombocytopenia defined as a platelet count of <100,000 cells/µL if the platelet count prior to the development of clinical symptoms was ⩾ 115,000 cells/mL or a decrease of >20% if the platelet count prior to the development of clinical symptoms was <115,000 cells/mL
f. Elevation of hepatic transaminases (ALT or AST) to 2 × upper limit of normal (applicable to nonliver transplant recipients)

Appendix 4 CMV GENETIC MUTATIONS ASSOCIATED WITH RESISTANCE TO ANTI-CMV DRUGS

Specific mutations in the UL97 and/or UL54 human cytomegalovirus (HCMV) genes are associated with resistance to certain anti-CMV drugs (ganciclovir/valganciclovir, foscarnet, or cidofovir). The UL97 gene encodes a viral protein kinase, while the UL54 gene encodes a viral DNA polymerase.

Ganciclovir (administered intravenously, orally, or through its oral prodrug valganciclovir) is a guanosine analog that acts as a chain terminator once incorporated into the elongating viral DNA chain. In order for the drug to be incorporated into the viral DNA chain, ganciclovir first needs to be monophosphorylated by the UL97 HCMV protein kinase. Cellular kinases then di- and tri-phosphorylate the drug into a form that can be incorporated into the viral DNA chain. Mutations in the UL97 gene that inactivate the UL97 kinase prevent the monophosphorylation step and result in resistance to ganciclovir/valganciclovir. Foscarnet is a pyrophosphate analog that blocks the release of pyrophosphate by the UL54 viral polymerase. Cidofovir is a cytosine monophosphate analog that is dependent on diphosphorylation by cellular kinases for its inhibition of viral DNA synthesis.

The tables below list the mutations in UL97 that are proven to confer resistance to ganciclovir/valganciclovir and the mutations in UL54 that confer resistance to one or multiple anti-CMV agents, mostly based on the phenotyping, except in the case of deletions, that do not need to be confirmed due to the location of the deleted residues.

Since foscarnet and cidofovir do not require phosphorylation by the viral UL97 kinase for their activity, they are unaffected by mutations in the UL97 gene. Mutations in the UL54 gene that inactivate the viral DNA polymerase prevent incorporation of ganciclovir/valganciclovir and/or cidofovir into the elongating viral DNA chain, leading to resistance to the drug(s). Similarly, mutations in the UL54 gene can lead to foscarnet resistance.

The tables below are the reference for the investigators while the full list of reportable mutations should they be found in the clinical study analyses will be provided in the resistance analysis plan.

Reference for the Investigators: UL97 Mutations Known to Confer Resistance to Ganciclovir/Valganciclovir

UL97 Mutation	Ganciclovir/Valganciclovir
L405P	R
D456N	R
M460I	R
M460L	R
M460T	R
M460V	R
V466G	R
C480R	R
C518Y	R
H520Q	R
P521L	R
del590 to 593	R
del590to 600	R
del590 to 603	R
del591 to 594	R
del591 to 607	R
C592F	R
C592G	R
del594 to 601	R
A594E	R
A594G	R
A594P	R
A594T	R
A594V	R
L595F	R
L595S	R
L595T	R
L595W	R
del595	R
del595 to 603	R
del597 to 599	R
del597 to 603	R

Reference for the Investigators: UL97 Mutations Known to Confer Resistance to Ganciclovir/Valganciclovir

UL97 Mutation	Ganciclovir/Valganciclovir
E596G	R
E596Y	R
E596D	R
N597D	R
N597I	R
G598D	R
G598S	R
G598V	R
K599T	R
del600	R
del601	R
del600 to 601	R
del601 to 602	R
del601 to 603	R
C603R	R
C603S	R
C603W	R
C603Y	R
C607F	R
C607Y	R
I610T	R
A613V	R

Source: Lurain and Chou, 2010; Komatsu et al., 2014

R=resistant

Mutations in bold letters are the most common mutations.

Reference for the Investigators: UL54 Mutations Known to Confer Resistance to One or More of the Anti-CMV drugs

UL54 Mutation	Cidofovir	Foscarnet	Ganciclovir
D301N	R	S	R
E303D[4]	R	S	R
E303G[4]	R	S	R
N408D	R	S	R
N408K[4]	R	S	R
N408S	R	S	R
N410K	R	S	R
F412C	R	S	R
F412L	R	S	R
F412S	R	S	R
F412V	R	S	R
D413A	R	S	R
D413E	R	S	R
D413N	R	S	R
D413Y[4]	R	S	R
P488R	R	S	R
N495K	S	R	S
K500N	R	S	R
L501I	R	S	R
T503I	R	S	R
A505V[3]	R	S	R
K513N	R	S	R
K513E	R	S	R
K513R	R	S	R
D515E	S	S	R
D515Y	S	R	R
L516R	R	S	R
L516W	R	S	R
I521T	R	S	R
P522A	R	S	R
P522S	R	S	R
del524	R	S	R

Reference for the Investigators: UL54 Mutations Known to Confer Resistance to One or More of the Anti-CMV drugs

UL54 Mutation	Cidofovir	Foscarnet	Ganciclovir
V526L	R	S	R
C539G	R	S	R
C539R	R	S	R
D542E[4]	R	S	S
L545S	R	S	R
L545W	R	S	R
T552N	S	R	S
Q578H	R	R	R
Q578L	S	R	S
S585A	S	R	S
D588E	S	R	S
D588N	S	R	R
F595I	S	R	S
T700A	S	R	S
V715M	S	R	S
V715A	S	R	S
I726T	S	S	R
I726V[3]	R	S	R
E756K	R or S[3]	R	R or S[3]
E756D	S	R	S
E756Q	S	R	S
L773V	R	R	R
L776M	S	R	R
V781I	S	R	R[3]
V787A	S	R	R
V787L	S	R	R
L802M	S	R	R or S[3]
K805Q	R	S	S
A809V	S	R	R
V812L[4]	R	R	R
T813S	R	R	R
T821I	S	R	R

Reference for the Investigators: UL54 Mutations Known to Confer Resistance to One or More of the Anti-CMV drugs

UL54 Mutation	Cidofovir	Foscarnet	Ganciclovir
P829S	S	S	R
A834P	R	R	R
T838A	S	R	S
G841A	R	R	R
G841S	S	R	R
M844V	S	R	R
V946L	S	R	S
L862F	S	S	R
D879G			R
L957F	ND	ND	R
A972V			R
del981 to 982	R	R	R
A987G	R	S	R

Source: Chou, 2011; Chou et al., 2008; Chevillotte et al., 2010; Erice, 1999; Komatsu et al., 2014

[1] Most UL54 mutations also have UL97 mutations.

[2] R and S denote resistant and sensitive, respectively. ND indicates Not Determined

[3] Low-grade or variable resistance.

[4] Also confers resistance to CMX001

Appendix 5 KARNOFSKY PERFORMANCE STATUS SCALE

The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

References:

Crooks, V, Waller S, et al. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol. 1991; 46: M139-M144.

[redacted]

O'Toole DM, Golden AM. Evaluating cancer patients for rehabilitation potential. West J Med. 1991; 155:384-387.

Oxford Textbook of Palliative Medicine, Oxford University Press. 1993;109.

Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: Reliability, validity, and guidelines. J Clin Oncology. 1984; 2:187-193.

Appendix 6 LANSKY PERFORMANCE STATUS SCALE

Lansky play-performance scale for pediatric patients

This scale may be used with children age 1-16 who have any type of malignancy. It may be used for both inpatients & outpatients, and for patients undergoing active treatment as well as long-term follow-up. It is rated by parents based on their child's activity over the past week. Parents fill out the assessment based on the directions on the form, and the form is readministered over time to assess for changes in performance status.

An excerpt of the relevant directions for parents is as follows:

"Think about your child's play and activity over the past week. Think about both good days and bad days. Average out this period. Now read the descriptions and pick the one that best describes your child's play during the past week."

Rating	Description
100	fully active, normal
90	minor restrictions with strenuous physical activity
80	active, but gets tired more quickly
70	both greater restriction of, and less time spent in, active play
60	up and around, but minimal active play; keeps busy with quieter activities
50	lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities
40	mostly in bed; participates in quiet activities
30	stuck in bed; needs help even for quiet play
20	often sleeping; play is entirely limited to very passive activities
10	does not play nor get out of bed
0	unresponsive

Appendix 7 SCALES AND ASSESSMENTS

The following scales/assessments will be utilized in this study:

[redacted]

A separate master file containing each scale/assessment listed above will be provided to the site. Updates to scales/assessments during the study (if applicable) will be documented in the tables above and a new master file containing the revised scale/assessment will be provided to the site.

Appendix 8 ACUTE GRAFT-VERSUS-HOST DISEASE: CLINICAL STAGING AND GRADING

The clinical staging and grading of acute GVHD is done through evaluation of the skin, liver, and gastrointestinal tract (upper and lower) (Harris et al., 2016).

GVHD Target Organ Staging

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: <500 mL/day or <3 episodes/day Child: <10 mL/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting or anorexia	Adult: 500-999 mL/day or 3-4 episodes/day Child: 10-19.9 mL/kg/day or 4-6 episodes/day
2	Maculopapular rash 25-50% BSA	3.1-6 mg/dL		Adult: 1000-1500 mL/day or 5-7 episodes/day Child: 20-30 mL/kg/day or 7-10 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dL		Adult: >1500 mL/day or >7 episodes/day Child: >30 mL/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume

Source: Table 1, Harris et al., 2016

Overall clinical grade (based on most severe target organ involvement):

Grade 0: No stage 1-4 of any organ.

Grade I: Stage 1-2 skin without liver, upper GI, or lower GI involvement.

Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.

Grade III: Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI. Grade IV: Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI.

The differences in GVHD diagnosis make it challenging to conduct multicenter trials because of the difficulty determining whether a patient truly experienced GVHD. To address these varying practices, Harris et al., 2016 developed a structure for collecting granular GVHD data and assigning confidence levels for the attribution of symptoms to GVHD based on the treatment decisions made by the clinician.

Confidence Level Criteria

Confidence Level	Pathologic Evidence	Clinical Assessment	Treatment for Acute GVHD	Comments
Confirmed	Unequivocal pathologic evidence of GVHD	GVHD is the etiology for symptoms	Not applicable	GVHD is clearly present even if other etiologies may coexist simultaneously.
Probable	Not required	GVHD most likely etiology for symptoms (as evidenced by treatment being provided)	Yes	GVHD is most likely present, but other etiologies may also explain the symptoms, and there is insufficient evidence to make a confirmed diagnosis.
Possible	Not required	GVHD in differential diagnosis (but no treatment is being provided)	No	GVHD may be present, but other etiologies are favored to the degree that GVHD treatment is not initiated.
Negative	Unequivocal evidence of a diagnosis other than GVHD (eg, drug rash)	GVHD is not considered as an explanation for the symptoms	No and the symptoms resolve without GVHD treatment	A "negative" biopsy (eg, normal skin) is not unequivocal evidence of a diagnosis other than GVHD.

Source: Table 2, Harris et al., 2016

Appendix 9 RECOMMENDATIONS FOR CHRONIC GVHD DIAGNOSIS AND GRADING

A. Organ Scoring of Chronic GVHD as published in NIH GVHD Consensus for GVHD Consensus for Clinical Trials: I. The 2014 Diagnosis and Staging Working Group Report, Jagasia et al., 2015 (Figure 1).

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS**				
Symptom score:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **%** FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

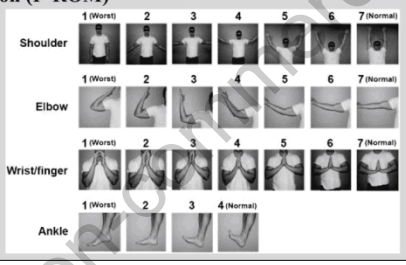
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ___ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)*	❑ **No GVHD**	❑ **Mild**	❑ **Moderate**	❑ **Severe**

Photographic Range of Motion (P-ROM)



Organ scoring of chronic GVHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. ‡To be completed by specialist or trained medical providers (see Supplemental Figure). **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

Source: Figure 1, Jagasia et al., 2015

Supplemental Genital Tract Chronic GVHD Scoring and Supplemental skin GVHD scoring (supplemental material for Jagasia et al., 2015)

Supplement Figure – Genital Tract Chronic Graft-versus-Host Assessment and Scoring Form

Name:_____ Date of birth: _____Assessment date: _____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
GENITAL TRACT ***Check:*** ☐ Male ☐ Female	☐ No signs	☐ Mild signs and females may have symptoms* WITH discomfort on exam	☐ Moderate signs and may have symptoms* with discomfort on exam	☐ Severe signs with or without symptoms *

Currently sexually active:
☐ Yes ☐ No

Check all signs that apply:

☐ Lichen planus-like features
☐ Lichen sclerosis-like features
☐ Vaginal scarring (female)
☐ Clitoral/labial agglutination (female)
☐ Labial resorption (female)
☐ Erosions
☐ Fissures
☐ Ulcers
☐ Phimosis (male)
☐ Urethral meatus scarring/ stenosis (male)

☐ *Abnormality present but NOT thought to represent GVHD (specify cause):*_____
☐ *Abnormality thought to represent GVHD PLUS other causes(specify cause):*_____

**Genital symptoms are not specific to cGVHD and can represent premature gonadal failure or genital tract infection.*

If a gynecologist is unavailable, external examination may be performed to determine "discomfort on exam" as follows:
a) Spread the labia majora to inspect the vulva for the above signs. Touch the vestibular gland openings (Skene's and Bartholin's), labia minora and majora gently with a qtip. Vulvar pain elicited by the gentle touch of a qtip is classified as discomfort on examination. Palpate the vaginal walls with a single digit to detect bands, shortening, narrowing or other signs of vaginal scarring.
b) If the woman is sexually active, determine whether qtip palpation or gentle palpation of scarred ridges elicits pain similar to that which the woman experiences during intercourse.

Female genitalia: Severity of signs:
1) Mild (any of the following): erythema on vulvar mucosal surfaces, vulvar lichen-planus or vulvar lichen-sclerosis.
2) Moderate (any of the following): erosive inflammatory changes of the vulvar mucosa, fissures in vulvar folds
3) Severe (any of the following): labial fusion, clitoral hood agglutination, fibrinous vaginal adhesions, circumferential fibrous vaginal banding, vaginal shortening, synechia, dense sclerotic changes, and complete vaginal stenosis.

Male genitalia: Diagnostic features include lichen planus-like or lichen sclerosis-like features and phymosis or urethral scarring or stenosis. Severity of signs:
1) Mild: lichen planus-like feature;
2) Moderate: lichen sclerosus-like feature or moderate erythema;
3) Severe: phimosis or urethral/meatal scarring.

Biopsy obtained: ☐ **Yes** ☐ **No** **Site biopsied:**_____**GVHD confirmed by histology:** ☐ **Yes** ☐ **No**

Change from previous evaluation: ☐ **No prior or current GVHD** ☐ **Improved** ☐ **Stable** ☐ **Worse** ☐ **N/A (baseline)**

Completed by (print name):_____**Date form completed:** _____

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Source: Supplemental Figure 1, supplemental material for Jagasia et al., 2015

B. NIH Severity Grading of Chronic GVHD as published in NIH GVHD Consensus for GVHD Consensus for Clinical Trials: I. The 2014 Diagnosis and Staging Working Group Report (Jagasia et al., 2015)

NIH Global Severity of chronic GVHD

Mild chronic GVHD
s involved with no more than score 1 plus
Lung score 0

Moderate chronic GVHD
gans involved with no more than score 1
OR

At least 1 organ (not lung) with a score of 2
OR

Lung score 1

Severe chronic GVHD
gan with a score of 3
OR

Lung score of 2 or 3

Key points:
er of the 2 scores to be used for calculating global severity.
In lung: FEV1 is used instead of clinical score for calculating global severity.
If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Source: Table 2, Jagasia et al., 2015

Appendix 10 DIAGNOSTIC CRITERIA FOR CHRONIC GVHD

A. Signs and Symptoms of Chronic GVHD (Table 1 in Jagasia et al., 2015)

Signs and Symptoms of chronic GVHD				
Organ or Site	**Diagnostic (Sufficient to Establish the Diagnosis of chronic GVHD)**	**Distinctive* (Seen in chronic GVHD, but Insufficient Alone to Establish a Diagnosis)**	**Other Features or Unclassified Entities†**	**Common‡ (Seen with Both Acute and chronic GVHD)**
Skin	Poikiloderma Lichen planus–like features Sclerotic features Morphea-like features Lichen sclerosus–like features	Depigmentation Papulosquamous lesions	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric, affects most nails)		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Loss of body hair Scaling	Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes) Premature gray hair	
Mouth	Lichen planus–like changes	Xerostomia Mucoceles Mucosal atrophy Ulcers Pseudomembranes		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes Cicatricial conjunctivitis KCS Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus–like features Lichen sclerosus–like features	Erosions Fissures Ulcers		
Females	Vaginal scarring or clitoral/labial agglutination			

Signs and Symptoms of chronic GVHD

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of chronic GVHD)	Distinctive* (Seen in chronic GVHD, but Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities†	Common‡ (Seen with Both Acute and chronic GVHD)
Males	Phimosis or urethral/meatus scarring or stenosis			
GI Tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children
Liver				Total bilirubin, alkaline phosphatase > 2 × upper limit of normal ALT > 2 × upper limit of normal
Lung	Bronchiolitis obliterans diagnosed with lung biopsy BOS§	Air trapping and bronchiectasis on chest CT	Cryptogenic organizing pneumonia Restrictive lung disease‖	
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to fasciitis or sclerosis	Myositis or polymyositis¶	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and Immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hyper-gammaglobulinemia Autoantibodies (AIHA, ITP) Raynaud's phenomenon	

Signs and Symptoms of chronic GVHD				
Organ or Site	**Diagnostic (Sufficient to Establish the Diagnosis of chronic GVHD)**	**Distinctive* (Seen in chronic GVHD, but Insufficient Alone to Establish a Diagnosis)**	**Other Features or Unclassified Entities†**	**Common‡ (Seen with Both Acute and chronic GVHD)**
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

ALT indicates alanine aminotransferase; AIHA, autoimmune hemolytic anemia; ITP, idiopathic thrombocytopenic purpura.

*In all cases, infection, drug effect, malignancy, or other causes must be excluded.

†Can be acknowledged as part of the chronic GVHD manifestations if diagnosis is confirmed.

‡Common refers to shared features by both acute and chronic GVHD.

§BOS can be diagnostic for lung chronic GVHD only if distinctive sign or symptom present in another organ (see text).

‖ Pulmonary entities under investigation or unclassified.

¶Diagnosis of chronic GVHD requires biopsy.

Source: Table 1, Jagasia et al., 2015

B. **Histological Criteria for GVHD by Organ system** according to NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: II. The 2014 Pathology Working Group Report **(**Table 1 in Shulman et al., 2015). Chronic GVHD is supported by histologic evidence of GVHD from any affected site. Investigators are expected to consider recommendations for chronic GVHD diagnosis including not only clinical but histological evidence.

Histological Criteria for GVHD by Organ System

Organ or System	Minimal Criteria for Acute/Active GVHD*	Specific Criteria for Chronic GVHD†
Liver	Global assessment of dysmorphic or destroyed small bile ducts ± cholestasis, lobular and portal inflammation	Ductopenia, portal fibrosis, chronic cholestasis reflect chronicity but are not specific for chronic GVHD
GI	Variable apoptotic criteria (≥1/piece) in crypts	Destruction of glands, ulceration or submucosal fibrosis may reflect severe or long-standing disease but are not specific for chronic GVHD
Skin, in general	Apoptosis in epidermal basal layer or lower Malphigian layer or infundibulum/outer root sheath/hair bulge of hair follicle or acrosyringium/sweat ducts ± lichenoid inflammation ± vacuolar change ± lymphocytic satellitosis	
Skin, lichen planus–like		Combination of epidermal orthohyperkeratosis, hypergranulosis and acanthosis resembling lichen planus ± lichenoid inflammation and/or vacuolar changes of eccrine units
Skin morpheic (localized or diffuse)		Thickening and homogenization of collagen bundles throughout reticular dermis or pandermal sclerosis with overlying interface changes ± thickening and homogenization of subcutaneous septa
Skin, lichen sclerosus–like		Homogenization ± sclerosis of papillary dermal collagen with overlying interface changes including melanophages in the papillary dermis and sparse lymphocytic infiltrate
Skin, fasciitis		Thickening of fascial septa with adjacent inflammation ± sclerosis of subcutis
Oral/oropharyngeal mucosa and conjunctiva	Lichenoid interface lymphocytes with infiltration of mucosa (exocytosis) and variable apoptosis‡	

Histological Criteria for GVHD by Organ System		
Organ or System	**Minimal Criteria for Acute/Active GVHD***	**Specific Criteria for Chronic GVHD†**
Minor salivary or lacrimal gland		Periductal lymphocytic infiltrate with infiltration and damaged intralobular ducts, fibroplasia in periductal stroma, mixed lymphocytic and plasmacytic inflammation with destruction of acinar tissue§
Lung		CBO: dense eosinophilic scarring beneath the respiratory epithelium, resulting in luminal narrowing or complete fibrous obliteration. May be preceded by lymphocytic bronchiolitis without intraluminal fibrosis‖
Kidney		Membranous nephropathy, minimal change disease
Lesions of Uncertain Pathogenesis		
Lung		COP
Skeletal Muscle		Myositis

∗ Conditions that result in lesser degrees of change include immunosuppressive treatment, biopsy very soon after onset of signs, suboptimal or small tissue sample, insufficient serial sectioning, confounding infection, drug reaction, or inflammatory conditions.

† After the diagnosis of chronic GVHD has been established or following immunosuppressive treatment, the histological manifestations of active disease may meet only minimal diagnostic criteria for activity. Different manifestations of cutaneous chronic GVHD may all be present together in 1 biopsy or in separate but concurrent biopsies.

‡ Inflammation of the oral mucosa and within the minor salivary glands may persist from prior chemo-irradiation or prior inflammation. The distinction between acute and chronic GVHD requires the addition of distinctive oral manifestations.

§ The distinction of past acinar destruction and fibrosis from ongoing chronic GVHD activity can be difficult and relies on assessing lobules that are not completely fibrotic. Acinar and periductal inflammation with features of damage to ducts, such as vacuolar change, lymphocytic exocytosis nuclear dropout, dyspolarity or apoptosis, and resultant fibroplasia indicate chronic GVHD activity.

‖ Constrictive bronchiolitis obliterans (CBO) should be distinguished from cryptogenic organizing pneumonia, which is also associated with GVHD but has a different clinicopathologic presentation and a more favorable outcome.

Source: Table 1, Shulman et al., 2015

C. Recommendations for Final Diagnosis Categories of GVHD (Shulman et al., 2015)

Recommendation for Final Diagnosis Categories			
Category	**Definition**	**Examples**	**Comments**
Not GVHD	No evidence for GVHD		
Possible GVHD	Evidence of GVHD but other possible explanations	• Obvious CMV enteritis with inclusions near the apoptotic changes • Focal colonic ulcers with marked apoptotic cryptitis and destruction of crypts associated with use of MMF • Coinfection with known active viral hepatitis • Clinical features which suggest or favor a drug reaction	Indicate possible alternate diagnoses and reasons for suspicion
Likely GVHD	Clear evidence of GVHD without a competing cause of injury OR Clear evidence of GVHD with mitigating factors OR GVHD most likely diagnosis but relevant clinical information is limited OR GVHD is validated by sequential biopsy or by absence of competing diagnosis	• Abundant epithelial apoptosis without clinical or histological evidence of drug injury or infection • Evidence of CMV yet abundant apoptotic epithelial changes that are not associated with CMV infected cells by immunostaining • Single or rare apoptotic epithelial changes without other features of active GVHD and no alternative explanations • Limited sample or minimal or focal findings • Proximity to recent chemotherapy or radiotherapy	Included old categories of "consistent with" and "unequivocal" GVHD

Source: Table 2, Shulman et al., 2015

Appendix 11 MODIFICATION OF DIET IN RENAL DISEASE (MDRD) AND SCHWARTZ FORMULAE

Subjects eligible for Study SHP620-303 must have estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2 as assessed by Modification of Diet in Renal Disease (MDRD) formula (Levey et al., 2006) for subjects ⩾18 years of age or Schwartz formula (Schwartz et al., 1976; Schwartz et al., 1984) for subjects <18 years of age.

MDRD formula

For creatinine in µmol/L:

$$\text{eGFR} = 32788 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.210\ if\ Black] \times [0.742\ if\ Female]$$

Creatinine levels in µmol/L can be converted to mg/dL by dividing those by 88.4.

For creatinine in mg/dL:

For standardized (IDMS-calibrated) serum creatinine assays:

eGFR (mL/min/1.73 m^2) = 175 × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if Female) × (1.212 if Black) (conventional units)

For non-standardized (non-IDMS-calibrated) serum creatinine assays:

$$\text{eGFR} = 186 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.210\ if\ Black] \times [0.742\ if\ Female]$$

Schwartz formula

GFR (ml/min/1.73m^2)=[length or height (cm) × k] / Scr (mg/dl)

k=0.55 mg creatinine/100 min × cm × 1.73m^2 for children 1-13 years old

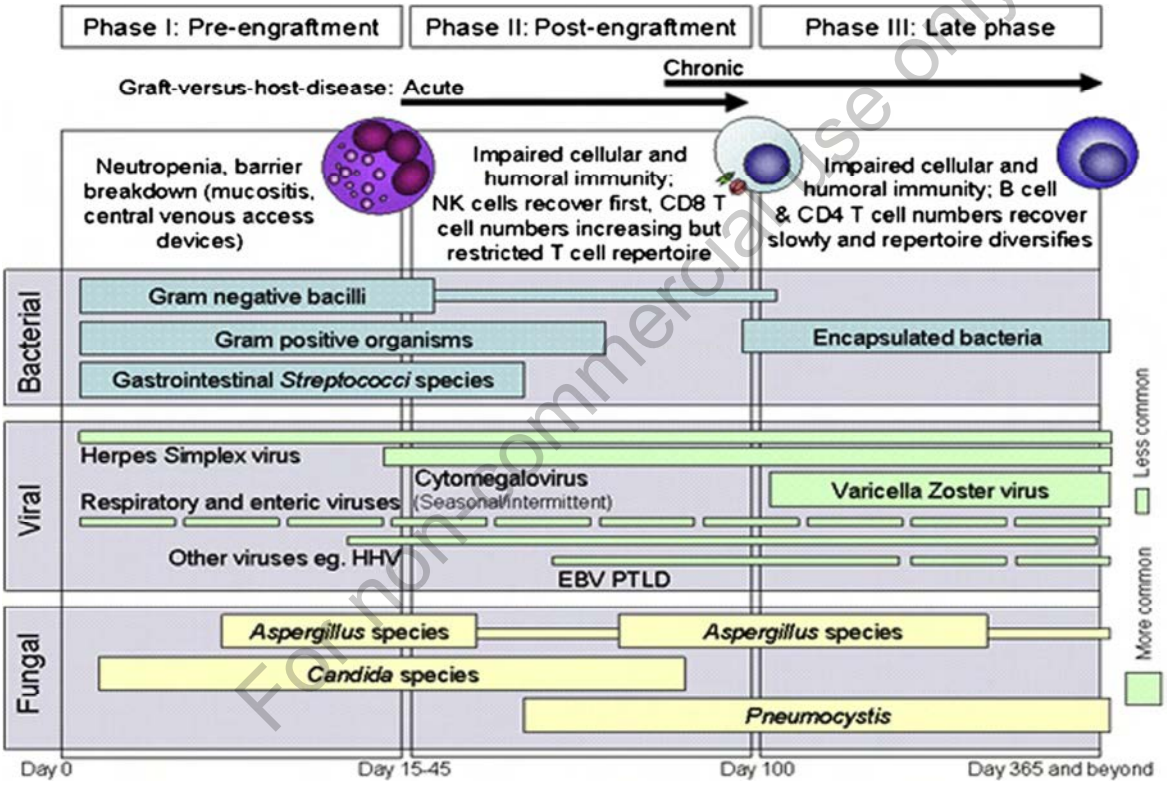
k=0.55 for adolescent females 13-18 years old

k=0.7 for adolescent males 13-18 years old

Appendix 12 BACTERIAL AND FUNGAL INFECTIONS ASSESSMENT

In HSCT population post-transplant infection remains a significant cause of morbidity and mortality, particularly after allogeneic transplantation. While the expected period of profound neutropenia after HSCT usually occurs during the pre-engraftment stage, normal neutrophil recovery is not always possible as neutrophil count is adversely affected by other risk factors and co-morbidities, such as graft failure or rejection, GVHD, relapse of the underlying neoplasm, drug-induced myelosuppression and concomitant infections (Klumpp, 1993).

Due to the gradual immune system reconstitution HSCT recipients are vulnerable to various opportunistic viral, bacterial or fungal pathogens at different stages after the transplant (Tomblyn et al., 2009). Opportunistic infection is defined as any infection that occurs with increased frequency or severity in HSCT population (Dykewicz, 2001).



Phases of opportunistic infections among allogeneic HSCT recipients Phase I: <15-45 days post transplant; Phase II: 30-100 days post transplant; Phase III: >100 days after HSCT. Abbreviations: EBV, Epstein-Barr virus; HHV, human herpes virus; PTLD, post-transplant lympho-proliferative disease (Figure 1, Tomblyn et al., 2009).

Infectious complications are most frequent in the pre-engraftment period due to cytopenias and immune ablation and immune suppression but may continue for months or years in HSCT recipients with delayed immune reconstitution (Majhail et al., 2012). During the early post-transplant period HSCT recipients are susceptible to bacteremia and fungal infections with Candida and Aspergillus species, along with herpes simplex virus (HSV) reactivation. Candida often causes superficial skin infection (thrush), with rare occasions of invasive disease manifested as esophagitis, endocarditis or hepatosplenic disease. During the early

post-engraftment phase infections relate primarily to impaired cell-mediated immunity, which is influenced by a history of GVHD and the requirement for ongoing immunosuppression. The predominant organisms in this phase are herpesviruses, along with *Pneumocystis jiroveci* and Aspergillus species. In the late post-engraftment period common pathogens include CMV, VZV and infections with encapsulated bacteria, such as Streptococcus pneumonia, Haemophilus influenzae (Tomblyn et al., 2009; Majhail et al., 2012).

Prolonged neutropenia in the pre-engraftment phase results is a substantial risk for bacterial and fungal infections, and has been the most important risk factor for invasive aspergillosis (Schwartz et al., 1984; Salzberger et al., 1997; Marr et al., 2002).

The most common bacterial infections in neutropenia are provided in the table below.

Common Bacterial Pathogens in Neutropenic Patients

Common gram-positive pathogens
Coagulase-negative staphylococci
Staphylococcus aureus, including methicillin-resistant strains
Enterococcus species, including vancomycin-resistant stains
Viridans group streptococci
Streptococcus pneumoniae
Common gram negative pathogens
Escherichia coli
Klebsiella species
Enterobacter species
Pseudomonas aeruginosa
Citrobacter species
Acinetobacter species
Stenotrophomonas maltophilia

Source: Table 1; Freifeld et al., 2011

Fever during neutropenia in immunocompromised patients may be the only indication of a severe underlying infection, because signs and symptoms of inflammation typically are attenuated; pulmonary infection may have no signs on infiltrates on radiographs, CSF pleocytosis might be low or absent in the setting of meningitis. The guidance document for management of neutropenic patients with fever (Freifeld et al., 2011) also provides the details of the evidence to be used for the confirmation of the relevant bacterial or viral infection.

In this study, a history of infections, including ongoing infections at baseline, will be documented as part of the subject's medical history. Any new infections that occur during the course of the study will be recorded as adverse events. It is recommended that invasive fungal

infections be diagnosed and reported as possible, probable or proven per the criteria described by Ascioglu et al., 2002 and later revised in De Pauw et al., 2008.

FUNGAL INFECTIONS

A. Aspergillus spp. or other mold infection:

- Proven: Clinical signs and symptoms plus a tissue biopsy revealing growth of an organism or positive histopathology.
- Probable: Clinical signs and symptoms with bronchoalveolar lavage (BAL) yielding positive growth or positive histopathology.
- Possible: at least 3 clinical signs or symptoms and growth of an organism from nonsterile fluid (ie, sputum).

B. Candida spp. or other yeast (e.g. T. glabrata):

- Proven fungemia: Any single positive blood culture that is culture positive for Candida spp. or T. glabrata. [Note: Removal of indwelling catheters is strongly encouraged.]
- Tissue documented: Clinical signs and symptoms compatible with invasive yeast infection and a positive culture from a normally sterile site with histologic evidence of tissue invasion (definite) or positive culture from sterile site without histologic evidence of invasion (probable).

BACTERIAL INFECTIONS

C. Bacteremia:

- Any single positive blood culture that is culture positive for bacterial pathogens consistent with a serious bloodstream infection.
    - Urinary tract infections will not be captured as opportunistic infections of interest

D. Invasive Bacterial Tissue Infection:

- Clinical signs and symptoms compatible with disease (sinusitis, pneumonia, intra-abdominal abscess)

and

- Radiographic evidence of disease and pure or predominant culture or pathogen detection from a sterile site biopsy.
    - Pathogen detection in respiratory secretion or sinus aspirates or CSF specimens will be considered if they are predominant and compatible with the clinical picture.