CLINICAL STUDY PROTOCOL

NCT Number: NCT02927067

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

Study Number: SHP620-303

Protocol Amendment and Date:

Amendment 9 (Version 10.0): 15 September 2021

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TAKEDA DEVELOPMENT CENTER AMERICAS, INC

PROTOCOL: SHP620-302

TITLE:	A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients
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IND:	IND 051001
EUDRACT NO.:	2015-004726-34
SPONSOR:	Takeda Development Center Americas, Inc (TDC Americas) 95 Hayden Avenue, Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	Multicenter
PROTOCOL HISTORY:	Amendment 9 (Version 10.0): 15 September 2021 Amendment 8 (Version 9.0): 02 July 2021 Amendment 7 (Version 8.0): 25 March 2021 Amendment 6 (Version 7.0): 07 December 2020 Amendment 5 (Version 6.0): 12 February 2020 Amendment 4 (Version 5.0): 05 February 2019 Amendment 3 (Version 4.0): 01 September 2017 Amendment 2 (Version 3.0): 01 June 2017 Amendment 1 (Version 2.0): 02 March 2017 Original Protocol (Version 1.0): 04 August 2016

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PROTOCOL SIGNATURE PAGE

Sponsor's (Takeda) Approval

Signature: [redacted]	Da[redacted]
[redacted], MD	

Investigator's Acknowledgement

I have read this protocol for Takeda Study SHP620-302.

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

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.

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Investigator Name and Address: (please hand print or type)	***The investigator completes the bottom section of the protocol signature page***

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION (AMENDMENT 8)

Noteworthy changes to the protocol are captured in the table below. The protocol has been amended to update the information on drug interactions and contraindications, consistent with the current Investigator's Brochure.

Other minor editorial revisions (including changes for consistency and clarity) are not described in this table.

Protocol Amendment		
Summary of Changes Since Protocol Version 8.0 (Protocol Amendment 7)		
Amendment Number **9**	**Amendment Date** **15 September 2021**	**Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated description of drug interactions consistent with the latest Investigator's Brochure		Section 1.2.1 Pharmacokinetics, Metabolism, and Drug-Drug Interactions Section 4.5.1 Reasons for Discontinuation and/or Withdrawal Section 5.2.1 Permitted Treatment Section 5.2.2 Prohibited Treatment

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EMERGENCY CONTACT INFORMATION

Please refer to Section 8.2.2 for information on serious adverse event reporting procedures.

For protocol- or safety-related issues (but with no information that would unblind the study treatment assignment) during normal business hours 8:00am - 5:00pm (local time per region), the investigator must contact the PPD blinded medical monitor:

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

North America: [redacted]

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

Fax numbers:

North America: [redacted] and [redacted]

EMEA/APAC: [redacted]

Email:

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]

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ABBREVIATIONS

AAG	alpha-1-1acid-glycoprotein
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immune deficiency syndrome
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
CI	confidence interval
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CMV	cytomegalovirus
CNS	central nervous system
CoD	Certificates of Destruction
COVID-19	Coronavirus Disease 2019
CRA	clinical research associate
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
DDI	drug-drug interaction
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DTP	direct-to-patient

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EC	ethics committee
ECG/EKG	electrocardiogram
eIC	electronic informed consent
EIND	emergency investigational new drug
EMA	European Medicines Agency
[redacted]	[redacted]
EU	European Union
FDA	Food and Drug Administration
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GI	gastrointestinal
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCMV	human cytomegalovirus
HCV	hepatitis C virus
HHC	home healthcare
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
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
IVIg	intravenous immunoglobulin
KPS	Karnofsky Performance Status
LAR	legally authorized representative
LLOQ	lower limit of quantification
MMF	mycophenolate mofetil
NCI	National Cancer Institute

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NI	noninferiority
NIH	National Institutes of Health
NPP	named patient program
OTC	over-the-counter
PBPK	physiologically-based pharmacokinetics
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PI	Principal Investigator
PO	per os (oral)
PT	preferred term
QD	once daily
qPCR	quantitative polymerase chain reaction
QTc	corrected QT interval
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	[redacted]
SMQ	standardized MedDRA queries
SOC	system organ class
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
WBC	white blood cell

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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 postbaseline 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 being unquantifiable (<LLOQ) for at least 5 days in 2 consecutive samples.
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 CMV disease	Defined as the presence of signs or symptoms of the tissue invasive CMV disease (same or new symptomatology) confirmed as per Ljungman et al. (2017), after the period of resolution of the disease in subjects symptomatic at baseline.
Refractory	Documented failure to achieve >1 $\log_{10}$ (common logarithm to base 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	Documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir, valganciclovir, foscarnet, and/or cidofovir.
Symptomatic subjects	HSCT recipients who *have* tissue-invasive CMV disease as determined by the investigator according to the criteria specified by Ljungman et al. (2017).
Asymptomatic subjects	HSCT recipients who *do not have* tissue-invasive CMV disease as determined by the investigator according to the criteria specified by Ljungman et al. (2017).

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STUDY SYNOPSIS

Protocol number: SHP620-302	**Drug:** Maribavir
Title of the study: A Phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled study to assess the efficacy and safety of maribavir compared to valganciclovir for the treatment of cytomegalovirus (CMV) infection in hematopoietic stem cell transplant recipients	
Number of subjects (total and for each treatment arm): Approximately 612 subjects will be screened to randomize approximately 550 subjects in the study, allowing for a 10% screen failure rate. Approximately 550 subjects will be randomized in a 1:1 ratio to a double-blind treatment with maribavir or valganciclovir. Assuming a 10% dropout rate during the double-blind phase, approximately 494 subjects (247 each in the maribavir and valganciclovir arms) are required to provide 90% power to assess the noninferiority of maribavir to valganciclovir.	
Investigator(s): A multicenter study to be conducted at approximately 105 sites worldwide.	
Site(s) and Region(s): Approximately 105 sites in North America, Europe, and Asia Pacific.	
Study periods (planned): 2017 - 2022	**Clinical phase:** 3

Primary Objective:

To compare the efficacy of maribavir to valganciclovir in CMV viremia clearance at the end of Study Week 8 in asymptomatic CMV infection in hematopoietic stem cell transplant (HSCT) recipients.

Key Secondary Objective:

To compare the efficacy of maribavir and valganciclovir on maintenance of CMV viremia clearance, achieved at the end of Study Week 8 through Study Week 16 (8 weeks of post-treatment/follow-up Phase).

Secondary Objectives:

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

Exploratory Objectives:

- [redacted]
- [redacted]
- [redacted]

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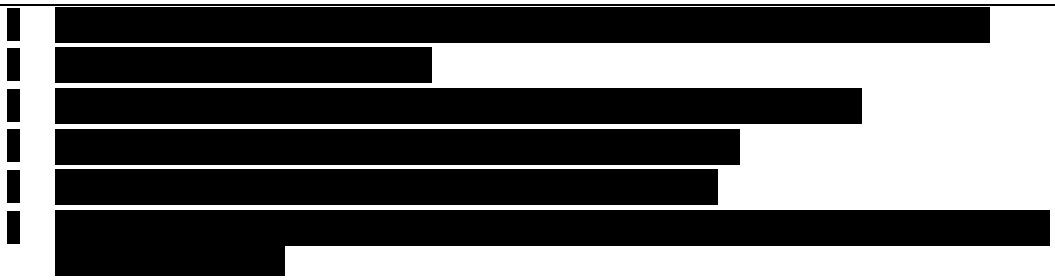

Rationale:

There are no anti-viral drugs specifically approved for treatment of CMV infection in transplant recipients. Both (IV) ganciclovir, approved for the treatment of CMV retinitis in immunocompromised patients including patients with HIV/AIDS and prevention of CMV disease in transplant recipients at risk for CMV disease, and oral valganciclovir approved for treatment of CMV retinitis in patients with HIV/AIDS and prevention of CMV disease in solid organ transplant recipient are widely used in clinical practice to treat CMV infection. The most common adverse effect of this treatment is bone marrow suppression, which is of particular concern for HSCT recipients whose marrow has been ablated and who are significantly immunosuppressed to prevent graft-versus-host disease (GVHD). The rates of valganciclovir-related neutropenia in HSCT range from 19% (Barkam et al., 2012) and 33% (Takahata et al., 2015) to 55% (Boeckh et al., 2015).

Maribavir is an anti-CMV agent that may be of particular benefit to HSCT patients as it does not appear to cause bone marrow suppression. In addition to the favorable safety profile of maribavir observed in earlier Phase 1-3 studies (studies evaluating prophylactic administration of maribavir), results from a recent large Phase 2 randomized trial (Study 1263-203) support the safety, tolerability, as well as anti-viral activity of maribavir as a potential option for the treatment of CMV infections in transplant recipients. Study 1263-203 was a multicenter, randomized, dose-ranging, parallel-group study of maribavir versus valganciclovir for the treatment of CMV infections in HSCT or solid organ transplant (SOT) recipients. Eligible subjects were randomized in a 1:1:1:1 allocation ratio (40 subjects per group) to receive oral maribavir at 400 mg, 800 mg, or 1200 mg twice daily (BID); or valganciclovir (900 mg BID for 3 weeks, 900 mg once daily (QD) after 3 weeks) for up to 12 weeks. Maribavir, at doses 400 mg BID, had comparable efficacy to valganciclovir at clearing CMV viremia and was generally well tolerated across the dose range studied. 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 of treatment. There was a higher incidence of neutropenia through Week 12 for valganciclovir-treated subjects compared with maribavir-treated subjects. This was evident for both measured degrees of neutropenia: 18% versus 5% (ANC<1000/mm^3), and 5% versus 2% (ANC<500/mm^3) through Week 12 for the valganciclovir and overall maribavir groups, respectively.

This Phase 3 study is designed to further assess and demonstrate the efficacy and safety of maribavir, administered at 400 mg BID, compared to valganciclovir administered at 900 mg BID for the treatment of asymptomatic CMV infection in HSCT recipients.

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Study treatment, dose, and mode of administration

Investigational product:

The sponsor will provide maribavir 200 mg strength tablets, which will be administered orally (PO) at 400 mg BID with food. Administration with food is not required for maribavir however it is required for valganciclovir (as per valganciclovir label), therefore same administration conditions (ie, with food) will be used to protect the blind.

Active control:

Valganciclovir will be provided in 450 mg strength tablets, which will be administered PO at 900 mg BID (or adjusted dosage, as required) with food.

Placebo:

To protect the study blind, maribavir and valganciclovir tablets will each have matching placebo tablets with same mode of administration.

Methodology:

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

All eligible subjects will be stratified based on the last prebaseline whole blood or plasma CMV DNA concentration as determined by the local or central specialty laboratory qPCR and acute GVHD (presence or absence at baseline):

- High viral load with CMV DNA ≥27300 IU/mL in whole blood or ≥9100 IU/mL in plasma;
- Low viral load with CMV DNA ≥2730 IU/mL to <27300 IU/mL in whole blood or ≥910 IU/mL to <9100 IU/mL in plasma, and
- Very low viral load and high-risk infection with CMV DNA ≥1365 IU/mL to <2730 IU/mL in whole blood or ≥455 IU/mL to <910 IU/mL in plasma

Subjects in each stratum will then be randomized in a 1:1 allocation ratio to receive double-blind maribavir 400 mg BID or valganciclovir 900 mg BID (with dose adjustment for renal function or neutropenia) for 8 weeks.

As shown in the study schematic in Study Design Flow Chart below, the study will have 3 phases: (1) Up to a 2-week screening phase; (2) 8-week double-blind study treatment phase; and (3) 12-week follow-up phase. Subjects will be required to visit the site up to 18 times for up to a 22-week period.

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Screening Phase

Approximately 612 subjects will be screened during an approximate 2-week screening phase to establish eligibility for study participation. If applicable, those subjects who meet eligibility requirements will undergo washout of any prohibited medications, the length of which will be specified in the eligibility criteria. Subjects treated with ganciclovir, valganciclovir, foscarnet, or letermovir for the current CMV infection must not be treated with these anti-CMV agents for longer than 72 hours prior to enrolling in the study. Subjects who discontinue from screening due to COVID-19-related factors but are otherwise qualified to participate in the trial may be rescreened at any time if the Takeda medical monitor agrees.

Study Treatment Phase

Approximately 550 subjects with an asymptomatic CMV infection who meet eligibility requirements during the screening phase, including the presence of quantifiable (local or central specialty laboratory) whole blood or plasma CMV DNA levels as specified, will be stratified based on their CMV viral load and GVHD status, and then randomized at Visit 2/Day 0 to receive either double-blind maribavir/placebo or valganciclovir/placebo (collectively, the study treatment) for 8 weeks.

Historical laboratory results for tests specified in the Schedule of Assessment 1 may be used for eligibility assessment (HIV test results, relevant hematology, and chemistry results) as long as those are obtained within the specified time period. The Screening and Visit 2/Day 0 visits can occur on the same day, if laboratory results are available for the determination of eligibility.

All Visit 2/Day 0 procedures and screening laboratory results needed to confirm eligibility must be completed and documented prior to randomization and study treatment administration and all clinical laboratory results required for eligibility verification must be available prior to randomization, including two separate CMV DNA assessments. 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 receive maribavir will take the 400 mg BID dose for the 8 weeks of the study treatment phase. Maribavir 200 mg strength tablets will be utilized for the daily dosing.

Although typically valganciclovir treatment in HSCT patients is started as an induction dose of 900 mg BID for up to 14 days and then reduced to a maintenance dose of 900 mg QD for a further 2 weeks or until CMV viral load clearance (Tomblyn et al., 2009), a different dosing strategy was selected for this study based on input from regulatory authorities. Treatment with valganciclovir 900 mg BID for the duration of 8 weeks was chosen in order to eliminate a potential bias for efficacy in favor of the investigational treatment (maribavir) by administering the comparator (valganciclovir) at a lower dose. Dosage for valganciclovir (450 mg QD up to 900 mg BID, as adjusted for renal function) will utilize 450 mg strength tablets.

Depending on the time of the first dose of study treatment on Visit 2/Day 0, a second dose should be administered on Visit 2/Day 0 provided that doses can be separated by a minimum of 8 hours; otherwise, only 1 dose should be administered on Visit 2/Day 0. Study treatment will then be administered (preferably) every 12 hours (q12h). When q12h dosing is not feasible, the doses should be separated by a minimum of 8 hours.

To protect the study blind, subjects will be required to take 2 tablets of their assigned study treatment and 2 tablets of the placebo q12h in a double-dummy format as shown in the table below.

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Study Treatment Dosing – Standard Regimen

Regimen		**AM**	**PM**
maribavir 400 mg BID	maribavir active	400 mg (2 tablets)	400 mg (2 tablets)
	valganciclovir placebo	placebo (2 tablets)	placebo (2 tablets)
valganciclovir 900 mg BID[a]	valganciclovir active	900 mg (2 tablets)	900 mg (2 tablets)
	maribavir placebo	placebo (2 tablets)	placebo (2 tablets)

BID: twice daily

[a] Starting dose for valganciclovir could be lower based on renal function results at screening (refer to dose adjustment tables for renal function).

Subjects randomized to receive valganciclovir will follow the 900 mg BID dosing regimen for the 8 weeks of the study treatment phase, with the exception of a permitted dose adjustment based on renal function and/or neutropenia. Subjects with estimated CrCl of ≥30 mL/min will be enrolled; adjustment of the valganciclovir dose for renal function will be allowed at study entry and during the study treatment phase consistent with valganciclovir label, as indicated in the table below. Placebo tablets will be assigned to make up for adjusted dose and decrease in valganciclovir tablets.

Valganciclovir Dosing – Adjustment for Renal Function

Valganciclovir 450 mg Tablets	
CrCl[a] (mL/min)	**Dose**
≥60	900 mg (2 tablets) BID
40 – 59	450 mg (1 tablet) BID
25 – 39	450 mg (1 tablet) QD
10 – 24	450 mg every 2 days

BID: twice daily; CrCl: creatinine clearance; QD: once daily

[a] An estimated creatinine clearance in adults is calculated from serum creatinine by the following formulas:
For Males = (140 – age [years]) × (body weight [kg]) / [(72) × (serum creatinine [mg/dL])]
For Females = 0.85 × male value.
Valganciclovir administration is not recommended below CrCl of 10 mL/min.

In addition, as shown in the table below, predefined criteria for valganciclovir dose adjustment based on ANC level and CMV DNA clearance may be used to manage subjects that experience neutropenia.

Valganciclovir Dose Adjustment Based on ANC level and CMV DNA Clearance

	ANC >1000/mm^3 [1.0×10^9/L] **ANC based on local or central laboratory results**	**ANC 500/mm^3 [0.5×10^9/L] to 1000/mm^3 [1.0×10^9/L]** **ANC based on local or central laboratory results**	**ANC<500/mm^3 [0.5×10^9/L]** **ANC based on local or central laboratory results**
CMV DNA ≤ LLOQ (based on local or central specialty laboratory, most recent result prior to dose assessment should be considered)	Continue valganciclovir 900 mg BID Hematopoietic growth factors may be used at investigator's discretion	May adjust valganciclovir dose to 450 mg BID or interrupt the dose and resume at 450 mg BID or 900 mg BID (dose choice at investigator's discretion) once ANC >1000/mm^3 [1.0×10^9/L] Hematopoietic growth factors may be used at investigator's discretion	May interrupt valganciclovir dose and resume at 450 mg BID or 900 mg BID (dose choice at investigator's discretion) once ANC >1000/mm^3 [1.0×10^9/L] Permanent valganciclovir discontinuation and alternative anti-CMV treatment may be considered at investigator's discretion Hematopoietic growth factors should be strongly considered
CMV DNA ≥LLOQ (based on local or central specialty laboratory, most recent result prior to dose assessment should be considered)	Continue valganciclovir 900 mg BID Hematopoietic growth factors may be used at investigator's discretion	May adjust valganciclovir dose to 450 mg BID Hematopoietic growth factors may be used at investigator's discretion	May interrupt valganciclovir dose and resume at resume at 450 mg BID or 900 mg BID (dose choice at investigator's discretion) once ANC >1000/mm^3 [1.0×10^9/L] Permanent valganciclovir discontinuation and alternative anti-CMV treatment may be considered at investigator's discretion Hematopoietic growth factors should be strongly considered

ANC=absolute neutrophil count; BID=twice daily; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; LLOQ=lower limit of quantitation; QD=once daily

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Various clinical scenarios of neutropenia will be programmed in the interactive response technology (IRT) and appropriate options will be selected by the investigator. Interruptions and discontinuation of study treatment will be conducted in a blinded manner; therefore, it is possible that treatment with either valganciclovir or maribavir will be interrupted or discontinued for neutropenia presence. The investigator may also select to interrupt study treatment, for other adverse events, regardless of the treatment assignment (maribavir or valganciclovir). The interruption for a maximum of 7 consecutive days will not result in permanent study treatment discontinuation. Up to 2 study treatment interruptions for a total of up to 7 days will be allowed. 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. A third study treatment interruption will lead to permanent study treatment discontinuation; the subject will complete the end of treatment procedures described for Visit 10/Study Week 8 in the Schedule of Assessment 1, and will follow 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.

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 permanently discontinue study treatment will complete the end of treatment procedures described for Visit 10/Study Week 8 in the Schedule of Assessment 1; these subjects will follow a modified schedule of assessments through the remaining weekly visits of 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 will be collected at the next visit scheduled 1 week after the treatment discontinuation. Subjects who discontinue study treatment early will not be asked to complete the following procedures 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-weeks specified for the study treatment phase, subjects will enter the 12-week follow-up phase. After the permanent discontinuation of study treatment and until the end of the study, subjects might be administered other anti-CMV treatment 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, 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 necessary by the investigator); no further follow-up will be performed.

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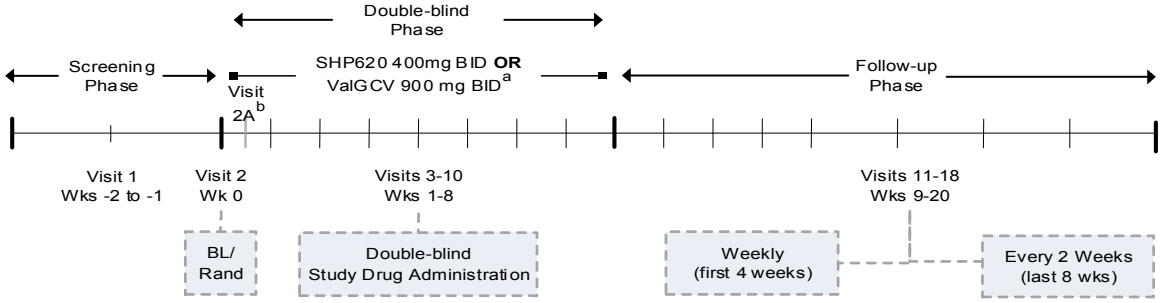
Follow-up Phase

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 Study Schedule 2 for a complete list of the evaluations.

Study Design Flow Chart



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

[a] Unless dose adjustment is required for moderate renal impairment.

[b] Visit 2A is required only for subjects receiving tacrolimus, cyclosporine, everolimus, or sirolimus at baseline.

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 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 testing at local specialty laboratories may be performed at more frequent intervals or using 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 two consecutive postbaseline samples, separated by at least 5 days.

Confirmed Recurrence or the confirmed CMV viremia recurrence 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 being unquantifiable (<LLOQ) for at least 5 days in 2 consecutive samples.

CMV Genotyping and Phenotyping

Subjects with known resistance to anti-CMV agents as determined by site local specialty laboratory (testing will be done as directed by the investigator) will be excluded from the study. At Visit 2/Day 0 plasma samples will be obtained and tested by the central specialty laboratory to identify mutations in the viral UL97 and UL54 genes known to confer resistance to anti-CMV agents. In addition, UL 27 will be tested. Given the urgency to treat the subjects, it is not possible to wait for this central specialty laboratory assessment prior to a subject's randomization to confirm lack of resistance to any previously used agents. In instances when a mutation will be reported in the baseline sample analyzed by the central specialty laboratory these subjects will be excluded from the Per Protocol Set for analysis. Subjects will be managed based on investigator clinical judgments, and if resistance is suspected genotyping may be conducted by a local specialty laboratory at investigator discretion. It is not expected that the genotyping results from central specialty laboratory will be available in time to direct patient management.

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[redacted]

Rebound is defined as increase in viral DNA load without prior clearance of viremia. The entire UL97, UL54, and UL27 CMV genes will be sequenced in every sample that meets the criteria for genotyping, including the baseline samples.

[redacted]

PK Assessment

Pharmacokinetic samples will be obtained for all subjects as in the Schedule of Assessments 1, but analyzed for only those subjects who are taking maribavir. Bioanalysis of PK samples will be conducted while the study is ongoing. The analysis will be conducted by unblinded staff from the bioanalysis lab/contract research organization (CRO) to allow for the identification of the PK samples from the subjects randomized to the maribavir treatment arm.

Inclusion and exclusion criteria:

Approximately 550 subjects, ≥16 years of age, who are HSCT recipients with asymptomatic CMV infections will be enrolled.

Inclusion Criteria:

Subjects must:

1. 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. During the COVID-19 public health emergency, informed consent from a potential or current trial participant may, if permitted by local laws and regulations, be obtained via electronic informed consent (eIC) capabilities or an electronic face-to-face consent interview when these individuals are unable to travel to the site (Food and Drug Administration [FDA] COVID-19 Guidance, 27 Jan 2021, Q11).
2. Be ≥16 years of age at the time of consent.
3. Be a recipient of hematopoietic stem cell transplant.
4. Have a documented asymptomatic CMV infection, with a screening value of CMV DNA ≥1365 IU/mL to ≤273000 IU/mL in whole blood or ≥455 IU/mL to ≤91000 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory quantitative polymerase chain reaction (qPCR) or comparable quantitative CMV DNA results. Both samples should be taken within 14 days prior to randomization with second sample obtained within 5 days prior to randomization. Same laboratory and same sample type (whole blood or plasma) should be used for these assessments. Asymptomatic CMV infection is defined as an infection that does not present with tissue invasive CMV disease, as assessed by the investigator. Subjects with CMV DNA <910 and ≥455 IU/mL in plasma or <2730 and ≥1365 IU/mL in whole blood will also need to meet at least 1 of the following criteria for high-risk CMV infection to be eligible:
   - Human leukocyte antigen (HLA)-related (sibling) donor with at least 1 mismatch at 1 of the following 3 HLA-gene loci: HLA-A, -B or -DR,
   - Haploidentical donor,
   - Unrelated donor with at least 1 mismatch at 1 of the following 4 HLA -gene loci: HLA-A, -B, -C and -DRB1,
   - Use of umbilical cord blood as stem cell source,
   - Use of ex vivo T-cell-depleted grafts,
   - Grade 2 or greater GVHD, requiring the use of systemic corticosteroids (defined as the use of ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid).
5. Have the current CMV infection as the first episode of CMV viremia after HSCT, either primary or reactivation, which, in the investigator's opinion, requires treatment.
6. Per investigator's judgment, be eligible for treatment with valganciclovir.
7. 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 ≥1000/mm^3 [1.0 x 10^9/L]
   b. Platelet count ≥25,000/mm^3 [25 x 10^9/L]
   c. Hemoglobin ≥8 g/dL
   d. Estimated creatinine clearance ≥30 mL/min
8. Have a negative serum beta human chorionic gonadotropin (β-hCG) pregnancy test at screening, if a female of childbearing potential. Urine pregnancy tests may be done per institutional requirements; however, they are not sufficient for eligibility determination. Sexually active females of childbearing 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 the last dose of study treatment.

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9. Be able to swallow tablets.
10. Have life expectancy of ≥8 weeks.
11. Weigh ≥40 kg.
12. Be willing and have an understanding and ability to fully comply with study procedures and restrictions defined in the protocol.

Exclusion Criteria:

Subjects must not:

1. Have CMV tissue invasive disease as assessed by the investigator at the time of screening and randomization at Visit 2/Day 0.
2. Have a CMV infection that is known to be genotypically resistant to ganciclovir, valganciclovir, foscarnet, or cidofovir based on documented evidence.
3. Be presenting with recurrent CMV infection (defined as a new detection of CMV infection in a subject who had at least one previously documented episode of CMV infection post-transplant, and who has had at least 2 weeks of undetectable CMV DNA between the episodes during active surveillance, based on same local laboratory and same sample type). The subject must also have been off any anti-CMV treatment between the current and prior infection. Otherwise, the current infection may be considered continuation of the prior infection.
4. Require ganciclovir, valganciclovir, foscarnet, or cidofovir administration for conditions other than CMV when study treatment is initiated (example: herpes simplex virus [HSV] co-infection requiring use of any of these agents after the randomization) or would need a co-administration with maribavir for CMV infection.
5. Be receiving leflunomide, letermovir, or artesunate when study treatment is initiated. NOTE: Subjects who may be 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 3 days prior to first dose of study treatment. Subjects receiving artesunate must discontinue the use prior to the first dose of study treatment.
6. Be on treatment with anti-CMV agents (ganciclovir, valganciclovir, foscarnet, or letermovir) for the current CMV infection for longer than 72 hours.
7. Have known hypersensitivity to the active substance or to an excipient of the study treatments.
8. 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 medication.
9. Require mechanical ventilation or vasopressors for hemodynamic support at the time of randomization.
10. Be female and pregnant or nursing.
11. Have previously completed, discontinued, or have been withdrawn from this study.
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 any clinically significant medical or surgical condition that, in the investigator's opinion, could interfere with interpretation of study results, contraindicate the administration of the assigned study treatment, or compromise the safety or well-being of the subject.
15. Have previously received maribavir.
16. 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), as analyzed by local or central lab.
17. Have known (previously documented) 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.

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18. Have active malignancy with the exception of nonmelanoma skin cancer, as determined by the investigator. Subjects who experience relapse or progression of their underlying malignancy (for which HSCT was performed), as determined by the investigator, are not to be enrolled.
19. Be undergoing treatment for acute or chronic hepatitis C.

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

Endpoints and statistical analysis:

Subject Populations:

- The Enrolled Set will consist of all subjects who have signed an informed consent and have begun some study procedures.
- The Randomized Set will consist of all subjects in the Enrolled Set for whom a randomization number has been assigned.
- The Modified Randomized Set will consist of all subjects in the Randomized Set who have taken at least 1 dose of assigned study treatment.
- The Safety Set will consist of all subjects who have taken at least 1 dose of study treatment.
- The Per Protocol (PP) Set will consist of all subjects in the Randomized Set who do not have major predefined 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 a subset of the PK set of subjects of ≥16-<18 years of age who had plasma samples drawn and tested for maribavir concentrations.

The Modified Randomized Set and PP Set will be used for efficacy analyses. Pharmacokinetic data will be analyzed using the Pharmacokinetic Set.

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Primary Efficacy Endpoint:

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

For clearance of CMV viremia at the end of Study Week 8, the subject must have received exclusively a study-assigned treatment.

Key Secondary Efficacy Endpoint:

The key secondary efficacy endpoint is defined as the maintenance of confirmed CMV viremia clearance achieved at the end of Study Week 8 through Week 16.

For clearance of CMV viremia achieved 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 and must also have symptom control.

Secondary Efficacy Endpoints:

- The achievement of the confirmed CMV viremia clearance after 8 weeks of receiving study-assigned treatment.
- The maintenance of the confirmed CMV viremia clearance achieved after completion of 8 weeks of study-assigned treatment, through Study Weeks 12 (4 weeks of post-treatment period), 16 (8 weeks of post-treatment/follow-up phase), and 20 (12 weeks post-treatment).

- The maintenance of confirmed CMV viremia clearance achieved 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. For maintenance effect to be achieved at a time point, the subject must have received exclusively study-assigned treatments up to that time point and also must have symptom control.
- The recurrence of confirmed CMV viremia in the 2 study treatment arms during the first 8 weeks of the study, during the 12 weeks of the follow-up study phase, and at any time during the study, regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy.
- The recurrence of confirmed CMV viremia in the 2 study treatment arms when subjects are on treatment and off treatment.
- The incidence of grade 3 or 4 neutropenia (defined as ANC <1,000/mm^3 [1.0×10^9/L] or ANC <500/mm^3 [0.5×10^9/L], respectively) while receiving study treatment, time to first neutropenia development while receiving study treatment.

Exploratory Efficacy Endpoints:

[redacted]

Safety Endpoints (Secondary):

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

Pharmacokinetic endpoints for maribavir treatment

Pharmacokinetic samples will be obtained for all subjects as in the Schedule of Assessment 1, but analyzed for only those subjects who are taking maribavir.

- 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]
- [redacted]

Statistical Methodology for Primary Efficacy Endpoint:

Confirmed CMV viremia clearance at the end of Study Week 8, irrespective of treatment duration 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 at the end of Study Week 8.

Assessments of Virological Responders at Study Week 8

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

[a] Week 9 data, if available to evaluate effect of study drug, to be used only if Week 8 data is unavailable or missing.

Notes: Scenarios in the table above are provided as examples and may not be 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, irrespective of treatment duration, between treatment groups (maribavir and valganciclovir) will be obtained using Cochran-Mantel-Haenszel (CMH) weighted average across strata with baseline plasma CMV DNA concentration levels and presence or absence of acute GVHD as the stratification factors. The baseline plasma CMV DNA concentration will be the last central laboratory assessment before the first dose of study treatment.

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The 2-sided 95% confidence interval (CI) of the weighted average of difference across strata will be calculated using the normal approximation method. If the lower limit of the 95% CI is greater than -7%, it will be concluded that maribavir is as efficacious as valganciclovir. The noninferiority analysis will be performed on the PP Set as the primary analysis and on the Modified Randomized Set as a secondary analysis.

Sensitivity and supportive analyses of the primary endpoint of confirmed CMV viremia clearance at Week 8 will be conducted to evaluate the robustness of the results from the primary method.

Subject to the multiplicity adjustment method, the superiority will be tested by comparing the lower limit of the 95% CI of the difference in proportion of subjects with confirmed CMV viremia clearance between maribavir and valganciclovir with 0. The superiority testing will be performed on the Modified Randomized Set.

Analyses will be conducted for the following subgroups (inclusive, but not limited to):

- Cytomegalovirus DNA viral load (high, low, very low/high-risk)
- Acute GVHD presence/absence at baseline
- Adolescents ≥16 to <18 years of age (exploratory analysis: may be conducted if sample size is adequate)

Statistical Methodology for Key Secondary Efficacy Endpoint:

The difference in proportion of subjects who achieve response as defined for the key secondary efficacy endpoint between treatment groups (maribavir and valganciclovir) will be obtained using CMH weighted average across strata with baseline plasma CMV DNA concentration (based on the last central laboratory assessment before the first dose of study treatment) and presence or absence of acute GVHD as the stratification factors. The 2-sided 95% CI of the weighted average of difference across strata will be calculated using the normal approximation method. Sensitivity analyses for the key secondary endpoint will also be conducted.

Subject to the multiplicity adjustment method, the noninferiority testing will be done using the same NI margin as the primary efficacy endpoint. If the lower limit of the 95% CI is greater than -7%, it will be concluded that maribavir is as efficacious as valganciclovir in maintaining treatment effect. The noninferiority analysis will be performed on the PP Set as the primary analysis and on the Modified Randomized Set as a secondary analysis.

Subject to the multiplicity adjustment method, the superiority in key secondary efficacy endpoint will be tested by comparing the lower limit of the 95% CI of the difference in proportion of subjects who achieve response as defined for the key secondary efficacy endpoint between maribavir and valganciclovir with 0. The superiority testing will be performed on the Modified Randomized Set.

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Multiplicity Adjustment:

The hypothesis testing of the primary and key secondary efficacy endpoints will be adjusted for multiple comparisons following the gatekeeping strategy as described below 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 NI hypothesis testing (H11) first, the superiority hypothesis testing for primary efficacy endpoint (H12) and the key secondary efficacy endpoint NI hypothesis testing (H21) second, and lastly the superiority testing for key secondary efficacy endpoint (H22).

- First, the NI hypothesis of the primary efficacy endpoint will be tested based on the 2-sided 95% CI of the adjusted difference in proportion of subjects who have CMV viremia clearance at the end of Study Week 8 stratified by baseline CMV DNA concentration level and presence/absence of acute GVHD at baseline. This analysis will be conducted using PP Set as the primary and Modified Randomized Set as secondary. If the lower limit of the 95% CI is above -7%, NI of the primary efficacy endpoint is considered established.
- If and only after the NI of the primary efficacy endpoint is established, the superiority hypothesis of the primary efficacy endpoint and the NI hypothesis of the key secondary endpoint will be tested in parallel. Hochberg procedure will be used to control family-wise Type 1 error rate at α=5% level.
- If and only if the superiority of the primary efficacy endpoint and NI of key secondary efficacy endpoint are established, the superiority hypothesis of the key secondary efficacy endpoint will be tested.

Statistical Methodology for Safety Endpoints:

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

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:

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

Treatment-emergent AEs (TEAEs) are defined as those with a start date on or after the first dose of study treatment, or with a start date before the date of first dose of study treatment, but increasing in severity after the first dose of study treatment.

The overall study AEs are those occurring during the overall-study observation period.

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 number of events, incidence, and percentage of TEAEs and overall-study AEs will be displayed for each treatment group 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 (AESIs) will be analyzed according to primary system organ classes (SOCs) and preferred terms (PTs). Standardized MedDRA queries (SMQs) may be used, as 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. Invasive bacterial and fungal infections, if any, will be noted.

Usage of concomitant medications will be summarized descriptively for each of the treatment groups for the on-treatment period and overall-study period. Additionally, administration of hematopoietic growth factors, blood, and blood products will be summarized.

Change from Baseline in vital signs and clinical laboratory tests will be summarized for each treatment group with descriptive statistics at each assessment visit. 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. Analyses of shifts in NCI CTC toxicity grades from baseline to maximum grade postbaseline for the on-treatment period and the overall-study period will be analyzed. Potentially clinically important findings will also be summarized.

Treatment-emergent grade 3 or 4 neutropenia (defined respectively as ANC <1,000/mm^3 [1.0 x 10^9/L]) or ANC <500/mm^3 [0.5 x 10^9/L]) will be summarized as shifts in laboratory results from lower grade to maximum grade of either 3 or 4 postbaseline for the on-treatment period and the overall-study period. Time to neutropenia development will be evaluated.

Study treatment dose adjustment, specifically valganciclovir dose adjustment, and interruptions for neutropenia or renal function impairment or other AE, and maribavir dose interruptions for any AE, will be summarized.

Abnormal physical examination findings will be listed.

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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.

PK Analysis:

In order to maintain the study blind, if needed, an interim population PK analysis of maribavir PK data obtained from the study subjects will be performed by an independent unblinded team.

Sample Size Justification:

The primary testing is to establish that maribavir is not inferior to valganciclovir in treatment of CMV infection in HSCT recipients. For ethical reasons it would not be possible to conduct a study of maribavir versus placebo since different treatment strategies are already used and well established in clinical practice to treat CMV infection. Valganciclovir has been selected as the active control because of its documented effectiveness for the treatment of CMV infection, including in patients after hematopoietic stem cell transplantation. While clinical trials of ganciclovir and valganciclovir versus placebo have been conducted for CMV prophylaxis, no placebo-controlled studies have been done to date for the treatment of CMV infection or disease. Therefore, the effect size of valganciclovir against placebo is not available, and treatment effect estimate had to be derived indirectly. Literature reports viremia clearance rate for valganciclovir at 70% to 100%. In the VICTOR study, a randomized controlled study to compare valganciclovir with ganciclovir for the treatment of CMV disease in SOT subjects (Asberg et al., 2007), the Week 7 viremia clearance rate was reported at 67% and the derived lower limit of the 95% CI was 60% for valganciclovir treatment group (n=164). In Phase 2 treatment SHP620-203 study, 75% of HSCT subjects (n=61 across 3 dose groups) in the maribavir group and 48% in valganciclovir group (n=21) had confirmed CMV viremia clearance within 6 weeks. Based on these available data, the proportion of subjects who achieve viremia clearance after 8 weeks of treatment in the current study is assumed at 60% for the valganciclovir treatment group.

A 7% NI margin is chosen for the current study based on the following considerations. First, a 7% of margin preserves at least 85% of the effect size assumed for the valganciclovir treatment group. Secondly, a 7% margin is less than half of 15%, a common NI margin used in antiviral trials and is considered very conservative. Two NI studies on comparing valganciclovir with ganciclovir in CMV treatment were identified after a thorough literature research. One study was reported by Chawla et al. 2011, and the other is VICTOR study (Asberg et al., 2007); both used a NI margin of 15%. Discussions with clinical experts confirmed that a 7% NI margin is considered a conservative choice and in clinical practice, a lower response rate might even be considered given the favorable safety profile of the test drug and where toxicities of available treatments such as valganciclovir limit their use.

Based on SHP620-203 study reporting 75% of HSCT subjects in the maribavir group and 48% in valganciclovir group having confirmed CMV viremia clearance within 6 weeks, it could be expected that maribavir may be superior to valganciclovir in the treatment setting in the HSCT population. However, given the uncertainties from the differences in this study design from that of SHP620-203, literature reported treatment effect for valganciclovir, and practical consideration for enrollment of sufficient number of patients in this orphan patient population, the primary objective of this study is testing for noninferiority, with testing for superiority to be conducted only after non inferiority is established.

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

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STUDY SCHEDULES

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

Phase	Screening Phase[a]		Double-blind Study Treatment Phase[a,b]								
Study Visit	**1[c]**	**2**	**2A[d]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (End of Treatment)**
Study Week[e]	**-2 to 0**	**0**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day (permitted window)	**-14 to 0**	**0[f]**	**4 (±1)**	**7 (+2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**35 (±3)**	**42 (±3)**	**49 (±3)**	**56**
Informed consent[g]	X										
Inclusion/exclusion criteria	X	X									
Randomization		X									
Physical examination (including weight)[h]		X					X				X
Height	X										
Weight	X				X				X		
Vital signs	X	X			X		X		X		X
Medical history	X	X[i]									
Prior medications, therapies, and procedures	X	X									
12-lead ECG[j]		X									X
Hematology/Chemistry[k]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[k]		X			X		X		X		X
Pregnancy test[l]	X	X					X				X
HIV status[m]	X										
HBV, HCV test		X[n]									
CMV DNA test[o]	X[p]	X		X	X	X	X	X	X	X	X
[redacted]											
Immunosuppressant drug concentration levels[d]		X[s]	X[s]	X[s]							X
PK samples[t]				X			X[s]				X
Interactive Response Technology[u]	X	X		X	X	X	X	X	X	X	
Study treatment dispensed[v]		X		X	X	X	X	X	X	X	

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

Phase	Screening Phase[a]		Double-blind Study Treatment Phase[a,b]								
Study Visit	**1[c]**	**2**	**2A[d]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (End of Treatment)**
Study Week[e]	**-2 to 0**	**0**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day (permitted window)	**-14 to 0**	**0[f]**	**4 (±1)**	**7 (+2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**35 (±3)**	**42 (±3)**	**49 (±3)**	**56**
Study diary[w]		X	X	X	X	X	X	X	X	X	X
Underlying disease assessment[x]	X	X		X	X	X	X	X	X	X	X
Invasive bacterial and fungal infection/transplant relevant infections assessment	X	X		X	X	X	X	X	X	X	X
GVHD assessment[y]	X	X		X	X	X	X	X	X	X	X
Liver function assessment by Child-Pugh classification		X									
Comorbidity status evaluation		X					X				X
[redacted]											
Concomitant medications, therapies, and procedures[z]		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; hx=history; IRT=interactive response technology PK=pharmacokinetic; SAE=serious adverse event; [redacted]

[a] Study Visit 1 (Screening) and Study Visit 2 (Randomization) must be done with the subject present at the investigative site. Study Visits 2A through 10 may be conducted at the clinic or by optional home healthcare visits to extend flexibility to subjects during the COVID-19 public health emergency, although it is preferable to conduct Study Visit 10 (End of Treatment) with the subject present at the investigative site. Home healthcare visits will be documented in the study records and eCRF.

[b] Subjects who permanently 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. The end of treatment sample for immunosuppressant drug concentration level will be collected at the next visit scheduled one week after the treatment discontinuation. 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 study 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.

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

Phase	Screening Phase[a]		Double-blind Study Treatment Phase[a,b]								
Study Visit	**1[c]**	**2**	**2A[d]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (End of Treatment)**
Study Week[e]	**-2 to 0**	**0**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day (permitted window)	**-14 to 0**	**0[f]**	**4 (±1)**	**7 (+2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**35 (±3)**	**42 (±3)**	**49 (±3)**	**56**

[c] Obtaining Informed Consent is not restricted to Study Visit 1 but can be obtained during the course of the screening phase (Study Weeks -2 to 0) as long as it is obtained before any study-specific procedures are performed. During the COVID-19 public health emergency, informed consent from a potential or current trial participant may be obtained via electronic informed consent (eIC) capabilities or an electronic face-to-face consent interview when these individuals are unable to travel to the site (FDA COVID-19 Guidance, 27 Jan 2021, Q11), if permitted by local laws and regulations. All other assessments must be done at the investigative site.

[d] Immunosuppressant drug concentration testing and Visit 2A are solely for subjects receiving immunosuppressive therapy with tacrolimus, cyclosporine, everolimus, or sirolimus. Visit 2A will occur at Day 4±1 day for subjects receiving immunosuppressive agent at baseline, or 4±1 days after initiating one of these immunosuppressive treatments for subjects who start during the study.

[e] Permissible assessment windows: Study Visit 2A, ±1 day, Study Visit 3 (Week 1) +2 days, Study Weeks 2-4, ±2 days; Study Weeks 5-8, ±3 days.

[f] 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. 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.

[g] 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 and verified within 3 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 ≥1365 IU/mL to <273000 IU/mL in whole blood or ≥455 IU/mL to <91000 IU/mL in plasma in 2 assessments, separated by at least one day, as determined by local or central specialty laboratory quantitative polymerase chain reaction (qPCR) or comparable quantitative CMV DNA results. Results should be available before the subject is randomized to verify subject eligibility for the study. Both samples should be taken within 14 days of randomization with second sample obtained within 5 days before randomization. Same laboratory and sample type (whole blood or plasma) should be used for these assessments.

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

[i] Updated medical history on Visit 2/Day 0 (Section 5.1).

[j] ECGs other than protocol-specified ECGs will be performed when clinically indicated. For home healthcare visits, ECGs may be performed by a qualified healthcare professional who is certified/authorized by the Principal Investigator to perform such tests routinely.

[k] Clinical laboratory tests will be performed at a central laboratory for all specified time points during the study with the exception of Visit 2A (for subjects receiving tacrolimus, cyclosporine, everolimus, or sirolimus); a local lab will assess potassium and magnesium at Visit 2A for these subjects. 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 beta human chronic gonadotropin test results can be used for the assessment of pregnancy on Visit 2/Day 0/Week 0, prior to study drug administration. Sample for hematology/chemistry/pregnancy will be taken for analyses by the central laboratory before study drug administration at baseline. For subsequent visits, in addition to samples taken for central laboratory analysis at the visit, samples for complete blood count with differential and serum creatinine should be drawn and analyzed by a local laboratory within 2 days prior to study treatment dispensation. These local laboratory results should be available and reviewed, to ascertain any dose adjustment of study drug (valganciclovir dose adjustment for renal function and/or neutropenia) can be conducted, if needed, prior to each study treatment dispensation during the treatment phase. For home healthcare visits, collection of clinical laboratory samples (blood specimen collection or other diagnostic tests) may be performed by the investigator or qualified site staff who can visit the trial participant's residence.

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

Phase	Screening Phase[a]		Double-blind Study Treatment Phase[a,b]								
Study Visit	**1[c]**	**2**	**2A[d]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (End of Treatment)**
Study Week[e]	**-2 to 0**	**0**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day (permitted window)	**-14 to 0**	**0[f]**	**4 (±1)**	**7 (+2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**35 (±3)**	**42 (±3)**	**49 (±3)**	**56**

[l] Female subjects of childbearing potential will have serum pregnancy testing performed at a central or local laboratory. Urine test results may be performed to accommodate institutional requirements, however, are not sufficient for eligibility determination.

[m] HIV status confirmed within 3 months prior to randomization will be used for the evaluation of this criterion. If a subject is known (previously documented) to be HIV positive, this information will be used in the eligibility assessment. Local testing during screening will be required for the eligibility assessment for subjects for whose HIV status within the 3 months prior to study entry is unknown; negative results must be confirmed prior to randomization.

[n] HBV 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 performed at Visit 2/Day 0. The results of test do not have to be available prior to start of dosing.

[o] 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. During screening period, local specialty laboratory results for CMV DNA quantitation (from whole blood or plasma as per site's standard practice) could be used for eligibility assessment; in this case CMV DNA results from central laboratory are not required. At baseline (Visit 2/Day 0/Week 0) a sample for the CMV DNA quantification will be taken and tested at the central specialty lab. At all other visits CMV DNA tests will be conducted at a central specialty laboratory, local specialty laboratory testing will be done at the investigator's discretion. The screening results, regardless whether from the local or central specialty laboratory, will be utilized for stratification for randomization.

[p] To be eligible for randomization, both CMV DNA results must be ≥455 IU/mL in plasma or ≥1365 IU/mL in whole blood.

[q] Subjects with CMV disease at screening/baseline will be excluded. Subjects will be assessed at subsequent visits during the study for the development of new tissue invasive CMV disease, and disease outcome (no change, improvement, resolution).

[redacted]

[s] If the subject is receiving immunosuppressant drugs (cyclosporine, tacrolimus, sirolimus, or everolimus), as mentioned in Section 7.2.3.4, on Study Day 0, then a blood sample to measure immunosuppressant drug concentration will be obtained on Visit Day 0 prior to study treatment administration, at Visit 2A (Day 4 ±1 day), and on Visit Day 7 (+2 day). 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±1 day after initiating the immunosuppressant), and at the next scheduled study visit. Tests will be performed at a local laboratory. For more details see Section 7.2.3.4.

[t] Pharmacokinetic (PK) samples should be obtained for all subjects and analyzed for only those subjects who are taking maribavir. A PK sample will be taken before the morning dose of study drug at all 3 PK visits. A PK sample will also be taken 2-4 hour after the morning dose of study at Visit 3/Week 1 and Visit 10/Week 8. There will be no postdose PK sample collected for Visit 6/Week 4. At Visit 3/Week 1 an intensive PK sampling for children ≥16 and <18 years of age will be performed as follows: premorning dose, 1, 2, 3, 4, 6, 8 (all ±5 min), and 12 hours (±15 min) postmorning dose. PK sample collection for children ≥16 and <18 years of age will also be performed at Visit 6/Week 4 (one premorning dose PK sample) and at Visit 10/Week 8 (one premorning dose and one between 2-4 hours postmorning dose PK samples). Additional PK samples will be collected from the subjects with biopsy proven GI graft-versus host-disease (GVHD) with diarrhea (>300 ml/day) or biopsy proven GI GVHD 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). See Section 7.2.4.1 for more details.

[u] The IRT system will be used for stratification and randomization of eligible subjects at baseline. IRT will be used for dispensing study treatment.

[v] All dispensed study treatments will be documented on the CRFs and/or other investigational product records, and may include additional information as required per applicable regulations. The disposition of unused supply of dispensed study treatment that has been prescribed to the subject will be documented in the accountability log.

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

Phase	Screening Phase[a]		Double-blind Study Treatment Phase[a,b]								
Study Visit	**1[c]**	**2**	**2A[d]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (End of Treatment)**
Study Week[e]	**-2 to 0**	**0**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day (permitted window)	**-14 to 0**	**0[f]**	**4 (±1)**	**7 (+2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**35 (±3)**	**42 (±3)**	**49 (±3)**	**56**

[w] The study diary will be dispensed at baseline and will be collected at the last follow-up visit. [redacted]

[x] Underlying disease that led to HSCT, including relapse/progression, will be assessed at all visits throughout the study treatment phase.

[y] Subjects will be stratified at baseline according to presence/absence of acute GVHD.

[z] Includes recording of medications and transfusions of blood products. Changes in immunosuppression regimens will also be recorded.

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

Phase	Follow-up Phase[a,b]							
Visit	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18 (End of Study)**
Study Week (Follow-up Week)[c]	**9 (1)**	**10 (2)**	**11 (3)**	**12 (4)**	**14(6)**	**16 (8)**	**18 (10)**	**20 (12)**
Study Day (Follow-up Day)	**63 (7)**	**70 (14)**	**77 (21)**	**84 (28)**	**98(42)**	**112 (56)**	**126 (70)**	**140 (84)**
Physical examination (including weight)								X
Vital signs								X
12-lead ECG[d]								X
Hematology/Chemistry[e]		X		X		X		X
Urinalysis[e]								X
Immunosuppressant drug concentration level[f]	X							
Underlying disease assessment[g]	X	X	X	X	X	X	X	X
Invasive bacterial and fungal infection(s) assessment	X	X	X	X	X	X	X	X
CMV DNA test[h]	X	X	X	X	X	X	X	X
[redacted]								
GVHD assessment	X	X	X	X	X	X	X	X
Comorbidity status evaluation				X		X		X
[redacted]								
AE monitoring[k]	X	X	X	X	X	X	X	X
SAE monitoring[k]	X	X	X	X	X	X	X	X
Concomitant medications, therapies, and procedures[l]	X	X	X	X	X	X	X	X

AE=adverse event; CMV=cytomegalovirus; ECG=electrocardiogram; GVHD=graft-versus-host-disease; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IRT=interactive response system; SAE=serious adverse event; [redacted]

[a] 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.

[b] 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 and authorized Principal Investigator's designee, and only if permitted by local laws and regulations. However, it is preferable to conduct Study Visit 18 (End of Study) with the subject present at the investigative site. Blood sample for CMV DNA quantitation and clinical laboratory assessments will be collected. AE and SAE collection may be completed by telephone follow-up call on the day of the scheduled visit.

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

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

[c] 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.
[d] ECGs other than protocol-specified ECGs will be performed when clinically indicated. For home healthcare visits, ECGs may be performed by a qualified healthcare professional who is certified/authorized by the Principal Investigator to perform such tests routinely.
[e] Clinical laboratory testing performed at a central laboratory for all specified time points during the follow-up phase.
[f] See Section 7.2.3.4 for more details.
[g] Underlying disease that led to HSCT, including relapse/progression, will be assessed at all visits throughout the follow-up phase.
[redacted]
[k] SAEs and nonserious AEs deemed related to study drug will be monitored and recorded through Visit 18/Week 20/Follow-up Week 12 (end of study). Nonserious AEs will be recorded through 30 days after the last dose of study medication.
[l] All medications, therapies, and procedures used to treat AEs will be recorded through Visit 18/Week 20 (Follow-up Week 12/end of study).

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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). It is one of the most important complications associated with significant morbidity and mortality in the individuals with compromised immune systems after allogenic hematopoietic stem cell transplantation (HSCT) (de la Hoz et al., 2002; Razonable and Emery, 2004; Maffini et al., 2016). Cytomegalovirus can cause multiorgan disease in recipients of stem cell transplants, including pneumonia, hepatitis, gastroenteritis, retinitis, and encephalitis, and the disease can develop both early and late after the transplantation procedure (Boeckh et al., 2003; Boeckh and Ljungman, 2009; Krause et al., 1997; Zaia et al., 1997). 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), and reduced survival in HSCT patients (Boeckh and Ljungman, 2009). 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.

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Prevention strategies based on prophylactic antiviral therapy have not been common in HSCT in contrast with solid organ transplant (SOT). Before the introduction of ganciclovir (one of the available anti-CMV agents), the vast majority of CMV infections occurred in the time period between engraftment and day 100 after hematopoietic SCT, with sporadic occurrences before engraftment (Bueno et al., 2002). However, whereas the prevalence of early CMV disease declined with intense antiviral drug use, the incidence of bacterial and fungal infections as well as late CMV disease increased, without an impact on the mortality rate (Ariza-Heredia et al., 2014; Boeckh et al., 2003; Zaia et al., 1997).

Although 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, however, 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; Maffini et al., 2016; Reusser et al., 2002; Salzberger et al., 1997). These toxicities are of particular concern in HSCT recipients, in whom the bone marrow has been ablated or significantly suppressed, who receive ongoing immunosuppressants to prevent GVHD, or who may require the use of other therapies that are potentially toxic to the kidneys or other organs.

Regardless of currently available antiviral strategies that exist for various high-risk transplant subjects, the adverse effects of these strategies have led to low use of prophylaxis in the HSCT recipients who continue to remain at risk for CMV infection within the early (initial ~3 months) or later post-transplantation time periods (Boeckh et al., 2003; Legendre and Pascual, 2008).

In contrast, pre-emptive strategies are widely preferred as a prevention method by transplant centers and include close surveillance of target viral DNA concentration (CMV viremia), which varies depending on host's risk for CMV disease, current immunosuppression, and treatment center practice. Cytomegalovirus viremia is considered one of the most important predictors of development of CMV disease (Emery et al., 2000; Humar et al., 1999).

The currently available anti-CMV agents (ganciclovir, valganciclovir, foscarnet, or cidofovir) albeit extensively used in preemptive and treatment setting for CMV infection are not approved for this indication, and their use is limited by their toxicities. Also, development of anti-viral resistance to these anti-CMV agents is an ongoing clinical problem leading to graft loss and even mortality for some transplant patients, including HSCT patients.

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 (HSCT and SOT). Based on clinical studies completed to date, maribavir does not appear to cause bone marrow suppression or renal toxicities and therefore may offer a safer option for CMV treatment in HSCT patients.

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1.2 Maribavir 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

Following oral administration, maribavir was rapidly and well absorbed with mean peak plasma concentrations generally achieved between 1 and 3 hours postdose. Total exposure to maribavir, as measured by area under the curve (AUC), was approximately dose-proportional following a single dose from 50 to 1600 mg, or multiple doses from 300 to 2400 mg per day. Maribavir demonstrates time independent pharmacokinetics (PK). When coadministered with a moderate fat meal, maribavir AUC was not changed, while the maximum observed plasma concentration (C_{max}) was reduced by 28%. Maribavir can be taken with or without food, as the slight to moderate decrease in exposure is not considered clinically significant based on the accumulated efficacy and safety data. Bioavailability of a 100 mg tablet was unaffected by crushing the tablet or changes in gastric pH. Maribavir is highly bound to plasma proteins (98.0% in vitro and 98.5% to 99.0% ex vivo), and binding appears to be independent of maribavir plasma concentrations at the therapeutic doses and populations (healthy subjects, subjects with renal or hepatic impairment, and transplant patients). Maribavir can penetrate the blood-retinal barrier, with the ratio of vitreous humor to plasma maribavir concentrations ranging from 0.026 to 0.281, which is greater than the free fraction in plasma. Maribavir is not expected to cross the blood brain barrier in human based on the nonclinical data. Following 400 mg BID doses, the elimination half-life (t1/2) of maribavir was estimated to be 4.32 hours in adult transplant patients. Due to the relatively short t1/2, steady state was reached within 2 days of dosing, with the accumulation ratio ranging from 1.24 to 1.49 for AUC after BID dosing. Maribavir is metabolized primarily in the liver through cytochrome P450 (CYP) 3A4 (primary) and CYP1A2 (secondary) pathways with the formation of the primary metabolite, VP44469. Renal clearance is a minor route of elimination of maribavir.

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Based on in vivo data and population PK analysis, no maribavir dose adjustment is needed based on transplant type, age, gender, race, in patients with mild or moderate hepatic impairment, or in patients with mild, moderate, or severe renal impairment.

Maribavir is contraindicated with valganciclovir/ganciclovir as it may antagonize ganciclovir's antiviral effects due to maribavir's inhibitory effect on UL97 serine/threonine kinase, which is required for activation/phosphorylation of ganciclovir. Maribavir can be administered with other anti-CMV drugs, including letermovir, foscarnet, and cidofovir as clinically significant PK- or pharmacodynamic-based drug-drug interactions (DDIs) are not expected. Based on extensive in vitro and in vivo data, maribavir has a low propensity to cause, or be the victim of DDIs. Dose adjustment of maribavir is only needed when maribavir is coadministered with a strong or moderate CYP3A4 inducer. With the exceptions of selected immunosuppressants and rosuvastatin, coadministration with maribavir does not impact the use or outcomes of a wide range of other drugs commonly used in the target patient population.

Strong or moderate CYP3A inducers may significantly decrease the plasma exposure to maribavir. Coadministration with rifampin (a strong inducer of CYP3A and moderate inducer of CYP1A2) decreased Cmax, AUC and predose trough concentration (C_{trough}) by 39%, 60% and 82%, respectively, and therefore, is not recommended due to the potential for a decrease in efficacy of maribavir based on the magnitude of the reduction in maribavir C_{trough}. Alternative antimicrobial or antituberculosis therapy with a lower CYP3A induction potential (eg, pyrazinamide, ethionamide) should be considered.

Strong CYP3A4 inhibitors may increase the plasma exposure to maribavir. Coadministration with ketoconazole (a strong CYP3A and P-glycoprotein [P-gp] inhibitor) increased Cmax and AUC by 10% and 53%, respectively. Based on the less than 3-fold increase in maribavir exposure expected, lack of dose-limiting toxicity and a wide therapeutic window, maribavir can be coadministered with a strong CYP3A4 inhibitor (eg, clarithromycin, ketoconazole, itraconazole, posaconazole, and voriconazole) without dose adjustment.

Coadministration of 400 mg BID maribavir with tacrolimus (an immunosuppressant and a CYP3A4 and P-gp substrate) increased the tacrolimus whole blood Cmax, AUC, and Ctrough by 38%, 51%, and 57%, respectively. When immunosuppressants tacrolimus, cyclosporine, everolimus, or sirolimus are coadministered with maribavir, their whole blood concentrations should be frequently monitored during treatment and after discontinuation of maribavir.

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Maribavir is an in vitro inhibitor of breast cancer resistance protein (BCRP). To be cautious, it is recommended that when initiating maribavir dosing in patients who are taking rosuvastatin (a sensitive BCRP substrate), patients should be closely monitored for rosuvastatin-related events, especially the occurrence of myopathy and rhabdomyolysis.

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 17 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 show reduction in 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.

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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 useful for the treatment of CMV infections including these 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 these studies subjects received maribavir at 1 of 3 dose strengths: 400, 800, or 1200 mg BID. Both studies demonstrated favorable anti-CMV activity of maribavir and showed that maribavir 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 results (<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.

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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 have been planned 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 17 Phase 1 studies in adult healthy volunteers, special populations (subjects with renal and hepatic impairment, and stable renal transplant recipients), and HIV-infected subjects.

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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, electrocardiogram (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 SHP620-303), 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 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.

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2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

There are no anti-viral drugs specifically approved for treatment of CMV infection in transplant recipients, including in pediatric populations. However, both (IV) ganciclovir, approved for the treatment of CMV retinitis in immunocompromised patients including patients with AIDS and prevention of CMV disease in transplant recipients at risk for CMV disease, and oral valganciclovir approved for treatment of CMV retinitis in patients with AIDS and prevention of CMV disease in solid organ transplant recipient are widely used in clinical practice to treat CMV infection. The most common adverse effect of both treatments is bone marrow suppression, which is of particular concern for HSCT recipients whose marrow has been ablated or who are significantly immunosuppressed to prevent GVHD. Contributing factors for development of cytopenias include viral infection, septicemia, GVHD, and myelotoxic drugs in addition to valganciclovir. Of the commonly used drugs with myelotoxic potential, ganciclovir is particularly prone to cause neutropenia. The underlying mechanism of ganciclovir-related neutropenia is a dose-dependent inhibition of DNA-polymerase in hematopoietic progenitor cells (Sommadossi and Carlisle, 1987). The rates of valganciclovir-related neutropenia in HSCT range from 19% (Barkam et al., 2012) and 33% (Takahata et al., 2015) to 55% (Boeckh et al., 2015). In the study by Salzberger et al. (1997), a clear trend was observed between the degree of neutropenia and the rate of bacterial infections while an increased incidence of fungal infections was present only in patients with an absolute neutrophil count (ANC) of less than 200/µL, whereas there was no significant trend over the different degrees of neutropenia. In the same study neutropenia was found to be an independent risk factor for poor long-term outcome. This was shown as a negative effect on overall survival and nonrelapse mortality.

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Maribavir is an anti-CMV agent that may be of particular benefit to transplant patients as it does not appear to cause bone marrow suppression. In addition to the favorable safety profile of maribavir observed in earlier Phase 1-3 studies (studies evaluating prophylactic administration of maribavir), results from a recent large Phase 2 randomized trial (Study 1263-203) support the safety, tolerability, as well as anti-viral activity of maribavir as a potential option for the treatment of CMV infections in transplant recipients. Study 1263-203 was a multicenter, randomized, dose-ranging, parallel-group study of maribavir versus valganciclovir for the treatment of CMV infections in HSCT or SOT recipients. Eligible subjects were randomized in a 1:1:1:1 allocation ratio (40 subjects per group) to receive oral maribavir at 400 mg, 800 mg, or 1200 mg BID; or valganciclovir (900 mg BID for 3 weeks, 900 mg once daily (QD) after 3 weeks) for up to 12 weeks. Maribavir, at doses ≥400 mg BID, had comparable efficacy to valganciclovir at clearing CMV viremia and was generally well tolerated across the dose range studied.

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 of treatment. There was a higher incidence of neutropenia through Week 12 for valganciclovir-treated subjects compared with maribavir-treated subjects. This was evident for both measured degrees of neutropenia: 18% versus 5% (absolute neutrophil count [ANC] <1000/mm^3), and 5% versus 2% (ANC<500/mm^3) through Week 12 for the valganciclovir and overall maribavir groups, respectively.

This Phase 3 study is designed to further assess and demonstrate the efficacy and safety of maribavir, administered at 400 mg BID, compared to valganciclovir administered at 900 mg BID for the treatment of asymptomatic CMV infection in HSCT recipients.

2.2 Rationale for the Study Design

This Phase 3 study will be conducted in HSCT recipients due to the relatively high risk for CMV infection resulting from ongoing immunosuppression to prevent GVHD. Ganciclovir and valganciclovir are commonly used to treat CMV infection in HSCT recipients and are generally considered effective, but present toxicity issues with respect to bone marrow suppression which may require management with hematopoietic growth factors, discontinuation of treatment, and may increase risk for opportunistic infections (Busca et al., 2007; Reusser et al., 2002). Additional constraints are present if treatment initiation is required in the pre-engraftment period. Alternative treatment by foscarnet or cidofovir is limited by nephrotoxicity of these medications (Reusser et al., 2002; Tomblyn et al., 2009). Maribavir may address safety limitations of currently available treatment.

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Oral valganciclovir is the active control for this study to allow for the interpretation of virologic response to maribavir. While IV ganciclovir may be appropriate for certain patients, it presents the challenges inherently associated with administration of any IV medication, particularly when treatment may last longer. Oral valganciclovir (Valcyte®) 900 mg provides ganciclovir exposure comparable to that of IV ganciclovir 5 mg/kg (refer to the Valcyte Prescribing Information as documented in the Study Pharmacy Manual; Winston et al., 2006) and the VICTOR study provided evidence that valganciclovir has comparable safety and is not inferior to standard IV ganciclovir treatment for eradication of viremia and clinical success in solid organ transplant recipients with CMV disease (Asberg et al., 2007; Tomblyn et al., 2009).

Study subjects will be randomized to receive either maribavir or valganciclovir for 8 weeks during the double-blind treatment phase. In the SHP620-203 study (HSCT and SOT recipients with asymptomatic CMV infection), the majority of maribavir and valganciclovir subjects achieved confirmed undetectable plasma CMV DNA levels by Week 6 of study drug treatment, while CMV recurrence occurred at rates expected for such a population with continued immunosuppression. Maribavir administered at 400 mg, 800 mg, and 1200 mg BID achieved CMV viremia clearance within 3 weeks to 6 weeks after starting the study drug treatment. Therefore, an 8-week treatment regimen will be administered in this Phase 3 study to account for maximum treatment period of 6 weeks where maribavir demonstrated a comparable efficacy to valganciclovir (900 mg BID from Weeks 1-3, and 900 mg QD after Week 3) in Study SHP620-203, adding 2 weeks for secondary prophylaxis.

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 ≥16 to <18 years of age.

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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 both Phase 2 studies, the most common treatment-emergent adverse events included dysgeusia, 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.

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. Per Lu and Rosenbaum (2014), the expression of CYP3A4 and CYP 2C19, which are primary enzymes for maribavir metabolism in the liver, occurs during the first weeks of life. The expression of CYP1A2, which is also involved with maribavir metabolism, the last enzyme to develop, is present by 1 to 3 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 (≥16 and <18 years of age) is not expected to be different from adults at the same oral dose.

Although typically valganciclovir treatment in HSCT patients is started as an induction dose of 900 mg BID for up to 14 days and then reduced to a maintenance dose of 900 mg QD for a further 2 weeks or until CMV viral load clearance (Tomblyn et al., 2009), a different dosing strategy was selected for this study based on input from regulatory authorities. Treatment with valganciclovir 900 mg BID for the duration of 8 weeks was chosen in order to eliminate a potential bias for efficacy in favor of the investigational treatment (maribavir) by administering the comparator (valganciclovir) at the higher dosage throughout. Treatment with valganciclovir at a lower dosage based on CrCl would be allowed to ensure comparable exposures in renally impaired subjects.

2.4 Study Objectives

2.4.1 Primary Objective

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

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2.4.2 Key Secondary Objective

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

2.4.3 Secondary Objectives

The secondary objectives of this study are:

- To compare the efficacy of maribavir to valganciclovir in CMV viremia clearance after completion of 8 weeks of treatment for asymptomatic CMV infection in HSCT recipients.
- To compare the efficacy of maribavir and valganciclovir on maintenance of CMV viremia clearance, achieved after completion of 8 weeks of treatment, through Study Weeks 12 (4 weeks of post-treatment period), 16 (8 weeks of post-treatment/follow-up phase), and 20 (12 weeks post-treatment).
- To assess the maintenance of CMV viremia clearance, achieved at the end of Study Week 8, through Weeks 12 (4 weeks of post-treatment period), and 20 (12 weeks post-treatment).
- To evaluate the incidence of recurrence of confirmed CMV viremia in the 2 study treatment arms during the first 8 weeks of the study, during the 12 weeks of the follow-up study phase, and at any time during the study.

- To evaluate the incidence of recurrence of confirmed CMV viremia in the 2 study treatment arms when subjects are on treatment and off treatment.

- To evaluate the incidence of treatment-emergent grade 3 or 4 neutropenia (defined as ANC<1000/mm^3 or ANC<500/mm^3) while on treatment.

- To assess the safety and tolerability of maribavir compared to valganciclovir.

- To characterize the PK of maribavir.

2.4.4 Exploratory Objectives

[redacted]

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3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a multicenter, randomized, double-blind, double-dummy, active-controlled study of maribavir compared to valganciclovir for the treatment of asymptomatic CMV infection in HSCT recipients. "***Asymptomatic subjects***" at baseline will be defined as HSCT recipients who do not have tissue-invasive CMV disease as determined by the investigator according to the criteria specified by Ljungman et al. (2017). The study will assess the efficacy of maribavir by measuring the plasma CMV DNA clearance. To be eligible for the study, subjects must have a documented asymptomatic CMV infection with a screening value of CMV DNA ≥1365 IU/mL to ≤273000 IU/mL in whole blood or ≥455 IU/mL to ≤91000 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory quantitative polymerase chain reaction (qPCR) or comparable quantitative CMV DNA results. Results for CMV and, in subjects with very low viral load, evaluations for high-risk CMV infection (Section 7.1.1) should be available before the subject is randomized to verify subject eligibility for the study. Both samples should be taken within 14 days prior to randomization with the second sample obtained within 5 days before randomization. The same laboratory and sample type should be used for these assessments. Subjects must not have CMV tissue invasive disease (symptomatic CMV infection), must not have a CMV infection that is known to be genotypically resistant to anti-CMV drugs, and must meet the remaining specified eligibility criteria. Subjects treated with ganciclovir, valganciclovir, foscarnet, or letermovir for the current CMV infection should not be treated with these anti-CMV agents for longer than 72 hours prior to enrolling in the study.

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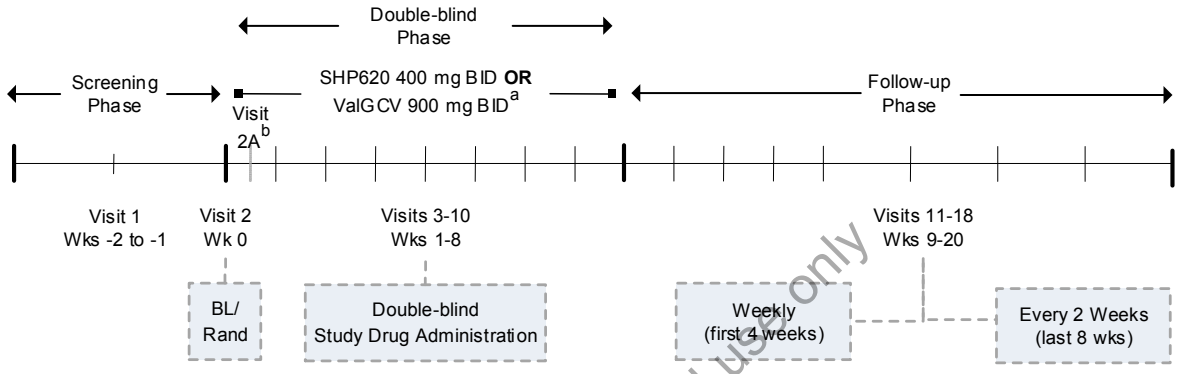
All eligible subjects will be stratified based on last prebaseline whole blood or plasma CMV DNA concentration (high viral load with CMV DNA ≥27300 IU/mL in whole blood or ≥9100 IU/mL in plasma, low viral load with CMV DNA ≥2730 IU/mL to <27300 IU/mL in whole blood or ≥910 IU/mL to <9100 IU/mL in plasma,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

An independent Data Monitoring Committee (DMC) will be established to assess the data at specified periodic intervals for safety and to ensure the validity and scientific merit of the trial.

Detailed plans for the DMC's purpose and responsibilities will be described in the DMC charter and the statistical analysis plan.

As shown in the study schematic in Figure 1 (Study Design Flow Chart) below, the study will have 3 phases: (1) Up to a 2-week screening phase; (2) 8-week double-blind study treatment phase; and (3) 12-week follow-up phase.

Figure 1. Study Design Flow Chart



BID=twice daily; BL=baseline; Rand=randomized; Wks=weeks

[a] Unless dose adjustment is required for moderate renal impairment.

[b] Visit 2A is required only for subjects receiving tacrolimus, cyclosporine, everolimus, or sirolimus at baseline.

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Subjects will be required to visit the site up to 18 times for up to a 22-week period. During the COVID-19 public health emergency, remote visits may be conducted by phone (eg, collection of AEs and monitoring), video conferencing (Telehealth or Telemedicine, physician), or site staff visiting the participant's residence. Local visits and telemedicine must comply with national and local laws and regulations. The type of alternative visit must be recorded on the eCRF.

For home healthcare visits, collection of clinical laboratory samples (blood specimen collection or other diagnostic tests) may be performed by a qualified and authorized Principal Investigator's (PI) designee who can visit the trial participant's residence.

Screening Phase

As presented in Schedule of Assessment 1, Table 1, approximately 612 subjects will be screened 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 3 days prior to initiation of study treatment.

2. Subjects must have a documented CMV infection with a screening value of CMV DNA ≥1365 IU/mL to ≤273000 IU/mL in whole blood or ≥455 IU/mL to ≤91000 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory qPCR or comparable quantitative CMV DNA results. The first sample must be obtained within 14 days prior to study enrollment (ie, start of study treatment) at Visit 2/Day 0. The second sample must be obtained within 5 days prior to the study enrollment.
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.

Study Treatment Phase

Approximately 550 subjects with an asymptomatic CMV infection who meet eligibility requirements during the screening phase, including the presence of quantifiable (local or central specialty laboratory) whole blood or plasma CMV DNA levels as specified (≥1365 IU/mL in whole blood or ≥455 IU/mL in plasma), will be stratified based on their CMV viral load and GVHD status, and then randomized 1:1 at Visit 2/Day 0 to receive either double-blind maribavir/placebo or valganciclovir/placebo (collectively, the study treatment) for 8 weeks.

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Historical laboratory results for tests within the time period specified in the Schedule of Assessment 1 (Table 1) may be used for eligibility assessment (HIV test results within 3 months, relevant hematology, and chemistry results). The Screening and Visit 2/Day 0 visits can occur on the same day, if laboratory results are available for the determination of eligibility. Local laboratory results may be used for stratification and randomization if central laboratory results are not available at Visit 2/Day 0.

All Visit 2/Day 0 procedures, 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 and all clinical laboratory results required for eligibility verification must be available prior to randomization, including 2 separate CMV DNA assessments. 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 subjects. 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. Blood sample for central laboratory CMV DNA quantification and genotyping will be obtained at Visit 2/Day 0.

If baseline central laboratory CMV DNA quantification results do not meet the specified screening value of ≥455 IU/mL, the subject will remain in the study, but will be excluded from the Per Protocol population for efficacy analysis.

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 receive maribavir will take the 400 mg BID dose for the 8 weeks of the study treatment phase. Maribavir 200 mg strengths will be utilized for the daily dosing. Subjects randomized to valganciclovir will take the 900 mg BID for the duration of 8 weeks of the study treatment phase (unless dose adjustment is required for moderate renal impairment) and will utilize 450 mg strength tablets.

Depending on the time of the first dose of study treatment on Visit 2/Day 0, a second dose should be administered on Visit 2/Day 0 provided that doses can be separated by a minimum of 8 hours; otherwise, only 1 dose should be administered on Visit 2/Day 0. Study treatment will then be administered (preferably) every 12 hours (q12h). When q12h dosing is not feasible, the doses should be separated by a minimum of 8 hours.

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To protect the study blind, subjects will be required to take 2 tablets of their assigned study treatment and 2 tablets of the placebo q12h in a double-dummy format as shown in Table 5 in Section 6.2.3.

Subjects randomized to receive valganciclovir will follow the 900 mg BID dosing regimen for the 8 weeks of the study treatment phase, with the exceptions of permitted lower starting dose based on renal function, or dose adjustments based on renal function and/or neutropenia (Table 6 and Table 7, respectively; see Section 6.2.3). The clinical laboratory test results (see Section 7.2.3.4) for a minimum of complete blood count with differential and serum creatinine will be verified before providing the revised valganciclovir dose.

In exceptional situations, eg, neutropenia or other adverse events, study treatment may be interrupted at investigator's discretion for a maximum of 7 consecutive days, and this interruption will not result in permanent study treatment discontinuation. Up to 2 study treatment interruptions for a total of up 7 days will be allowed. A third study treatment interruption will lead to permanent study treatment discontinuation; the subjects will complete the end of treatment procedures described for Visit 10/Study Week 8 in the Schedule of Assessment 1 (Table 1), and will follow 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 as described in Section 4.5.

Various clinical scenarios of neutropenia, as shown in Table 7, will be programmed in the interactive response technology (IRT) and appropriate options will be selected by the investigator. Interruptions and discontinuation of study treatment will be conducted in a blinded manner; therefore, it is possible that treatment with either valganciclovir or maribavir will be interrupted or discontinued for neutropenia presence. The investigator may also select to interrupt study treatment, for other adverse events, regardless of the treatment assignment (maribavir or valganciclovir). 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.

If the subject is unable to travel to the site for the treatment visits, these visits may be on exceptional basis performed remotely (ie, at subjects' home) by a qualified and authorized PI's designee, and only if permitted by local laws and regulations. Clinical laboratory samples 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.

All subjects who complete the study treatment phase through Visit 10/Week 8 will enter the 12-week follow-up phase. See Section 4.5 for details regarding discontinuation and/or withdrawal from the study treatment/study.

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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. See Schedule of Assessment 2 (Table 2) for a complete list of evaluations. See Section 4.5 for details regarding discontinuation and withdrawal.

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 and authorized PI's designee, and only if permitted by local laws and regulations. Clinical laboratory samples 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; double-blind study treatment 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.

The study will be completed in approximately 48 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 105 sites in North America, Europe, and Asia Pacific will participate.

3.4 Changes to Study Procedures Due to COVID-19 Pandemic

The following information provides guidance regarding changes to study procedures that may be implemented for study participants or study sites affected by a pandemic (eg, coronavirus disease [COVID-19]) that require physical distancing that may result in subjects missing their visits. This guidance takes references from the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency – Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, updated 27 January 2021; the EMA Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic, Version 4 (04 February 2021); and the EMA Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, dated 26 June 2020.

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Because a pandemic (eg, COVID-19) may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case-by-case basis by the principal investigator in consultation with the study team and the medical team as needed, while maintaining patient safety and confidentiality as the priority.

Procedural changes due to COVID-19 may include the following (refer to DTP guidance document for further details):

- Allow study sites to follow COVID-19 screening requirements per local regulations.
- Informed Consent Procedure: If necessary and permitted by local laws and regulations, informed consent from a potential or current trial participant may be obtained via electronic informed consent (eIC) capabilities, or an electronic face-to-face consent interview when these individuals are unable to travel to the site (see Section 4). The site must contact the sponsor for approval of the alternative method for obtaining informed consent prior to implementation.

- Study Visit 1 (Screening) and Study Visit 2 (Randomization) must be done with the subject present at the investigative site. Study Visits 2A through 10 may be conducted at the clinic or by optional home healthcare visits to extend flexibility to subjects during the COVID-19 public health emergency, although it is preferable to conduct Study Visit 10 (End of Treatment) and Study Visit 18 (End of Study) with the subject present at the investigative site. The data collected from home healthcare visits may be handled differently in the final data analysis, with this documented in the statistical analysis plan.
- More flexibility by allowing some assessments and, where allowed per local laws and regulations, remote source document verification to be conducted remotely (see Study Schedule).
- 'Remote visits' via virtual communications (eg, TeleHealth application) may be performed as a safety check on subject well-being, concomitant medication use, etc.
- For home healthcare visits, collection of clinical laboratory samples (blood specimen collection or other diagnostic tests) may be performed by a qualified and authorized PI's designee who can visit the trial participant's residence.
- ECG procedures: For home healthcare visits, ECGs may be performed by a qualified health care professional who is certified/authorized by the PI to perform such tests routinely.
- Missed clinic visits or subject withdrawals due to COVID-19 must be recorded on the eCRF (see Section 4.5, Discontinuation and/or Withdrawal of Subjects).
- Subjects who discontinued from screening due to COVID-19-related factors but were otherwise qualified to participate in the trial may be rescreened at any time if the Takeda medical monitor agrees (see Section 7.1.1, Screening Period).
- Allow transfer of study participants to investigational sites away from risk zones or closer to their home to sites already participating in the trial or new ones.
- Deviations from the protocol-specified procedures (eg, not collecting a protocol-specified specimen, such as post-dose bloodwork) will be recorded as related to COVID-19.
- Alternative study drug deliveries may include dispensing additional study drug at clinic visits or direct-to-patient (DTP) delivery of the study drug from the investigational site to subjects in compliance with national laws or temporary national emergency measures (see Section 6.4, Drug Accountability). When utilizing DTP, the investigator remains responsible for ensuring the safety of subjects and the dispensation of the investigational product.
- In accordance with local laws and regulations, relevant health authorities are to be notified of participants who contract COVID-19 during the study.

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4. STUDY POPULATION

Approximately 550 subjects, ≥16 years of age, who are HSCT recipients with asymptomatic CMV infections 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.

Subjects must:

1. 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. During the COVID-19 public health emergency, informed consent from a potential or current trial participant may, if permitted by local laws and regulations, be obtained via electronic informed consent (eIC) capabilities or an electronic face-to-face consent interview when these individuals are unable to travel to the site (FDA COVID-19 Guidance, 27 Jan 2021, Q11).
2. Be ≥16 years of age at the time of consent.
3. Be a recipient of hematopoietic stem cell transplant.
4. Have a documented asymptomatic CMV infection, with a screening value of CMV DNA ≥1365 IU/mL to ≤273000 IU/mL in whole blood or ≥455 IU/mL to ≤91000 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory quantitative polymerase chain reaction (qPCR) or comparable quantitative CMV DNA results. Both samples should be taken within 14 days prior to randomization with second sample obtained within 5 days prior to randomization. Same laboratory and same sample type (whole blood or plasma) should be used for these assessments. Asymptomatic CMV infection is defined as an infection that does not present with tissue invasive CMV disease, as assessed by the investigator.

   Subjects with CMV DNA <910 and ≥455 IU/mL in plasma or <2730 and ≥1365 IU/mL in whole blood will also need to meet at least 1 of the following criteria for high-risk CMV infection to be eligible:

   - Human leukocyte antigen (HLA)-related (sibling) donor with at least 1 mismatch at 1 of the following 3 HLA-gene loci: HLA-A, -B or -DR,

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- Haploidentical donor,
- Unrelated donor with at least 1 mismatch at 1 of the following 4 HLA -gene loci: HLA-A, -B, -C and -DRB1,
- Use of umbilical cord blood as stem cell source,
- Use of ex vivo T-cell-depleted grafts,
- Grade 2 or greater GVHD, requiring the use of systemic corticosteroids (defined as the use of ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid).

5. Have the current CMV infection as the first episode of CMV viremia after HSCT, either primary or reactivation, which in the investigator's opinion requires treatment.
6. Per investigator's judgment, be eligible for treatment with valganciclovir.
7. 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 ≥1000/mm^3 [1.0 x 10^9/L]
   b. Platelet count ≥25,000/mm^3 [25 x 10^9/L]
   c. Hemoglobin ≥8 g/dL
   d. Estimated creatinine clearance ≥30 mL/min.
8. Have a negative serum beta human chorionic gonadotropin (β-hCG) pregnancy test at screening, if a female of childbearing potential. Urine pregnancy tests may be done per institutional requirements; however, they are not sufficient for eligibility determination. Sexually active females of childbearing 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 the last dose of study treatment.
9. Be able to swallow tablets.
10. Have life expectancy of ≥8 weeks.
11. Weigh ≥40 kg.
12. Be willing and have an understanding and ability to fully comply with study procedures and restrictions defined in the protocol.

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4.2 Exclusion Criteria

Subjects must not:

1. Have CMV tissue invasive disease as assessed by the investigator at the time of screening and randomization at Visit 2/Day 0.
2. Have a CMV infection that is known to be genotypically resistant to ganciclovir, valganciclovir, foscarnet, or cidofovir based on documented evidence.
3. Be presenting with recurrent CMV infection (defined as a new detection of CMV infection in a subject who had at least one previously documented episode of CMV infection post-transplant, and who has had at least 2 weeks of undetectable CMV DNA between the episodes during active surveillance, based on same local laboratory and same sample type). The subject must also have been off any anti-CMV treatment between the current and prior infection. Otherwise, the current infection may be considered continuation of the prior infection.
4. Require ganciclovir, valganciclovir, foscarnet, or cidofovir administration for conditions other than CMV when study treatment is initiated (example: herpes simplex virus [HSV] co-infection requiring use of any of these agents after the randomization) or would need a co-administration with maribavir for CMV infection.
5. Be receiving leflunomide, letermovir, or artesunate when study treatment is initiated. Note: Subjects who may be 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 3 days prior to first dose of study treatment. Subjects receiving artesunate must discontinue the use prior to the first dose of study treatment.
6. Be on treatment with anti-CMV agents (ganciclovir, valganciclovir, foscarnet, or letermovir) for the current CMV infection for longer than 72 hours.
7. Have known hypersensitivity to the active substance or to an excipient of the study treatments.
8. 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 medication.
9. Require mechanical ventilation or vasopressors for hemodynamic support at the time of randomization.

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10. Be female and pregnant or nursing.
11. Have previously completed, discontinued, or have been withdrawn from this study.
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 any clinically significant medical or surgical condition that, in the investigator's opinion, could interfere with interpretation of study results, contraindicate the administration of the assigned study treatment, or compromise the safety or well-being of the subject.
15. Have previously received maribavir.
16. 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), as analyzed by local or central laboratory.
17. Have known (previously documented) 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.
18. Have active malignancy with the exception of nonmelanoma skin cancer, as determined by the investigator. Subjects who experience relapse or progression of their underlying malignancy (for which HSCT was performed), as determined by the investigator, are not to be enrolled.
19. Be undergoing treatment for acute or chronic hepatitis C.

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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.

There are no data from the use of valganciclovir in pregnant subjects. Its active metabolite, ganciclovir, readily diffuses across the human placenta. Based on its pharmacological mechanism of action and reproductive toxicity observed in animal studies with ganciclovir, valganciclovir should be considered a potential teratogen and carcinogen in humans (refer to the Valcyte Prescribing Information and Valcyte Summary of Product Characteristics as documented in the Study Pharmacy Manual).

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 contraception, as defined below.

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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 childbearing 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 16 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 below.

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.

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4.4.2 Male Contraception

Per Clinical Trial Facilitation Group requirements (CTFG), male subjects will be required to use a condom in conjunction with a highly effective method of birth control for their female partners of childbearing age. 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 or valganciclovir). 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. Male subjects must not donate sperm until 90 days after the last dose of study treatment.

4.5 Discontinuation and/or Withdrawal of Subjects

Subjects Who Withdraw from the Study

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; no further follow-up will be performed.

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 Discontinue from Screening

Subjects who discontinue from screening due to COVID-19-related factors but are otherwise qualified to participate in the trial may be rescreened at any time if the Takeda medical monitor agrees.

Subjects Who Discontinue Study Treatment

Subjects who permanently discontinue study treatment, but do not withdraw consent, 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 follow 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 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 duration specified for the study treatment phase, subjects will enter the 12-week follow-up phase. After the permanent study treatment discontinuation and until the end of the study, subjects might be administered other anti-CMV treatment as deemed necessary by the investigator.

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Subjects who discontinue will not be replaced.

4.5.1 Reasons for Discontinuation and/or Withdrawal

The reason for study treatment discontinuation and/or withdrawal must be determined by the investigator and recorded in the subject's medical record and on the case report form (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). If a subject chooses to withdraw from study participation due to personal concerns related to the COVID-19 pandemic (other than a COVID-19-related AE), this should be specified as the reason for subject withdrawal in the eCRF.
- Adverse event (must specify on the CRF)
- CMV central nervous system (CNS) infection (Note: Maribavir is unlikely to penetrate the blood-brain barrier in humans based on animal data. 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, including unavoidable circumstances such as the COVID-19 pandemic)

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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**	*Preparative/conditioning regimen*[a]	Including but not limited to:
		• Pretransplant irradiation
		• Various agents including:
		  ○ Chemotherapy agents
		  ○ Lymphocyte depleting and nondepleting therapies, including monoclonal, polyclonal, and anti-thymocyte globulin preparations

	Anti-CMV prophylaxis and treatment[b]	Including, but not limited to: • Ganciclovir • Valganciclovir • Foscarnet • Cidofovir • Cytomegalovirus immune globulin • Intravenous immunoglobulin (IVIG) • Leflunomide • Artesunate • Letermovir • Cytomegalovirus specific T-cell transfer (considered investigational)
	GVHD prophylaxis, treatment, adjuvant therapies, and other related therapies	Including, but not limited to: • Cyclosporin • Methotrexate • Tacrolimus • Sirolimus • T-cell depleting therapies, including antithymocyte globulin, alemtuzumab • Mycophenylate mofetil • Steroids • Photopheresis
	Transplant maintenance therapy	Including, but not limited to • Systemic steroids • Cyclosporine, tacrolimus, sirolimus, everolimus, mycophenylate mofetil

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Table 3. Prior Medications, Therapies, and Procedures

Time Period (prior to Visit 2/Day 0)	***Category***	***Prior Medications, Therapies, and Procedures***
All medications **within 3 months** prior to the first dose of study treatment on **Visit 2/Week 0/Day 0**	*Hematopoietic growth factors*	
	Treatment for the underlying disease	
	Blood or blood product transfusions	
	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 herbal supplements • All other over-the-counter (OTC) medications
Any therapeutic or diagnostic intervention/ procedure 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) • X-rays, CT scans (along with results) • Dialysis • Total parenteral nutrition

CMV=cytomegalovirus; CT=computerized tomography; GVHD=graft-versus-host-disease; IVIg=intravenous immunoglobulin; OTC=over-the-counter medications

[a] Subjects for whom transplant was performed >3 months from the time of screening, limited (no dose data) information for preparative/conditioning regimen will be collected.

[b] NOTE: as only subjects with first CMV infection after HSCT will be enrolled, prior anti-CMV medications may include anti-CMV prophylaxis; subjects should not have been on treatment with anti-CMV agents (ganciclovir, valganciclovir, foscarnet, or letermovir) for the current CMV infection for longer than 72 hours prior to enrollment.

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5.2 Concomitant Medications, Therapies, and Procedures

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. A concomitant procedure is any therapeutic and diagnostic intervention (eg, surgery, biopsy) or diagnostic assessment (eg, bacterial cultures, imaging such as X-ray, computerized tomography [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

All concomitant treatment information must be recorded on the appropriate CRF page.

Additional treatment strategies may complement the use of the study treatments (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, therefore, whenever possible, investigators should maintain a stable regimen of immunosuppressant drugs during the study drug administration period, particularly through Study Visit 10/Week 8. 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.

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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 varicella zoster virus (VZV). At baseline, investigators will assess subjects to determine whether prophylaxis for these viruses is appropriate according to institutional guidelines or standard practices; the need for continued prophylaxis or initiation of prophylaxis will be assessed. 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 medications will be allowed as deemed appropriate by the investigator for prophylaxis or treatment.

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 1200 mg BID in Phase 2 studies.

The following concomitant medications should be taken with caution:

Maribavir has the potential to inhibit P-gp and therefore, may increase the concentration of drugs that are substrates of 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 CYP3A4 and P-gp) with C_{max} and AUC increased by 38% and 51%, respectively.

Therefore, monitoring tacrolimus 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 P-gp and have narrow therapeutic window, such as other immunosuppressants including cyclosporine, sirolimus, and everolimus, careful monitoring is recommended both after initiation of maribavir (when substrate levels may increase) and after discontinuation of maribavir (when substrate levels may decrease).

Maribavir is an inhibitor of BCRP based on in vitro data, therefore has the potential to increase the drug concentration of rosuvastatin which is a sensitive BCRP substrate. When initiating maribavir dosing in patients who are on a stable dose of rosuvastatin, patients should be closely monitored for the signs of myopathy and rhabdomyolysis.

5.2.2 Prohibited Treatment

Maribavir is contraindicated with valganciclovir/ganciclovir as it may antagonize ganciclovir's antiviral effects due to maribavir's inhibitory effect on HCMV UL97 encoded kinase which is required for activation/phosphorylation of ganciclovir.

Table 4 details the washout period for common prior treatments that are excluded medications for this study.

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Table 4. Common Excluded Treatments and Associated Washout Period

	Minimum Number of Days Before First Dose				
Treatment	**Prior to the first dose of study treatment**	**3**	**7**	**14**	**30**
Ganciclovir, valganciclovir[a], foscarnet, artesunate	X				
Letermovir		X			
Cidofovir, leflunomide				X	
Any investigational anti-CMV agent					X
Any unapproved agent or device					X
CMV vaccine	Any time before or during study				

CMV=cytomegalovirus

[a] Valganciclovir will be provided by the Sponsor for this study; commercially available/prescribed valganciclovir is not allowed through the study and must be discontinued prior to the first dose of the study treatment.

Use of any investigational anti-CMV agents, or unapproved agents or devices during the study is not permitted. Infusion of T cells specific for CMV or regulatory T cells (Tregs), which is considered an experimental treatment, is not allowed.

Besides the medications indicated in Table 4, concomitant use of any of the following medications is prohibited while the subject is receiving the study treatment (maribavir/placebo or valganciclovir/placebo).

- 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)

Except for ganciclovir/valganciclovir, maribavir does not antagonize the effects of other antiviral (anti-CMV) agents.

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 (refer to the Valcyte Summary of Product Characteristics as documented in the Study Pharmacy Manual).

Administration of any of the prohibited treatments (except coadministration of foscarnet or cidofovir for indications other than CMV infection) will require discontinuation of study treatment.

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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, onset 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 INVESTIGATIONAL PRODUCTS

6.1 Identity of Investigational Product

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

The reference/comparator product is valganciclovir which will be provided by the sponsor in 450 mg strength tablet form. Refer to the local approved product information for additional details.

Matching placebo will be provided for both maribavir and valganciclovir.

6.2 Administration of Investigational Product(s)

6.2.1 Interactive Response Technology for Investigational Product Management

An IRT will be employed in this study to manage the tracking and confirmation of shipment, supply, inventory, ordering, expiration, randomization, site-assignments, and dose modifications of the study treatment. The IRT provider will provide a user manual and training to each site, with detailed instruction on the use of the IRT and unblinding procedures when situation arises.

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6.2.2 Allocation of Subjects to Treatment

This is a double-blind, double-dummy, active-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule.

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.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined.

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

1. By last prebaseline 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 ≥27300 IU/mL to ≤273000 IU/mL in whole blood or ≥9100 IU/mL to ≤91000 IU/mL in plasma

- Low viral load with CMV DNA ≥2730 IU/mL to <27300 IU/mL in whole blood or ≥910 IU/mL to <9100 IU/mL in plasma

- Very low viral load and high risk with CMV DNA≥1365 IU/mL to <2730 IU/mL in whole blood OR ≥455 IU/mL to <910 IU/mL in plasma and high-risk infection

2. By presence or absence of acute GVHD

Following stratification, subjects will be randomized in a 1:1 allocation ratio to receive either double-blind maribavir or valganciclovir for 8 weeks.

The actual treatment given to individual subjects is determined by a randomization schedule automatically assigned by the 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.

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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.

Depending on the time of the first maribavir/placebo or valganciclovir/placebo 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. The second dose 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.

Maribavir 200 mg strength tablets will be utilized for the daily dosing. Subjects will take the maribavir 400 mg BID dose for the 8 weeks of the study treatment phase. There are no dose modifications for maribavir.

Daily dosage for valganciclovir (450 mg QD to 900 mg BID as adjusted for renal function, based on chemistry labs at screening) will utilize 450 mg strength tablets. Subjects will take valganciclovir for the 8 weeks of the study treatment phase. To protect the study blind, subjects will be required to take 2 tablets of their assigned study treatment and 2 tablets of the placebo q12h in a double-dummy format as shown in Table 5.

Table 5. Study Treatment Dosing – Standard Regimen

Regimen		AM	PM
maribavir 400 mg BID	maribavir active valganciclovir placebo	400 mg (2 tablets) placebo (2 tablets)	400 mg (2 tablets) placebo (2 tablets)
valganciclovir 900 mg BID	valganciclovir active maribavir placebo	900 mg (2 tablets) placebo (2 tablets)	900 mg (2 tablets) placebo (2 tablets)

BID=twice daily

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Valganciclovir tablets should be administered with food, and should not be broken or crushed (refer to the Valcyte Prescribing Information and Valcyte Summary of Product Characteristics as documented in the Study Pharmacy Manual). In order to maintain the blind, maribavir will also be administered with food and will not be broken or crushed for administration. Therefore, all subjects eligible for this study must be able to swallow tablets. Based on the evaluation of the effect of food on the PK of 200 mg tablet formulation of maribavir in Phase 1 Study 1263-104, only a modest effect on C_{max} and no effect on AUC was observed; therefore, no clinically important food effect is expected with tablet formulation.

Subjects with estimated CrCl of ≥30 mL/min will be enrolled; adjustment of the valganciclovir dose for renal function will be allowed at entry and during the study, as deemed necessary by the investigator and consistent with the suggested doses in the valganciclovir label (shown in Table 6). The decision to modify the dose will be at investigator's discretion and it will be done in a manner, through IRT, so that the treatment assignment remains blinded. Placebo tablets will be assigned in a blinded manner to make up for adjusted dose and decrease in valganciclovir tablets.

Table 6. Valganciclovir Dosing – Adjustment for Renal Function

Valganciclovir 450 mg Tablets	
CrCl[a] (mL/min)	**Dose**
≥60	900 mg (2 tablets) BID
40 – 59	450 mg (1 tablet) BID
25 – 39	450 mg (1 tablet) QD
10 – 24	450 mg every 2 days

BID=twice daily; CrCl=creatinine clearance; QD=once daily

[a] An estimated creatinine clearance in adults is calculated from serum creatinine by the following formulas:
For males, eCrCl [mL/min] = (140 – age [years]) × (body weight [kg]) / (72) × (serum creatinine [mg/dL])
For females, eCrCl [mL/min] = 0.85 × (male value)
Valganciclovir administration is not recommended below CrCl of 10 mL/min.

Patients on valganciclovir are at risk for bone marrow suppression and development of neutropenia. In the Phase 2 study (SHP620-203) of maribavir, measured degrees of neutropenia were 18% versus 5% (ANC<1000/mm^3) and 5% versus 2% (ANC<500/mm^3) through Week 12 study for the valganciclovir and overall maribavir groups, respectively. Based on discussions with regulatory authorities, dose of valganciclovir has been chosen as 900 mg BID for 8 weeks of study treatment period duration, given ANC ≥1000/mm^3 and CrCl ≥60 mL/min. Since neutropenia is an identified risk with valganciclovir intake, and specifically with the induction dose maintained through the treatment duration, subjects will be assessed for neutropenia development and valganciclovir dose may be adjusted based on ANC level. It is recommended that ANC level and creatinine clearance is verified and taken into consideration before the study drug is dispensed at each study visit. Therefore, complete blood count with differential count and serum creatinine analysis will be performed within 2 days of each visit by the local laboratory to confirm ANC level and creatinine clearance (see Section 7.2.3.4). Table 7 shows predefined criteria for valganciclovir dose adjustment based on ANC level and CMV DNA clearance which may be used, as deemed necessary by the investigator and in a manner that the treatment assignment remains blinded, to manage treatment of subjects who experience neutropenia.

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Valganciclovir should not be administered if the ANC is <500/mm^3 (per the product label), the platelet count is <25,000/µL, or the hemoglobin is <8 g/dL. Consistent with the product label and peer reviewed published literature; two different ANC levels have been selected to guide valganciclovir dose adjustment. Three studies identifying risk factors for neutropenia reported ANC level <1000/mm^3 (Venton et al., 2014; Tomonari et al., 2008) or <1500/mm^3 (Salzberger et al., 1997). Salzberger et al. (1997) concluded that ANC level of <1000/mm^3 is predictive of both progression of neutropenia and mortality and postulated that ganciclovir should be discontinued when the ANC reached 1000/mm^3 rather than at an ANC level of 750/mm^3 (the threshold ANC level specified in the study).

In addition, in this study, a clear trend was observed between the degree of neutropenia and the rate of bacterial infection; for the fungal infection the increased trend was only present when ANC was <200/µL. Other studies (Goodrich et al., 1993; Boeckh et al., 1996) reviewed in Salzberger et al. (1997) showed that neutropenia with an ANC of <750/µL occurs in 30% of ganciclovir recipients and has been associated with increased rates of bacterial sepsis and invasive fungal infection in marrow transplant recipients.

Subjects who do not achieve CMV viremia clearance may need to continue treatment to resolve viremia, even though ANC level is between 500-1000/mm^3, at the discretion of the investigator and with the support of hematopoietic growth factors, if needed. However, considering the presence of neutropenia, the dose of valganciclovir may be adjusted to 450 mg BID. For subjects who achieve CMV viremia clearance and have ANC level between 500-1000/mm^3, benefit/risk assessment for continued treatment may need to be considered by the investigator, and the option of either valganciclovir dose adjustment or dose interruption may be chosen. In each of the clinical scenarios hematopoietic growth factors may be used as deemed necessary by the investigator to prevent/manage neutropenia in addition to other strategies such as modification of other treatments that may be contributing to neutropenia development (eg, mycophenolate mofetil, Bactrim).

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Table 7. Valganciclovir Dose Adjustment Based on ANC Level and CMV DNA Clearance

	ANC >1000/mm^3 [1.0 × 10^9/L] **ANC based on local or central laboratory results**	**ANC 500/mm^3 [0.5 ×10^9/L] to 1000/mm^3 [1.0 × 10^9/L]** **ANC based on local or central laboratory results**	**ANC<500/mm^3 [0.5 × 10^9/L]** **ANC based on local or central laboratory results**
CMV DNA ≤LLOQ (based on local or central specialty laboratory, most recent result prior to dose assessment should be considered).	Continue valganciclovir 900 mg BID. Hematopoietic growth factors may be used at investigator's discretion.	May adjust valganciclovir dose to 450 mg BID or interrupt the dose and resume at 450 mg BID or 900 mg BID (dose choice at investigator's discretion) once ANC >1000/mm^3 [1.0×10^9/L]. Hematopoietic growth factors may be used at investigator's discretion.	May interrupt valganciclovir dose and resume at 450 mg BID or 900 mg BID (dose choice at investigator's discretion) once ANC >1000/mm^3 [1.0×10^9/L]. Permanent valganciclovir discontinuation and alternative anti-CMV treatment may be considered at investigator's discretion. Hematopoietic growth factors should be strongly considered.

Table 7. Valganciclovir Dose Adjustment Based on ANC Level and CMV DNA Clearance

	ANC >1000/mm^3 [1.0 × 10^9/L] ANC based on local or central laboratory results	ANC 500/mm^3 [0.5 ×10^9/L] to 1000/mm^3 [1.0 × 10^9/L] ANC based on local or central laboratory results	ANC<500/mm^3 [0.5 × 10^9/L] ANC based on local or central laboratory results
CMV DNA ≥LLOQ (based on local or central specialty laboratory, most recent result prior to dose assessment should be considered).	Continue valganciclovir 900 mg BID. Hematopoietic growth factors may be used at investigator' discretion.	May adjust valganciclovir dose to 450 mg BID. Hematopoietic growth factors may be used at investigator's discretion.	May interrupt valganciclovir dose and resume at 450 mg BID or 900 mg BID (dose choice at investigator's discretion) once ANC >1000/mm^3 [1.0×10^9/L]. Permanent valganciclovir discontinuation and alternative anti-CMV treatment may be considered at investigator's discretion. Hematopoietic growth factors should be strongly considered.

ANC=absolute neutrophil count; BID=twice daily; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; LLOQ=lower limit of quantitation; QD=once daily

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Drug kit dispensing for dose adjustments will be managed by the IRT system in order to maintain the blind. Subjects that require a dose adjustment for renal function or ANC level, regardless of study treatment, will be assigned a new study drug kit.

Various clinical scenarios of neutropenia, as shown in Table 7, will be programmed in the IRT and appropriate options will be selected by the investigator. Interruptions and discontinuation of study treatment will be conducted in a blinded manner; therefore, it is possible that treatment with either valganciclovir or maribavir will be interrupted or discontinued for neutropenia presence. The investigator may also select to interrupt study treatment, for other adverse events, regardless of the treatment assignment (maribavir or valganciclovir). The interruption for a maximum of 7 consecutive days will not result in permanent study treatment discontinuation. Up to 2 study treatment interruptions for a total of up to 7 days will be allowed. 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. A third study treatment interruption will lead to permanent study treatment discontinuation; the subjects will complete the end of treatment procedures described for Visit 10/Study Week 8 in the Schedule of Assessment 1 (Table 1), and will follow 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 as described in Section 4.5.

If valganciclovir dose adjustment is required for both renal function and neutropenia, the lowest dose/dose selection as specified in Table 7 will occur through the IRT.

6.2.4 Blinding Procedures

This is a randomized, double-blind, double-dummy, active-controlled study. Qualified subjects will be randomized in a 1:1 allocation ratio to receive maribavir or valganciclovir using a centralized procedure. An IRT will be used to randomize subjects and provide the treatment assignment to the blinded pharmacist or a blinded designated study staff member.

To accomplish the blind, exact matching placebo tablets will be provided for both maribavir and valganciclovir, ie, each subject will receive maribavir and placebo (identical to valganciclovir) tablets if randomized to maribavir treatment, or valganciclovir and placebo (identical to maribavir) if randomized to valganciclovir treatment To protect the study blind, subjects will be required to take at a maximum, 2 tablets of their assigned study treatment and 2 tablets of the placebo q12h in a double-dummy format as shown in Table 5.

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In order to protect the study blind during the study conduct, it is imperative that the investigator, subjects and their families, or any member of the study team, either at the study site or that of the Sponsor remain blinded to the subject treatment assignments until the data base lock (after the last subject has completed the study). The investigator and the sponsor will also be blinded to the PK data. Every effort will be made to maintain the blind except in those emergency situations when the identification of the investigational product is required for further treatment of the subject.

Unblinding the Treatment Assignment

There will be a provision for unblinding to ensure adequate treatment of the subject in the case of an emergency (details will be provided in the study manual). The Sponsor medical monitor should oversee this process. An unblinded medical monitor independent from the study will be identified by the sponsor for any situations that may need unblinding during the study.

In order to maintain the overall quality of the clinical conduct of the trial and integrity of the study data, the treatment assignment must not be broken during the study except in emergency situations where the identification of the investigational product is required for further treatment decisions for the subject. The investigators are encouraged to contact the designated blinded study medical monitor whenever possible to discuss the circumstances and the potential need for unblinding. If this is not possible, in the event of emergency unblinding, the investigator must notify the designated blinded study medical monitor and the sponsor, as soon as possible after breaking the blind, taking care not to reveal the subject's randomization code (see emergency contact information in Section 8.2.2).

The date and reason for unblinding will be recorded in subject's source documents. An unblinded medical monitor will be contacted if needed for any matters where treatment assignment will need to be revealed.

The investigators will be provided by the Sponsor with a clear procedure on how to access the central randomization system for code-breaking for each subject, disclosing the details of the allocated treatment (details provided in the study manual). The code will be broken only in case of emergency where the further treatment of the subject is dependent on the trial medication he/she received. In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded on the IRT and the source documents. Any code break that occurs must be reported to the contract research organization (CRO)/sponsor.

Since the PK samples for only those subjects who are taking maribavir will be analyzed while the study is ongoing, the bioanalysis will be conducted by unblinded staff from the bioanalysis laboratory/CRO to allow for the identification of the PK samples from the subjects randomized to the maribavir treatment arm. If needed, an interim PK analysis of maribavir PK data obtained from the subjects may be performed by an independent unblinded team/CRO outside of the blinded study team, who will also receive the reports of the drug concentrations for the interim population PK analysis.

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The DMC may be unblinded as described in the DMC charter.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Packaging and Labeling

Maribavir, valganciclovir, and matching placebos will be packaged and labeled such that the products will be indistinguishable from their respective match placebos by the investigator, study site, and subjects (refer to the pharmacy manual for further information).

Study drug kits 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.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor. Additional labels may not be added without the sponsor's prior full agreement.

6.3.2 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility for storage 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.

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Investigational products must be stored in accordance with labeled storage conditions which state "Do not store above 25°C. Do not freeze." 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 products 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 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 only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered/dispensed medication will be documented on the CRFs and/or other investigational product records and may include additional information as required per applicable regulations. The investigator is responsible for ensuring the retrieval of all study supplies from subjects. Compliance will be collected in the subject's diary. The disposition of the unused supply of the dispensed investigational product will be documented in the accountability log.

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During the COVID-19 public health emergency, alternative study drug delivery to trial participants may be necessary to avoid unnecessary subject visits to sites while providing needed study drug. Additional study drug may be dispensed during a scheduled study visit or study drug may be shipped directly from investigational sites to participants' residences by a contracted logistics provider or distributor (direct-to-patient [DTP] shipment) in compliance with national laws or temporary national emergency measures and Takeda processes. When utilizing DTP, the investigator remains responsible for ensuring the safety of subjects and the dispensation of the investigational product.

No investigational product stock or returned inventory from a Takeda-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 provided the blind of the study is not compromised.

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 standard operating procedure. 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.

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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 diary and CRF, as appropriate.

During the COVID-19 public health emergency, study drug may be administered by a healthcare professional as part of home nursing or home healthcare. If a subject participates in home healthcare in the treatment phase, they will receive study drug through DTP and the site will follow-up with the subject. When utilizing DTP, the investigator remains responsible for ensuring the safety of subjects and the dispensation of the investigational product.

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 reconciliation must be assessed for all dispensed investigational product. Unused investigational product will not be redispensed. Instructions will be provided in the pharmacy manual.

7. STUDY PROCEDURES

7.1 Study Schedule

See Table 1 for study procedures for the double-blind 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 Section 4.1 and Section 4.2)
- Height and body weight (Section 7.2.3.1)
- Vital signs (Section 7.2.3.2)
- Medical history, including transplant history (eg, underlying disease that led to the HSCT, transplant type, other details related to transplant) and CMV history, HIV status
- Prior medication, therapies, and procedures, including any prior anti-CMV medication used to treat the current CMV infection (Section 5.1)
- Hematology/Chemistry (Section 7.2.3.4). Tests required for eligibility must be performed and results verified within 3 days prior to randomization.
- Pregnancy test (serum) for all females of childbearing potential (Section 7.2.3.4). This must be performed and results verified within 3 days prior to randomization.
- HIV status: Historical results for human immunodeficiency virus (HIV) tests performed within 3 months prior to randomization 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).
- Cytomegalovirus disease assessment (Section 7.2.2.3)
- Interactive response technology (IRT; Section 6.2.1) to manage screening and site enrollment
- Invasive bacterial and fungal infections/transplant relevant infection assessment (see Section 8.1.4)
- Graft-versus-host-disease assessment

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- Cytomegalovirus DNA test (quantitation): Documentation of CMV infection in whole blood or plasma with a screening value of ≥1365 IU/mL to ≤273000 IU/mL in whole blood or ≥455 IU/mL to ≤91000 IU/mL in plasma 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. The 2 CMV DNA results must be ≥455 IU/mL in plasma or ≥1365 IU/mL in whole blood. High-risk CMV infection is defined as meeting any of the following criteria:
    - Human leukocyte antigen (HLA)-related (sibling) donor with at least 1 mismatch at 1 of the following 3 HLA-gene loci: HLA-A, -B or -DR;
    - Haploidentical donor;
    - Unrelated donor with at least 1 mismatch at 1 of the following 4 HLA gene loci: HLA-A, -B, -C, -DRB1;
    - Use of umbilical cord blood as stem cell source;
    - Use of ex vivo T-cell-depleted grafts;
    - Grade 2 or greater GVHD requiring the use of systemic corticosteroids (defined as the use of ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid).
- 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.

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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 the following:

- Clinical laboratory tests (hematology, chemistry, and pregnancy), must be performed and verified within 3 days prior to study treatment initiation. At screening, either central or local laboratory results for 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 or 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 study.

In addition, subjects who discontinued from screening due to COVID-19-related factors but were otherwise qualified to participate in the trial may be rescreened at any time if the Takeda medical monitor agrees.

The screening visit (Visit 1) and Visit 2/Week 0/Day 0 visits can occur in 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 Day 4 ± 1 day, Study Week 1 + 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 7.2.3.1)
- 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 7.2.3.1)
- 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 7.2.3.2)
- 12-lead ECG at Visit 2/Week 0, Visit 10/Week 8 (Section 7.2.3.3)
- Hematology/Chemistry assessment by the central laboratory at all visits through the study treatment phase; potassium and magnesium at Visit 2A (Section 7.2.3.4). In addition, blood samples for complete blood count with differential count and serum creatinine should be drawn for the analysis by the local laboratory within 2 days prior to study treatment dispensation for any postbaseline visits so that the test results are available for review prior to each study treatment dispensation. Additional analysis by local laboratory may be conducted at the investigator's discretion.
- Urinalysis at Visit 2/Week 0, Visit 4/Week 2, Visit 6/Week 4, Visit 8/Week 6, and Visit 10/Week 8 (Section 7.2.3.4)
- Pregnancy test at Visit 2/Week 0, Visit 6/Week 4, Visit 10/Week 8 (Section 7.2.3.4)

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- Hepatitis B virus (HBV) and hepatitis C virus (HCV) test at Visit 2/Week 0 (Historical results available within 3 months prior to study treatment initiation will be accepted. A test will be performed at Visit 2/Week 0 if the historical results are not available.)
- Cytomegalovirus DNA test: CMV DNA quantification in the plasma samples obtained at all visits (including baseline) of study treatment phase will be conducted at central specialty laboratory. CMV genotyping by the central specialty laboratory to assess for mutations in the UL97, UL27, and UL54 genes will be conducted only on the following samples: at baseline; [redacted]
- Tissue invasive CMV disease assessment (see Appendix 4) at all visits through the study treatment phase

[redacted]

- Immunosuppressant drug concentration measured at Visit 2/Week 0, Visit 2A/Day 4, Visit 3/Week 1, and Visit 10/Week 8 (see Section 7.2.3.4)
- Pharmacokinetic sample collection for adult subjects ≥18 years of age will be as follows: at Visit 3/Day 7/Week 1 (premorning dose and between 2-4 hours postmorning dose), Visit 6/Week 4 (only premorning dose), and Visit 10/Week 8 (premorning dose and between 2-4 hours postmorning dose). Pharmacokinetic sample collection for adolescent subjects ≥16 to <18 years of age will be as follows: intensive PK sampling at Visit 3/Week 1 (premorning dose and 1, 2, 3, 4, 6, 8 [all ±5 min], and 12 hours [±15 min] postmorning dose); at Visit 6/Week 4 (one premorning dose PK sample); at Visit 10/Week 8 (one premorning dose and one between 2-4 hours postmorning dose PK samples).
- Interactive response technology at all visits through the study treatment phase; except for the end-of-treatment visit (Visit 10/Week 8), IRT will be used for study treatment dispensing at all other visits through the study treatment phase.
- 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)

[redacted]

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- Assessment of underlying disease that led to HSCT will be performed at all visits through study treatment phase
- Invasive bacterial and fungal infections/transplant relevant infection assessed at all visits throughout the study treatment phase
- Hepatic function grading according to the Child-Pugh classification (see Appendix 2 and Section 7.2.2.8) at baseline, Visit 2/Week 0
- Graft-versus-host-disease assessment at all visits through the study treatment phase
- Comorbidity status evaluation 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
- Adverse event/SAE monitoring throughout the study treatment phase

For subjects who permanently discontinue study treatment early but do not withdraw consent, refer to Section 4.5 regarding modified schedule of assessments.

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7.1.3 Follow-up Period

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 to 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 Visit 18/Week 20
- Vital signs at Visit 18/Week 20
- 12-Lead ECG at Visit 18/Week 20
- Hematology/Chemistry assessment by the central laboratory 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)
- Assessment of underlying disease that led to HSCT will be performed at all visits during the follow-up phase
- Invasive bacterial and fungal infection assessment at all visits during the follow-up phase
- Cytomegalovirus DNA test: Cytomegalovirus DNA quantification in the plasma samples taken at each visit of study follow-up phase will be conducted at central specialty laboratory. Cytomegalovirus genotyping will be conducted only on the samples: [redacted]
- Tissue invasive CMV disease assessment (see Appendix 4) at all visits during the follow-up phase
- Graft-versus-host-disease assessment at all visits through the follow-up phase (Section 7.2.2.5; Appendix 8, and Appendix 9)
- Comorbidity status evaluation at Visit 14/Week 12, Visit 16/Week 16, and Visit 18/Week 20

[redacted]

- Monitoring of nonserious AEs not deemed related to the investigational product up to 30 days after the last dose of study medication (all AEs deemed related to the investigational product are collected until Visit 18/Week 20)
- SAE monitoring through the follow-up phase
- Concomitant medications, therapies, and procedures collected throughout the follow-up phase

All SAEs not resolved at the time of end of study visit (Visit 18/Week 20 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.

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7.1.4 Additional Care of Subjects after the Study

No aftercare 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

Blood samples 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 testing at local specialty laboratories may be performed and collected at more frequent intervals or using 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 postbaseline samples, separated by at least 5 days.

Confirmed Recurrence or the confirmed CMV viremia recurrence 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 being unquantifiable (<LLOQ) for at least 5 days in 2 consecutive samples.

7.2.2.2 CMV Genotyping and Phenotyping

Subjects with known resistance to anti-CMV agents, as determined by the local specialty laboratory (testing will be done as directed by the investigator) at the site, will be excluded from the study. At Visit 2/Day 0 plasma samples will be obtained and tested by the central specialty laboratory to identify mutations in the viral UL97 and UL54 genes known to confer resistance to anti-CMV agents. In addition, UL27 gene will be tested. Given the urgency to treat subjects, it is not possible to wait for this central specialty laboratory assessment prior to a subject's randomization. Potential for mutation conferring resistance at baseline will be limited, given that for the current infection, any anti-CMV treatment will not be administered for longer than 72 hours.

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In instances when a mutation conferring resistance to anti-CMV agents will be reported in the baseline sample analyzed by the central specialty laboratory these subjects will be excluded from the Per Protocol Set for analysis.

[redacted] ***Rebound*** is defined as increase in viral DNA load without prior clearance of viremia. The entire UL97, UL54, and UL27 CMV genes will be sequenced in every sample that meets the criteria for genotyping, including the baseline samples.

[redacted]

The list of CMV mutations known to confer resistance to valganciclovir, and other commercially available anti-CMV agents (ganciclovir, foscarnet, and cidofovir) is presented in Appendix 3.

7.2.2.3 [redacted]

[redacted]

[redacted]

[redacted]

7.2.2.4 [redacted]

[redacted]

7.2.2.5 Underlying Disease Assessment

Hematopoietic stem cell transplant offers potentially life-saving treatment for advanced malignancies and other diseases of hematologic, immunologic or metabolic origin. Underlying disease that led to HSCT, including relapse/progression, will be assessed at all visits throughout the study as indicated in Table 1 and Table 2. Dates of relapse or progression of the underlying disease/malignancy during the study will be documented. All available methods of detection, such as hematological, cytogenetic, molecular, cytological/histological, organs or sites involved etc., will be provided as appropriate for the underlying condition.

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7.2.2.6 Graft-versus-host-disease Assessments

Graft-versus-host-disease is a well-recognized complication of transplantation, and all blood stem cell sources can lead to this complication. Graft-versus-host-disease 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. A recent National Institute of Health classification also includes late-onset acute GVHD (after day 100) and an overlap syndrome with features of both acute and chronic GVHD (Cho et al., 2009).

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 8 and Appendix 9 (Jagasia et al., 2015; Shulman et al., 2015). Detailed information on GVHD at screening, baseline or 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 7 (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.

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 two treatment arms and to account for the subjects' health status when assessing overall and individual subject response. Comorbidity assessment will be performed at time points indicated in Table 1 and Table 2. The difference between treatment arms in terms of baseline comorbidities might be controlled for in the analyses, if determined to be substantial.

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Comorbidity assessment will utilize Karnofsky Performance Status (KPS) scale for subjects (Peus et al., 2013; Schag et al., 1984). Karnofsky Performance Status is a valuable tool for measurement of and comparison between the functional statuses of individual patients.). Refer to Appendix 5 for the KPS performance status scale forms.

7.2.2.8 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, disease/condition that led to the transplant, the number of past transplants prior to the current transplant; the details of transplant, such as cell source and transplant type; the human leukocyte antigen (HLA) matching level; the date and the history of the current transplant including complications; transplant related infections; preparatory regimen 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 and date of onset of the current CMV infection.

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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

7.2.2.9 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.

7.2.3 Safety

7.2.3.1 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.

7.2.3.2 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 changes from baseline (Visit 2/Day 0/Week 0) which are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

7.2.3.3 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. ECG data will include heart rate, RR duration, PR duration, QT duration, QRS duration. The corrected QT interval (QTc) will be calculated using the Fridericia's formula. The investigator will be responsible for providing the interpretation for all ECGs in terms of clinical significance to the subject.

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7.2.3.4 Clinical Laboratory Evaluations

Clinical laboratory tests (hematology, chemistry, urinalysis, HBV, HCV, pregnancy) will be performed by a central laboratory at the time points, including baseline, specified in Table 1 and Table 2. During screening, clinical laboratory tests (hematology, chemistry parameters required for eligibility verification, pregnancy) must be performed and results verified within 3 days prior to randomization; either central or local laboratory results can be used for qualification. This also applies to CMV DNA quantification results. 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 eligibility, the reference ranges must be provided. Local laboratory results will be recorded in the CRF.

Historical results available within 3 months prior to study treatment initiation will be accepted for HBV and HCV at Visit 2/Week 0; however, a test will be performed if historical results are not available.

At baseline (Visit 2/Week 0) blood samples will be taken for CMV DNA quantification and genotyping, hematology and chemistry and tested in the central specialty laboratories. At assigned visits, blood samples and urine for clinical safety laboratory testing should be collected prior to the administration of study drug.

All clinical laboratory assays will be performed according to the central laboratory's standard procedures. In addition, blood samples for complete blood count with differential and serum creatinine should be drawn and analyzed by the local laboratory within 2 days prior to study treatment dispensation so that results are available and reviewed prior to each study treatment dispensation during the treatment phase.

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:

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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), and triglycerides. 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.

A local laboratory will be used to assess potassium and magnesium levels at Visit 2A (Day 4±1 day for subjects receiving tacrolimus, cyclosporine, everolimus, or sirolimus at baseline, and at 4±1 days after initiating any of these agents for subjects starting the immunosuppressive therapy after baseline and during the study treatment period).

Hematology

White blood cell (WBC) and differential counts (including ANC), hemoglobin, hematocrit, red blood cell (RBC) count, reticulocytes, platelet count.

Urinalysis

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

Virology

- Hepatitis (hepatitis B surface antigen and/or viral DNA, hepatitis C antibody and/or viral RNA) at baseline only, if applicable. 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 laboratory 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 resting done locally during the screening period, and must have the results available prior to randomization.

Other

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

- Immunoglobulins IgG and immunoglobulins total (a total of IgG + IgA + IgM) with no reference ranges associated with the immunoglobulins total value

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Local Laboratory Test to Monitor Immunosuppressant Drug Concentration Levels

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:

- At Visit 2/Day 0/Week 0 prior to initiation of study treatment

- At Visit 2A/Day 4±1 day

- At the Visit 3/Day 7 (±2 day)/Week 1 study visit

- At Visit 10/Week 8 (±2 days) 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:

- At 4±1 days after initiating treatment with tacrolimus, cyclosporine, everolimus, or sirolimus
- 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 days) or on end of treatment (if earlier than Week 8)
- At the Week 1 post-treatment follow-up visit (ie, 1 week [±2 days] after discontinuation of study 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. Local laboratory test results can be used for the assessment of pregnancy on Day 0/Week 0.

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7.2.3.5 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 are collected from the time informed consent is signed through 30 days after the last dose of study medication. All AEs deemed related to the investigational product and all SAEs are collected through the end of the study (Visit 18/Week 20 [Follow-up Week 12]).

7.2.4 Others

7.2.4.1 Clinical Pharmacology Assessments

Pharmacokinetic samples will be obtained for all subjects as in the Schedule of Assessments (Table 1), but analyzed for only those subjects who are taking maribavir. Bioanalysis of PK samples will be conducted while the study is ongoing. The analysis will be conducted by unblinded staff from the bioanalysis laboratory/CRO to allow for the identification of the PK samples from the subjects randomized to the maribavir treatment arm.

For subjects ≥18 years of age (Table 8), 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 to 4 hours after the morning dose.

Any episode of vomiting occurring within 2 to 4 hours after the morning dose at Visit3/Week 1 and Visit 10/Week 8 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.

Table 8. Subjects ≥18 Years Sparse PK Schedule

Week 1, Day 7 (±1d)	Week 4, Day 28 (±2d)	Week 8, Day 56 (±2d)
Study Treatment Period		
• Premorning dose • 2-4 hours postmorning dose	• One premorning dose	• Premorning dose • 2-4 hours postmorning dose

For subjects ≥16 to <18 years of age (Table 9), an intensive PK sampling will be performed at Visit 3/Week 1. Subjects will be asked to complete the 12-hour postmorning dose PK sample prior to taking their evening dose. Sparse PK sampling similar to adults (≥18 years) will be performed at Week 4 and Week 8.

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Table 9. Subjects ≥16 to <18 Years 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) postmorning dose	• One premorning dose	• Premorning dose and • 2-4 hours postmorning dose

The following will be recorded in the study diary and/or CRF:

- Date and time of the last dose of blinded study treatment 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 blinded study treatment 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 study treatment dose interrupted for 2 consecutive days prior to the morning 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 blinded study treatment 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, GIGVHD is defined as any of the following (Boeckh et al., 2003):

- 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 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 study treatment in 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 Assessments).

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7.2.4.2 [redacted]

[redacted]

7.2.4.3 [redacted]

[redacted]

- [redacted]
  - [redacted]
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  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

7.2.5 Volume of Blood to Be Drawn from Each Subject

The volume of blood drawn from each subject per visit is shown in Table 10.

Table 10. Volume of Blood Drawn Per Study Visit

Study Visit	Blood Volume per Visit (mL)
Screening	29
Visit 2A[a]	11
Visit 2	51
Visit 3	42
Visit 4, Visit 5, Visit 7, Visit 8, Visit 9	31
Visit 6	37
Visit 10	60
Visit 11	20
Visit 12, Visit 14, Visit 16	23
Visit 13, Visit 15, Visit 17	15
Visit 18	43
Additional PK	**PK Blood Volume per Blood Draw (mL)**
See Section 7.2.4.1	4

PK=pharmacokinetic

[a] To be drawn only from subjects receiving immunosuppressive agents tacrolimus, cyclosporine, everolimus, or sirolimus at baseline (on Day 4 ±1 day), or from subjects who initiate treatment with any of these agents after baseline (4 ±1 day after starting the immunosuppressant).

Note: See Schedule of Assessment 1 (Table 1) and Schedule of Assessment 2 (Table 2).

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During this study, it is expected that approximately 551 mL of blood will be drawn from all subjects, regardless of sex. Subjects between the ages of 16 to 18 years will have an additional 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) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. 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.

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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 investigational product, 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 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 4.0.

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8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product 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 investigational product. 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 investigational product 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:

Related: The temporal relationship between the event and the administration of the investigational product 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 investigational product 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 adverse event of special interest (AESI) as mentioned below:

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Adverse Events of Special Interest (severity grading based on CTCAE Version 4.0)

1. Tissue invasive CMV disease. Any new development or onset of tissue invasive CMV disease in the asymptomatic subjects (at baseline) will be monitored throughout the study. At each visit the investigator will provide the evaluation of the tissue invasive CMV disease, 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 for a given subject. When these events are entered into the CRF, they should be recorded using the terminology shown in Appendix 4 (eg, 'CMV pneumonitis', 'CMV colitis', etc.). For details on how the disease under study will be reported see Section 8.1.5.

2. Relapse or progression of the underlying disease (disease for which transplant was performed).

3. 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. These adverse events are common for both maribavir and valganciclovir.

5. Adverse event of neutropenia will be recorded based on laboratory results (central or local) considered clinically significant by the investigator. In addition, to the adverse events of neutropenia reported by the investigator, incidence of neutropenia defined as ANC <500/mm^3 [0.5 x 10^9/L] or ANC <1,000/mm^3 [1.0 x 10^9/L]) based on central laboratory data will be analyzed.

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 7.2.3.4. High to toxic levels will be recorded as AEs.

2. 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 (see Appendix 10).

3. Graft-versus-host-disease: GVHD will be diagnosed based on the investigator's judgment (see Section 7.2.2.5). Severity of Acute GVHD (Grading I-IV) will be assessed using grading scale provided in Appendix 7 (Harris et al., 2016) and for chronic GVHD using severity grading into mild, moderate and severe according to the scoring provided in Appendix 8, as in the consensus project by Jagasia et al. (2015). Harris et al. (2016) provides the confidence levels of the diagnosis (refer to Table 2 in Harris et al., 2016). 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) or the end 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 (≥1365 IU/mL to ≤273000 IU/mL in whole blood or ≥455 IU/mL to ≤91000 IU/mL in plasma) and their viral load will be monitored throughout the study. Viremia clearance, persistence, or recurrence will be analyzed as the part of efficacy assessment based on central laboratory result.

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It is anticipated that some subjects, although asymptomatic at baseline, may have a new onset of tissue invasive CMV disease during the 8 week of study treatment or in the 12-week follow-up phase. Since new tissue invasive CMV disease 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. Cytomegalovirus disease involving specific organ is to be reported, for example CMV disease involving liver will be reported as CMV hepatitis.

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.

The terminology used for reporting should be:

- Asymptomatic CMV infection
- Tissue invasive CMV disease, specify organ for example CMV pneumonitis, CMV colitis

Table 11 presents the criteria for reporting tissue invasive CMV disease as an AE or as an SAE during its clinical course during the study.

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Table 11. Criteria for Reporting Tissue Invasive CMV Disease as an AE or as an SAE

	Course during the study (based on the investigator's assessment)	Reportable as AE	Reportable as SAE
New onset of/ change in tissue invasive CMV disease	New onset	No	Yes
	Improving	No	No
	Worsening	No	Yes, but same event with upgraded severity
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

AE=adverse event; CMV=cytomegalovirus; IV=intravenous; 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 treatment with the investigational product, 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 treatment 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, 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.

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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 must be reported within 24 hours to the Takeda Global Pharmacovigilance and Risk Management Department using the 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 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 Clinical Study Serious Adverse Event and Nonserious AEs Required by the Protocol Form as well as the 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 investigational product 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 investigational product 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 prespecified total daily dose.
  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. Assuming a normal or only mildly impaired renal function and serum creatinine levels, a maximum dose of 900 mg valganciclovir should be administered at a time (refer to the Valcyte Prescribing Information and Valcyte Summary of Product Characteristics as documented in the Study Pharmacy Manual). Valganciclovir dose may be adjusted based on renal function and ANC level (see Section 6.2.3).

- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

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Cases of subjects missing doses of the investigational product are not considered reportable as medication errors. Medication errors should be collected/reported for all products under investigation. The administration and/or use of the unassigned treatment is/are always reportable as a medication error. The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent(s)/legally authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the maribavir investigator's brochure, which the sponsor has provided under separate cover to all investigators.

The reference for safety information for the comparator/reference product, valganciclovir, in this study is the summary of product characteristics (SmPC), which the sponsor has provided under separate cover to all investigators.

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8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Takeda Global Pharmacovigilance and Risk Management Department within 24 hours of the first awareness of the event (but with no information that would unblind the study treatment assignment).
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 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 Takeda Global Pharmacovigilance and Risk Management Department.

In the event of an SAE, the investigator must:

1. Fax or e-mail the clinical trial serious adverse event form within 24 hours to the Takeda Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover) and are provided below:

Global
Fax: +1-484-595-8155
Email: DrugSafety@shire.com

8.2.3 Serious Adverse Event Definition

An 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.

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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

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 defined follow-up period stated in Section 7.1.3 and must be reported to the Takeda Global Drug Safety Department 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 Takeda 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 date 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.

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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 investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product 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 recipients with CMV infections. The following SAEs are common in this study population and are anticipated to occur, hence these SAEs (including fatal outcome) 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 (Maribavir Phase 2 [Studies 1263-202 and 1263-203] data will be used as reference):

- Any CMV infection, including CMV reactivation/recurrence, [redacted]
- Any other viral, bacterial, or fungal infection
- Acute and chronic GVHD
- Reactivation/progression of the malignancy or other disease, which is an underlying disease, that led to the transplant

This includes fatal outcomes of the aforementioned SAEs.

However, these are AESI and will be closely monitored and recorded on the CRF. See 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 9.5.

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.

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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.

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9.3 Data Handling Considerations

Data that may potentially unblind the treatment assignment (ie, valganciclovir dose adjustment for CrCl/neutropenia, investigational product serum concentrations, CMV DNA plasma or blood concentrations, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 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.

[redacted] The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and study conclusions. 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.

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9.5 Data Monitoring Committee

An independent 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 study.

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

9.6 Sample Size Calculation and Power Considerations

The primary testing is to establish that maribavir is not inferior to valganciclovir in treatment of CMV infection in HSCT recipients. For ethical reasons it would not be possible to conduct a study of maribavir versus placebo since different treatment strategies are already used and well established in clinical practice to treat CMV infection. Valganciclovir has been selected as the active control because of its documented effectiveness for the treatment of CMV infection, including in patients after hematopoietic stem cell transplantation. While clinical trials of ganciclovir and valganciclovir versus placebo have been conducted for CMV prophylaxis, no placebo-controlled studies have been done to date for the treatment of CMV infection or disease. Therefore, the effect size of valganciclovir against placebo is not available, and treatment effect estimate had to be derived indirectly. Literature reports viremia clearance rate for valganciclovir at 70% to 100%. In the VICTOR study, a randomized controlled study to compare valganciclovir with ganciclovir for the treatment of CMV disease in SOT subjects (Asberg et al., 2007), the Week 7 viremia clearance rate was reported at 67% and the derived lower limit of the 95% CI was 60% for valganciclovir treatment group (n=164).

In Phase 2 treatment SHP620-203 study, 75% of HSCT subjects (n=61 across 3 dose groups) in the maribavir group and 48% in valganciclovir group (n=21) had confirmed CMV viremia clearance within 6 weeks. Based on these available data, the proportion of subjects who achieve viremia clearance after 8 weeks of treatment in the current study is assumed at 60% for the valganciclovir treatment group.

A 7% noninferiority (NI) margin is chosen for the current study based on the following considerations. First, a 7% of margin preserves at least 85% of the effect size assumed for the valganciclovir treatment group. Secondly, a 7% margin is less than half of 15%, a common NI margin used in antiviral trials and is considered very conservative. Two NI studies on comparing valganciclovir with ganciclovir in CMV treatment were identified after a thorough literature research. One study was reported by Chawla et al. (2012), and the other is VICTOR study (Asberg et al., 2007); both used a NI margin of 15%. Discussions with clinical experts confirmed that a 7% NI margin is considered a conservative choice and in clinical practice, a lower response rate might even be considered given the favorable safety profile of the test drug and where toxicities of available treatments such as valganciclovir limit their use.

Although based on the SHP620-203 study result 75% of HSCT subjects in the maribavir group and 48% in valganciclovir group had confirmed CMV viremia clearance within 6 weeks, it is expected that maribavir may be superior to valganciclovir in the treatment setting. Given the uncertainties regarding the differences in this study design from that of SHP620-203, literature reported treatment effect for valganciclovir, and practical consideration for enrollment of sufficient number of patients in this orphan patient population, the primary objective of this study is testing for noninferiority with testing for superiority to be conducted only after noninferiority is established.

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

9.7 Study 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 for whom a randomization number has been assigned.
- The Modified Randomized Set will consist of all subjects in the Randomized Set who have taken at least 1 dose of assigned study treatment.
- The Safety Set will consist of all subjects who have taken at least 1 dose of study treatment.
- The PP Set will consist of all subjects in the Randomized Set who do not have major predefined protocol deviations that may affect the primary efficacy assessment.
- The PK 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 of 16 to <18 years of age in the safety set who had plasma samples drawn and tested for maribavir concentrations.

The Modified Randomized Set and PP Sets will be used for efficacy analyses. The Safety Set will be used for safety analyses. Pharmacokinetic data will be analyzed using the Pharmacokinetic Set.

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9.8 Efficacy Analyses

Efficacy measurements assessed after the initiation of prohibited anti-CMV treatment will be excluded from the efficacy analysis for the assigned study drug. Efficacy measurements after initiation of alternative anti-CMV treatment will be marked in data listings. Summary descriptive 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 in the analysis set unless otherwise specified. 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.

9.8.1 Primary Efficacy Endpoint

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

Confirmed CMV viremia clearance at the end of Study Week 8/Study Visit 10 (study treatment phase) 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, 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. This is further described with examples in Table 12. 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.

Table 12. Assessments of Virological Responders at Study Week 8

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

CMV=cytomegalovirus; NA=not available for evaluation of study drug effect; reason could be not assessable by lab, or starting alternative anti-CMV treatment or withdrawal from study etc.
[a] Week 9 data, if available to evaluate effect of study drug, only to be used if Week 8 data are unavailable or missing.
Notes: Scenarios in the table above are provided as examples and may not be all-inclusive of all possibilities.
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.

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Statistical Methodology for Primary Efficacy Endpoint:

The proportion of subjects with confirmed CMV viremia clearance, at the end of Study Week 8 and the corresponding 95% CIs will be calculated for each treatment group. The difference in proportion of subjects with confirmed CMV viremia clearance, at the end of Study Week 8, between treatment groups (maribavir and valganciclovir) will be obtained using Cochran-Mantel-Haenszel (CMH) weighted average across strata with baseline plasma CMV DNA concentration levels and presence or absence of acute GVHD as the stratification factors. The baseline plasma CMV DNA concentration will be the last central laboratory assessment before the first dose of study treatment.

The 2-sided 95% CI of the weighted average of difference across strata will be calculated using the normal approximation method. If the lower limit of the 95% CI is greater than -7%, it will be concluded that maribavir is as efficacious as valganciclovir. The noninferiority analysis will be performed on the PP Set as the primary analysis and on the Modified Randomized Set as a secondary analysis.

Sensitivity and supportive analyses of the primary endpoint of confirmed 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. Some examples are given below:

- The primary efficacy endpoint analysis will be repeated by using the CMV DNA level used for the randomization rather than the CMV DNA levels based on central laboratory values as one of the stratification factors.
- Subjects who discontinue study treatment early, with no CMV DNA measurement for responder evaluation of study drug effect at Study Week 8 (see Table 12), however, they meet the criteria of confirmed CMV viremia clearance defined as 2 consecutive postbaseline assessments of CMV DNA target <LLOQ, separated by at least 5 days within Study Week 8, 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 CMV viral load, CMV serostatus, immune function status, presence of acute GVHD, high dose steroids use at baseline, prior use of CMV prophylaxis.
- Subjects with missing data due to alternative anti-CMV treatment or death due to CMV infection by Study Week 8 will be considered treatment failure, hence non-responder. Subjects with missing data due to early discontinuation from study with reason other than alternative anti-CMV treatment or death due to CMV infection at Study Week 8 may have the response data imputed.

Subject to the multiplicity adjustment method described in Section 9.8.3, the superiority hypothesis of the primary efficacy endpoint will be tested by comparing the lower limit of the 95% CI of the difference with 0 in the proportion of subjects with confirmed CMV viremia clearance at the end of Study Week 8 between maribavir and valganciclovir. The superiority testing will be performed on the Modified Randomized Set.

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9.8.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is defined as the maintenance of confirmed CMV viremia clearance achieved at the end of Study Week 8 through Week 16. Example criteria for defining responders at Study Week 16 are presented in Table 13.

For clearance of CMV viremia achieved at the end of Study Week 8, regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy, and maintenance of such effect through Week 16, the subject must have received exclusively a study-assigned treatment and must also have symptom control.

Table 13. 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[b]	Rationale
	9	10	11	12	14	16	18[a]		
Yes	+/-	+/-	+/-	+/-	+/-	+/-	+/- /NA	No	Any 2 consecutive "+" in FU by Week 16
Yes	+/-	+/-	+/-	+/-	+/-	-	+/- /NA	Yes	Week 16 is "-" and no 2 consecutive "+" during FU
Yes	+/-	+/-	+/-	+/-	+/-	+	+/- /NA	No	Week 16 is "+" and Week 18 is "+" or NA, criteria of 2 consecutive "+" 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	

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

[a] Week 18 data will be used only if Week 16 data are unavailable or missing.

[b] Must also meet the criterion of CMV infection symptom control to be a responder.

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

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

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Statistical Methodology for Key Secondary Efficacy Endpoint:

The proportion of subjects who achieve response, as defined for the key secondary efficacy endpoint, and the corresponding 95% CIs will be calculated for each treatment group.

The difference in proportion between treatment groups (maribavir and valganciclovir) will be obtained using CMH weighted average across strata with baseline plasma CMV DNA concentration level (based on the last central laboratory assessment before the first dose of study treatment) and presence or absence of acute GVHD as the stratification factors. The 2-sided 95% CI of the weighted average of difference across strata will be calculated using the normal approximation method. Sensitivity analyses for the key secondary endpoint will also be performed.

Subject to the multiplicity adjustment method described in Section 9.8.3, the noninferiority testing will be done by comparing the lower limit of the 95% CI with the same NI margin as the primary efficacy endpoint. If the lower limit of the 95% CI is greater than -7%, it will be concluded that maribavir is as efficacious as valganciclovir in maintaining treatment effect. The noninferiority analysis will be performed on the PP Set as the primary analysis and on the Modified Randomized Set as a secondary analysis.

Subject to the multiplicity adjustment method described in Section 9.8.3, the superiority in key secondary efficacy endpoint will be tested by comparing the lower limit of the 95% CI of the difference with 0 in the proportion of subjects who achieve response as defined for the key secondary efficacy endpoint between maribavir and valganciclovir. The superiority testing will be performed on the Modified Randomized Set.

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9.8.3 Multiplicity Adjustment

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

- First, the NI testing of the primary efficacy endpoint will be assessed based on the 2-sided 95% CI of the adjusted difference in proportion of subjects who have CMV viremia clearance at the end of Study Week 8 stratified by baseline CMV DNA level and presence/absence of acute GVHD at baseline. This analysis will be conducted using Per Protocol Set as the primary and Modified Randomized Set as secondary. If the lower limit of the 95% CI is above the predefined NI margin of -7%, NI is considered established.

- If and only after the NI of the primary efficacy endpoint is established, the superiority hypothesis of the primary efficacy endpoint and the NI hypothesis of the key secondary endpoint will be tested in parallel. Hochberg procedure will be used to control family-wise Type 1 error rate at 2-sided α=5% level.
- If and only if the superiority of the primary efficacy endpoint and NI of key secondary efficacy endpoint are established, the superiority hypothesis of the key secondary efficacy endpoint will be tested.

9.8.4 Subgroup Analyses

The proportion of responders and the corresponding 95% CI will be summarized for primary and key secondary endpoints by treatment group for the following subgroups (inclusive, but not limited to):

- Cytomegalovirus DNA viral load (high, low, very low/high-risk)
- Acute GVHD presence/absence at baseline
- Adolescents ≥16 to <18 years of age (exploratory analysis: may be conducted if sample size is adequate)
- Enrolling regions (enrolling centers will be grouped by geographic locations to explore homogeneity of treatment effect across regions).

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9.8.5 Secondary Efficacy Endpoints

The other secondary endpoints of this study are:

- 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 acute GVHD and baseline CMV DNA concentration as 2 stratification factors.

- The maintenance of the confirmed CMV viremia clearance after completion of 8 weeks of receiving study-assigned treatment, through Study Weeks 12 (4 weeks post-treatment period), 16 (8 weeks of post-treatment/follow-up phase), and 20 (12 weeks post-treatment).

    - The proportion of subjects who maintained the confirmed CMV viremia clearance achieved after receiving 8 weeks of study-assigned treatment, 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 acute GVHD and baseline CMV DNA concentration as 2 stratification factors.

- The maintenance of the CMV viremia clearance achieved at the end of Study Week 8 through Study Weeks 12, and 20, regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. For maintenance effect to be achieved at a time point, the subjects must have received exclusively study-assigned treatments up to that time point and also must have symptom control.

    - The proportion of subjects maintaining the CMV viremia clearance from the end of Study Week 8 through Study Weeks 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 baseline CMV DNA concentration and presence or absence of acute GVHD as 2 stratification factors.

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- 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 confirmed recurrence of viremia during the first 8 weeks of the study, when off treatment in the 12-week follow-up phase, at any time during the 20 weeks of the study will be calculated.

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

    - The proportion of subjects with confirmed recurrence of viremia while on study treatment and when off treatment will be calculated.

- The incidence of grade 3 or 4 neutropenia (defined as ANC <1,000/mm^3 [1.0×10^9/L]) or ANC <500/mm^3 [0.5×10^9/L], respectively)

    - The proportions of subjects with neutropenia while receiving study treatment will be calculated for each treatment group.

The time to first neutropenia while receiving study treatment will be summarized using the Kaplan-Meier method. The analysis of the secondary efficacy endpoints will be conducted using the Modified Randomized Set and PP Set unless otherwise specified. Secondary efficacy endpoints will be summarized by treatment arm, and, if indicated, analyzed statistically at α=0.05 (2-sided), without adjustment for multiple comparisons.

9.8.6 Exploratory Efficacy Endpoints

[redacted]

9.9 Safety Analyses

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

Statistical Methodology for Safety Endpoints

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. For subjects who transfer from the study treatment to a nonstudy anti-CMV treatment, the on-treatment observation period starts at the time of the study treatment initiation through 7 days after the last dose of study treatment, or until the nonstudy anti-CMV treatment initiation, whichever is earlier. This will serve as the primary analysis of safety.

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

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).

The overall study AEs are those occurring during the overall-study observation period.

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.

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The safety endpoints for this study are as follows:

- TEAEs and treatment-emergent SAEs, overall study AEs and overall study SAEs

- Clinical laboratory evaluations (including incidence of neutropenia defined as ANC $<500/mm^3$ [$0.5 \times 10^9/L$] or ANC $<1,000/mm^3$ [$1.0 \times 10^9/L$] at any time during the study [on treatment and overall study period], time to neutropenia development), and study treatment dose adjustment due to AEs

- Safety assessments 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 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 AESIs will be provided.

Adverse events of special interest as defined in Section 8.1.4, will be analyzed according to primary system organ classes (SOCs) and preferred terms (PTs). Standardized MedDRA queries (SMQs) may be used, as 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. Invasive bacterial and fungal infections, if any, will be noted.

Usage of concomitant medications will be summarized descriptively for each of the treatment groups for the on-treatment period and overall study period. Additionally, summary of hematopoietic growth factors, blood, and blood products transfusions will be provided.

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Change from Baseline in vital signs and clinical laboratory test s will be summarized for each treatment group with descriptive statistics at each assessment visit. 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. Analyses of shifts in NCI CTC toxicity grades from baseline to maximum grade postbaseline for the on-treatment period and the overall-study period will be provided. Potentially clinically important findings will also be summarized.

Treatment-emergent grade 3 or 4 neutropenia (defined respectively as ANC <1,000/mm^3 [1.0×10^9/L]) or ANC <500/mm^3 [0.5×10^9/L]) will be summarized as shifts in laboratory results from lower grade to maximum grade of either 3 or 4 postbaseline for the on-treatment period and the overall-study period. Time to neutropenia development will be evaluated.

Study treatment dose adjustment, specifically valganciclovir dose adjustment and interruptions for neutropenia or renal function impairment or other AE, and maribavir dose interruptions for any AE, will be summarized.

Abnormal physical examination findings will be listed.

Summary of ECG findings will be provided by treatment groups.

An independent 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 SAP.

9.10 Other Analyses

9.10.1 [redacted]

[redacted]

9.10.2 [redacted]

[redacted]

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9.10.3 Pharmacokinetic and Pharmacokinetic/pharmacodynamic Analyses

The PK Population will be used to analyze the PK endpoints. Since this is a double-blind study, PK samples will be obtained for all subjects as in the Schedule of Assessments (Table 1), but analyzed for only those subjects who are taking maribavir.

Pharmacokinetic endpoints for this study are as follows:

Secondary endpoint:

For all subjects:

- 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

[redacted]

Blood samples will be analyzed for plasma maribavir concentration levels. Maribavir 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.

[redacted]

In a separate analysis and report, maribavir concentrations will be analyzed by population PK analysis approach using nonlinear mixed effect model approach using NONMEM Version 7 or above. Post hoc maribavir PK parameters such as AUC, C_{max}, and C_{min} will be generated and summarized by identified covariates; [redacted] This analysis maybe conducted by combining maribavir PK data from other Phase 2 and Phase 3 studies.

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

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10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, International Conference on Harmonisation (ICH), EU Directive 2001/20/EC and its revisions/updates, 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 (1996), EU Directive 2001/20/EC, Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2) Current Step 4 version dated 09 November 2016, as well as all applicable national and local laws and regulations, and any updates and/or revisions.

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.

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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 Reporting of COVID-19 Cases During the Study

The sponsor will, complying with local laws and regulations, notify relevant health authorities of any participant who contracts COVID-19 during the study.

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10.1.6 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.

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 (1996), EU Directive 2001/20/EC, Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2) Current Step 4 version dated 09 November 2016, applicable regulatory requirements and guidelines, and any updates or revisions.

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 sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study and request any medical history of the subject (with the subject's consent).

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 as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

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, received study-specific training and should implement procedures to ensure the integrity of the study tasks performed and any data generated.

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10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators 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 cards, original clinical laboratory reports, and histology and pathology reports.

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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) will check or will verify 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. Due to the COVID-19 public health emergency, remote source document verification can be utilized where allowed by local laws and regulations.

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], European Medicines Agency [EMA], United Kingdom 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.

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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 their parent(s)/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.

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

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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; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by 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) of 1996. 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 representatives 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 maribavir; 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.

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10.5 Study Results/Publication Policy

Takeda 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, Takeda adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which may be done for large, multicenter Phase 2-4 and certain other studies as determined by Takeda. 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.

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.

All publications relating to Takeda products or projects must undergo appropriate technical and intellectual property review, with Takeda 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.

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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 Takeda, 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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APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	04 Aug 2016	Global
Amendment 1	02 Mar 2017	Global
Amendment 2	01 Jun 2017	Global
Amendment 3	01 Sep 2017	Global
Amendment 4	05 Feb 2019	Global
Amendment 5	12 Feb 2020	Global
Amendment 6	07 Dec 2020	Global
Amendment 6.1	10 Mar 2021	Country (CHN)
Amendment 7	25 Mar 2021	Global
Amendment 7.1 (CHN)	17 May 2021	Country (CHN)
Amendment 8	02 Jul 2021	Global
Amendment 8.1 (CHN)	02 Jul 2021	Country (CHN)
Amendment 9	15 Sept 2021	Global

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Amendment 8 was made to update the sponsor name and address from Shire ViroPharma, Inc (Shire) to Takeda Development Center Americas, Inc (TDC Americas; Takeda) and to clarify the secondary endpoints. Other minor editorial revisions (including changes for consistency and clarity) are not described in the table below.

Protocol Amendment		
Summary of Changes Since Protocol Version 8.0 (Protocol Amendment 7)		
Amendment Number **8**	**Amendment Date** **02 Jul 2021**	**Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated the sponsor (name and address) from Shire ViroPharma, Inc (Shire) to Takeda Development Center Americas, Inc (TDC Americas; Takeda) as the legal entity will change 01 July 2021.		Document headers; Title/Cover; Protocol Signature Page; Product Quality Complaints; Synopsis; Section 3.4, Changes to Study Procedures Due to COVID-19 Pandemic; Section 4.5, Discontinuation and/or Withdrawal of Subjects; Section 6.4, Drug Accountability; Section 7.1.1, Screening Period; Section 8.1.7, Pregnancy; Section 8.2.2, Reporting Procedures; Section 8.2.4, Serious Adverse Event Collection Time Frame; Section 10.5, Study Results/Publication Policy

Protocol Amendment		
Summary of Changes Since Protocol Version 8.0 (Protocol Amendment 7)		
Amendment Number **8**	**Amendment Date** **02 Jul 2021**	**Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Clarified the secondary efficacy endpoints on maintenance of viremia clearance achieved at Week 8 through Week 16 (key), 12, and 20 regardless if either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy, the subject must also have symptom control.		Synopsis; Section 9.8.2, Key Secondary Efficacy Endpoint; Section 9.8.5, Secondary Efficacy Endpoints

Amendment 7 to Protocol SPH620-302 incorporated agency concerns.

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.

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Protocol Amendment		
Summary of Changes Since Protocol Version 7.0 (Protocol Amendment 6)		
Amendment Number **7**	**Amendment Date** **25 Mar 2021**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Removed language extending measures to other situations beyond the COVID-19 pandemic ("or other future similar unexpected public health concerns" as this section applies only to the current COVID-19 pandemic.		Section 3.4, Changes to Study Procedures Due to COVID-19 Pandemic
Updated the guidance on management of clinical trials during the COVID-19 pandemic. Clarified that the site must contact the sponsor for approval of the alternative method for obtaining informed consent prior to implementation.		Synopsis; Table 1, Schedule of Assessment 1: Screening Phase and Study Treatment Phase; Section 3.4, Changes to Study Procedures Due to COVID-19 Pandemic; Section 4.1, Inclusion Criteria
Clarified the recording of abuse, misuse, overdose, and medication errors on the AE CRF.		Section 8.1.8, Abuse, Misuse, Overdose, and Medication Error

Amendment 6 to Protocol SHP620-302 incorporated the following major changes:

- The protocol was amended to maintain subject safety, confidentiality, and study integrity in the context of healthcare delivery challenges presented by the COVID-19 pandemic. Amendment 6 provided flexibility to study participants to opt for home healthcare (HHC) solutions as permitted by local regulations. This "hybrid study design" would offer study participants the option of in clinic or HHC for all study visits in the treatment phase.

- Guidance was provided regarding changes to the study procedures that could be implemented for study participants or study sites affected by the COVID-19 Public Health Emergency. The guidance took references from the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency - Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, updated 03 June 2020, and the EMA Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic, Version 3 (28 April 2020).

- As the COVID-19 pandemic could peak in different regions at different times and restrictions implemented by local laws and recommendations could vary, any decision on procedural changes was to be made on a case-by-case basis by the principal investigator in consultation with the study team and the medical team as needed, while maintaining patient safety and confidentiality as the priority

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.

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Protocol Amendment		
Summary of Changes Since Protocol Version 6.0 (Protocol Amendment 5)		
Amendment Number **6**	**Amendment Date** **07 Dec 2020**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated Sponsor Approval on Protocol Signature Page.		Protocol Signature Page
Updated number of completed Phase 1 studies from 15 to 17.		Section 1.2.2, Efficacy
Updated number of completed Phase 1 studies from 16 to 17.		Section 1.2.3, Safety
Included language regarding home healthcare services/remote visits for the treatment phase.		Study Schedules; Section 3.1, Study Design and Flow Chart; Section 3.4, Changes to Study Procedures Due to COVID-19 Pandemic; Section 6.4, Drug Accountability
Included language regarding Direct-to-Patient study drug services where allowed per local regulations.		Section 3.1, Study Design and Flow Chart; Section 3.4, Changes to Study Procedures Due to COVID-19 Pandemic; Section 6.4, Drug Accountability
Implementation of remote source document verification where allowed per local laws and regulations.		Section 3.4, Changes to Study Procedures Due to COVID-19 Pandemic; Section 10.2.3.2, Recording, Access, and Retention of Source Data and Study Documents

Protocol Amendment		
Summary of Changes Since Protocol Version 6.0 (Protocol Amendment 5)		
Amendment Number **6**	**Amendment Date** **07 Dec 2020**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Included language to cover subjects who discontinued due to COVID-19.		Section 3.4, Changes to Study Procedures Due to COVID-19 Pandemic; Section 4.5, Discontinuation and/or Withdrawal of Subjects
Included language to cover subjects who discontinued due to COVID-19.		Section 3.4, Changes to Study Procedures Due to COVID-19 Pandemic; Section 4.5, Discontinuation and/or Withdrawal of Subjects
Included language concerning the notification of relevant health authorities about participants who contract COVID-19 during the study.		Section 3.4, Changes to Study Procedures Due to COVID-19 Pandemic; Section 10.1.5, Reporting of COVID-19 Cases During the Study
Maribavir tablet strength corrected to 200 mg, which was previously inadvertently stated as 20 mg.		Section 3.1, Study Design and Flow Chart
Added the possibility of valganciclovir dose adjustments for subjects with moderate renal impairment to Figure 1, Study Design Flow Chart.		Section 3.1, Study Design and Flow Chart
Replaced cidofovir with letermovir in the list of anti-CMV agents that must not be taken for current CMV infection for longer than 72 hours.		Section 3.1, Study Design and Flow Chart; Section 4.2, Exclusion Criteria; Section 5.1, Prior Medications, Therapies, and Procedures
Reinserted the clinical laboratory assessment for immunoglobulins under the heading labeled “Other”, which was inadvertently removed from Protocol Amendment 5.		Section 7.2.3.5, Clinical Laboratory Evaluations
Changed the assessment of severity (intensity) of adverse events according to version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).		Section 8.1.1, Severity Categorization; Section 8.1.4, Adverse Events of Special Interest
Clarified the recording of abuse, misuse, overdose, and medication errors on the AE CRF.		Section 8.1.8, Abuse, Misuse, Overdose, and Medication Error
For subjects with CMV DNA ≤910 IU/mL in plasma or ≤2730 IU/mL in whole blood with high-risk CMV infection, the requirement was removed that the second result must be higher or decrease no more than 30% relative to the first result.		Section 7.1.1, Screening Period
Corrected value for inclusion criteria 4 from ≥730 IU/mL in whole blood to ≥2730 IU/mL in whole blood under changes for Protocol Amendment 4, which was inadvertently not stated correctly in Protocol Amendment 5.		Appendix 1, Protocol History
Updated data and sources in Table A-2 and Table A-3 listing CMV genetic mutations associated with resistance to anti-CMV drugs.		Appendix 3, CMV Genetic Mutations Associated with Resistance to Anti CMV Drugs

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Amendment 5 to Protocol SHP620-302 incorporated the following major changes:

- Added Modified Randomized Set, consisting of all subjects in Randomized Set who take at least 1 dose of assigned study treatment.
- [redacted].
- Updated comorbidity status evaluation.
- To align with the investigator's brochure, updated the C_{max} and AUC values for the increased tacrolimus when concomitantly administered with maribavir (400 mg BID) (33% changed to 38% and 54% changed to 51%, respectively) and changed 2D6 substrate to CYP2C19 substrate.
- Updated number of completed for Phase 1 studies in Section 1.2.3 from 15 to 16.
- Removed references to an electronic diary (e-diary) due to the introduction of paper back-up diaries.
- Updated the versions of the Valcyte Prescribing Information and Summary of Product Characteristics (SmPC) to specify the current version as documented in the Study Pharmacy Manual.
- Corrected the unit of measure for hemoglobin from mg/dL to g/dL.
- Clarified that timing of comorbidity status evaluation is at Visit 6/Week 4 and Visit 10/Week 8.
- Clarified follow-up to closure of unresolved serious adverse events (SAEs) rather than AEs at end of study.
- Corrected pregnancy reporting information to indicate that it is the investigator's responsibility to obtain pregnancy outcome/infant condition information within approximately 30 calendar days and 1 year postpartum. Removed requirement for a copy of the Investigational and Marketed Products Pregnancy Report Form being sent to the CRO/ Shire medical monitor using details specified in the emergency contact information section of protocol.

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- Corrected information regarding reporting of SAEs.
- Removed confidence intervals from 3 secondary efficacy endpoints as they are not clinically meaningful for these analyses.
- Removed the Ljungman 2002 reference, updated the Ljungman reference from 2016 (e-publication date) to 2017 (final publication date), and added a statement to refer to the citation for full details on the definition of CMV disease.

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 Amendment		
Summary of Changes Since Protocol Amendment 4 (Version 5.0)		
Amendment Number **5**	**Amendment Date** **12 Feb 2020**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated Sponsor Approval on Protocol Signature Page.		Protocol Signature Page
Updated study period dates to 2017-2021.		Synopsis
Added Modified Randomized Set, consisting of all subjects in Randomized Set who take at least 1 dose of assigned study treatment.		Synopsis; Section 9.7, Study Population; Section 9.8.1, Primary Efficacy Endpoint; Section 9.8.2, Key Secondary Efficacy Endpoint; Section 9.8.3, Multiplicity Adjustment; Section 9.8.5, Secondary Efficacy Endpoints; [redacted]
[redacted]		[redacted]
Updated comorbidity status evaluation.		Study Schedules, Table 1, Schedule of Assessment 1: Screening Phase and Study Treatment Phase
To align with the investigator's brochure, updated the C_{max} and AUC values for the increased tacrolimus when concomitantly administered with maribavir (400 mg BID) (33% changed to 38% and 54% changed to 51%, respectively) and changed 2D6 substrate to CYP2C19 substrate.		Section 1.2.1, Pharmacokinetics, Metabolism, and Drug-Drug Interactions; Section 5.2.1, Permitted Treatment
Updated number of completed Phase 1 studies from 15 to 16.		Section 1.2.3, Safety

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Protocol Amendment		
Summary of Changes Since Protocol Amendment 4 (Version 5.0)		
Amendment Number **5**	**Amendment Date** **12 Feb 2020**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Removed references to an electronic diary (e-diary) due to the introduction of paper back-up diaries.		Section 6.4, Drug Accountability; Section 6.5, Subject Compliance
Updated the versions of the Valcyte Prescribing Information and Summary of Product Characteristics (SmPC) to specify the current version as documented in the Study Pharmacy Manual.		Section 2.2, Rationale for the Study Design; Section 4.4.1, Female Contraception; Section 5.2.2, Prohibited Treatment; Section 6.2.3, Dosing; Section 8.1.8, Abuse, Misuse, Overdose, and Medication Error
Corrected the unit of measure for hemoglobin from mg/dL to g/dL.		Section 6.2.3, Dosing
Clarified timing of comorbidity status evaluation is at Visit 6/Week 4 and Visit 10/Week 8.		Section 7.1.2, Study Drug Administration Period
Clarified follow-up to closure of unresolved serious adverse events (SAEs) rather than AEs at end of study.		Section 7.1.3, Follow-up Period; Section 8.1, Definition of Adverse Events, Period of Observation, Recording of Adverse Events
Corrected pregnancy reporting information to indicate that it is the investigator's responsibility to obtain pregnancy outcome/infant condition information within approximately 30 calendar days and 1 year postpartum. Removed requirement for a copy of the Shire Investigational and Marketed Products Pregnancy Report Form being sent to the CRO/Shire medical monitor using details specified in the emergency contact information section of the protocol.		Section 8.1.7, Pregnancy
Corrected information regarding reporting of SAEs.		Section 8.2.2, Reporting Procedures
Removed confidence intervals from 3 secondary efficacy endpoints as they are not clinically meaningful for these analyses.		Section 9.8.5, Secondary Efficacy Endpoints
Updated Appendix 1, Protocol History to include Protocol Amendment 5 and added the summary of change information from Protocol Amendment 4.		Appendix 1, Protocol History
[redacted]		[redacted]

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Amendment 4 to Protocol SHP620-302 incorporated the following major changes:

- Expanded eligibility criteria for viral load and creatinine clearance rate (CrCl).

- Added a third viral-load stratum for subjects with very low viral load (CMV DNA ≥1365 IU/mL to <2730 IU/mL in whole blood or ≥455 IU/mL to <910 IU/mL in plasma at baseline) and high-risk infection, in addition to the existing low viral-load (CMV DNA ≥2730 IU/mL to <27300 IU/mL in whole blood or ≥910 IU/mL to <9100 IU/mL in plasma) and high viral-load (CMV DNA ≥27300 IU/mL in whole blood or ≥9100 IU/mL in plasma) strata.
- 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) for Study SHP620-303.
- Added a visit 4 days after starting new therapy with a narrow therapeutic index immunosuppressive agent for subjects who begin new therapy during the course of the treatment period to align the protocol with a recent recommendation from the DMC for Study SHP620-303.
- Updated contact list, including removal of contacts for sites in Latin America.
- Updated safety reporting contacts to a single Shire Global Safety e-mail and fax contact per revised safety reporting procedures.
- Added exclusion for concomitant letermovir and specified required washout period.
- Clarified end of period for collecting nonserious AEs as up to 30 days after the last dose of study medication.
- Modified the definition of overall study AEs to include events during the overall study period through the end of study observation, regardless of initiation of alternative anti-CMV treatment.
- Modified criteria for reporting of CMV as an AE or SAE to harmonize with the reporting format used in Study SHP620-303.
- Updated Table 12 Assessments of Responders for Key Secondary Endpoint (confirmed CMV viremia clearance at the end of Study Week 8 through Week 16) to ensure assessment of responder rates consistent with assessment specified in Study SHP620-303.
- Eliminated the Hematopoietic Cell Transplant Comorbidity Index (HCT-CI) assessment and deleted Appendix 5 containing the index.
- Clarified language regarding starting dosage regimens, as updated entry criteria require expansion of starting doses.

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- Added GVHD assessment criteria forms from publications cited in new Appendix 8 (formerly Appendix 9, containing only citation references) and added tables for GVHD diagnosis criteria to new Appendix 9 (formerly Appendix 10, containing only citation references).

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 Amendment		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **05 Feb 2019**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated Sponsor representative to [redacted], MD.		Protocol Signature Page
Removed HCT CI from list of abbreviations.		Abbreviations
Updated Emergency Contact Information, including removal of hotline numbers for Latin America, and removal of specific medical monitor contacts.		Emergency Contact Information
Updated product quality complaint reporting contact to a single e-mail and phone contact.		Product Quality Complaints
Removed Latin America from listed Sites and Regions.		Synopsis, Section 3.3 Sites and Regions
Modified inclusion criterion 4 for viral load from ≥910 IU/mL in plasma or ≥2730 IU/mL in whole blood to ≥455 IU/mL in plasma or ≥1365 IU/mL in whole blood to include a very low viral-load stratum for high-risk subjects, in addition to the existing high and low viral load strata.		Synopsis, Table 1, Section 3.1 Study Design and Flow Chart; Section 4.1 Inclusion Criteria; Section 8.1.5 Disease Under Study; Section 9.8.4 Subgroup Analyses
Modified inclusion criterion 7d for CrCl from 60 mL/min to 30 mL/min.		Synopsis, Section 4.1 Inclusion Criteria
Added letermovir to exclusion criterion 5 and specified washout.		Synopsis, Section 4.2 Exclusion Criteria
Removed details of washout for anti-CMV agents from exclusion criterion 6.		Synopsis, Section 4.2 Exclusion Criteria
Added requirement for negative result of HIV testing within 3 months prior to start of study treatment to exclusion criterion 17.		Synopsis, Table 1, Section 3.1 Study Design and Flow Chart; Section 4.2 Exclusion Criteria; Section 7.2.3.5
Specified that starting dosage of valganciclovir could be adjusted for renal function at screening; removed statement of assumption of only mild renal impairment.		Synopsis; Section 3.1 Study Design and Flow Chart

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Protocol Amendment		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **05 Feb 2019**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Removed additional table listing valganciclovir dose adjustments for subjects with both neutropenia and renal impairment as redundant with table describing dose adjustment for renal impairment.		Synopsis; Section 6.2.3 Dosing (previous Table 8)
Modified Study Flow Chart, Schedule, and Procedures to include new visit 2A for subjects receiving tacrolimus, cyclosporine, everolimus, or sirolimus at baseline, added description of local lab testing of potassium and magnesium.		Synopsis, Table 1, Section 3.1 Study Design and Flow Chart; Section 7.2.3.5 Clinical Laboratory Evaluations
Modified the definition of the overall study period for the summary of overall study AEs as including the entire study period through the end of study observation, regardless of initiation of alternative anti-CMV treatment.		Synopsis; Section 9.9
[redacted]		[redacted]
Added minimum washout window of 3 days prior to first dose of study medication for letermovir.		Section 5.2.2 Prohibited Treatment, Table 4
Updated event reporting procedure to specify a single e-mail and fax contact for reporting of SAEs and pregnancies and updated department name to Global Drug Safety.		Section 8.2.2 Reporting Procedures; Section 8.2.4 Serious Adverse Event Collection Time Frame
Added a column for additional visit 2A to collect the following assessments: Hematology/Chemistry, Immunosuppressant drug concentration levels, Adverse events, Study diary, Concomitant meds, Therapies, and Procedures.		Table 1; Section 7.1.2 Study Drug Administration Period
Added new footnote and text explanation that Visit 2A is required only for subjects receiving tacrolimus, cyclosporine, everolimus, or sirolimus, and will occur at Day 4±1 day for subjects receiving agent at baseline or 4±1 day after initiating for those subjects who start after baseline.		Table 1, Footnotes; Section 7.1.2 Study Drug Administration Period
Clarified that local laboratory will assess potassium and magnesium levels at Visit 2A (Day 4±1 day for subjects receiving tacrolimus, cyclosporine, everolimus, or sirolimus at baseline, and 4±1 day after initiation of treatment for subjects initiating treatment with any of these agents after baseline during the treatment period).		Table 1; Footnote h; Section 7.2.3.5 Clinical Laboratory Evaluations
Clarified that nonserious AEs occurring only during the study or within 30 days of last dose of study medication will be collected.		Table 2; Section 7.1.3 Follow-up Period; Section 7.2.3.6 Adverse Event Collection
Updated timeframe for collection of medical history data from 5 years to 2 years.		Section 7.2.3.1 Medical History
Specified requirements for prior hepatitis testing within 3 months before randomization.		Section 7.2.3.5 Clinical Laboratory Evaluations

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Protocol Amendment		
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Amendment Number **4**	**Amendment Date** **05 Feb 2019**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated the blood volume expected to be drawn from each subject to include additional volumes for subjects receiving tacrolimus, cyclosporine, everolimus, or sirolimus.		Section 7.2.5 Volume of Blood to Be Drawn from Each Subject, Table 8
Clarified criteria for reporting CMV infection as an AE or as an SAE.		Section 8.1.5 Disease Under Study, Table 9
Clarified that the Safety Set will be used for analyses of safety endpoints.		Section 9.7 Study Population
[redacted]		[redacted]
Clarified that the primary analysis of safety will be based on the on-treatment observation period.		Section 9.9 Safety Analyses
Redefined treatment-emergent adverse events to include events with start dates before initiation of study treatment that increase after the first dose of study treatment, as well as events with start dates after the first dose.		Section 9.9 Safety Analyses
Specified that clinical laboratory evaluations would be assessed for on-treatment and overall study periods.		Section 9.9 Safety Analyses
Added study treatment dose adjustments due to AEs as a single safety endpoint, and removed specific endpoints of valganciclovir dose adjustment/interruptions and maribavir dose interruptions for AEs.		Section 9.9 Safety Analyses
Removed specific examples of adverse events of special interest, and referred instead to Section 8.1.4.		Section 9.9 Safety Analyses
Removed blood product transfusions and invasive bacterial or fungal infections as separate safety endpoints, and noted inclusion of invasive bacterial and fungal infections with discussion of analyses of adverse events of special interest.		Synopsis, Section 9.9 Safety Analyses
Combined vital sign measurements, physical examination, and ECG as safety assessments.		Synopsis, Section 9.9 Safety Analyses
Removed statement that a shift table summarizing changes from normal and vice versa for all laboratory tests, and added a statement that shifts in National Cancer Institute Common Toxicity Criteria toxicity grades from baseline to maximum grade postbaseline will be analyzed for the on-treatment and overall study periods.		Section 9.9 Safety Analyses
Added statement that transfusions of hematopoietic growth factors, blood, and blood products will be summarized.		Section 9.9 Safety Analyses
Specified that treatment-emergent shifts to grade 3 or grade 4 neutropenia from lower grade to maximum grade will each be summarized for the on-treatment period and the overall study period, and that time to development of neutropenia will be evaluated.		Section 9.9 Safety Analyses

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Protocol Amendment		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **05 Feb 2019**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Added statement that study treatment dose adjustment, specifically valganciclovir dose adjustment and interruptions for neutropenia or renal function impairment or other AE, and maribavir dose interruptions for any AE, will be summarized.		Section 9.9 Safety Analyses
Revised assessment of responders for the key secondary endpoint to be aligned with assessment methods used in Study SHP620-303.		Synopsis; Table 11
Deleted previous Appendix 5, The Hematopoietic Cell Transplant Comorbidity Index; renumbered subsequent appendices 6 to 11 as Appendices 5 to 10.		(previous) Appendix 5; (new) Appendices 5 to 10.
Restored figure attachments for new Appendix 8, Recommendations for Chronic GVHD Diagnosis and Grading; restored tables to Appendix 9, Diagnostic Criteria for Chronic GVHD.		(new) Appendix 8, (new) Appendix 9

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Amendment 3 to Protocol SHP620-302 incorporated the following major changes:

- Storage conditions of investigational product were revised.

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 Amendment		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **01 Sep 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Added reference to the pharmacy manual		Section 6.3.1
Revised storage conditions: • The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. ~~Maribavir and corresponding placebo tablets will be stored at room temperature (15°C 30°C 86°F). Valgancielovir tablets do not require any special storage conditions and should be stored in a similar condition as maribavir tablets to maintain the blind.~~ Limited responsibility for storage 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.		Section 6.3.2

Protocol Amendment		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **01 Sep 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
• Investigational products must be stored in accordance with labeled storage conditions **of up to 25°C or 77°F.**		
Added sentence after final bullet point: **For subjects who permanently discontinue study treatment early but do not withdraw consent, refer to Section 4.5 regarding modified schedule of assessments.**		Section 7.1.2

Amendment 2 to Protocol SHP620-302 incorporated the following major changes:

- Stated "CMV central nervous system (CNS) infection" as one of the reasons for discontinuation and/or withdrawal.
- Added basic descriptive statistics generally for all endpoints.
- Added sensitivity analysis for investigation of homogeneity of treatment effect across centers/regions.
- Added rules for conducting the interim population PK analysis.

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.

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Protocol Amendment		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **01 Jun 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Revised definition of the terms: • **Resistant** to "~~Documented failure to achieve >1 log10 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).~~ Documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir, valganciclovir, foscarnet, and/or cidofovir." • **Symptomatic subjects** to: "~~Transplant recipients with refractory CMV infections, including CMV infections with confirmed resistance to 1 of the anti-CMV agents (ganciclovir, valganciclovir, foscarnet, or cidofovir), who have tissue invasive CMV disease, as initially determined by the investigator at baseline.~~ HSCT recipients who have tissue-invasive CMV		Definitions

Protocol Amendment		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **01 Jun 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
disease as determined by the investigator according to the criteria specified by Ljungman et al. 2016." • **Asymptomatic subjects** to "~~Transplant recipients with refractory CMV infections, including CMV infections with confirmed resistance to 1 of the anti-CMV agents (ganciclovir, valganciclovir, foscarnet, or cidofovir), who do not have tissue invasive CMV disease as diagnosed by the investigator at baseline~~. HSCT recipients who do not have tissue-invasive CMV disease as determined by the investigator according to the criteria specified by Ljungman et al. 2016."		
Added rationale for dosing of adolescents: 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. Per Lu and Rosenbaum (2014), the expression of CYP3A4 and CYP 2C19, which are primary enzymes for maribavir metabolism in the liver, occurs during the first weeks of life. The expression of CYP1A2, which is also involved with maribavir metabolism, the last enzyme to develop, is present by 1 to 3 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 (≥16 and <18 years of age) is not expected to be different from adults at the same oral dose.		Section 2.3
Moved CMV central nervous system (CNS) infection as a reason for discontinuation and/or withdrawal from Section 5.2.2 (Prohibited Treatment) to Section 4.5.1 (Reasons for Discontinuation and/or Withdrawal).		Section 4.5.1
Changed pharmacokinetic sample collection for adolescent subjects from ≥12 to <18 years of age to ≥16 to <18 years of age		Section 7.1.2
Moved description of summary statistical methods from "Exploratory Efficacy Endpoints" to "Efficacy Analyses": Summary descriptive 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~~ analysis set unless otherwise specified. 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.		Section 9.8, Section 9.8.6
Added another example of a sensitivity analysis of the primary endpoint of confirmed CMV viremia clearance at Week 8: • The primary efficacy endpoint analysis will be repeated by using the CMV DNA level used for the randomization rather than the CMV DNA levels based on central laboratory values as one of the stratification factors.		Section 9.8.1

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Amendment Number **2**	**Amendment Date** **01 Jun 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Revised description of subgroup analyses as follows: ~~The primary and key secondary endpoints will be examined for the following subgroups~~ The proportion of responders and the corresponding 95% CI will be summarized for primary and key secondary endpoints by treatment group for the following subgroups (inclusive, but not limited to): • Cytomegalovirus DNA viral load (high, low) • Acute GVHD presence/absence at baseline • Adolescents ≥16 to <18 years of age (exploratory analysis: may be conducted if sample size is adequate) • Enrolling regions (enrolling centers will be grouped by geographic locations to explore homogeneity of treatment effect across regions).		Section 9.8.4
Added more information regarding interim analyses: If needed, an interim population PK analysis of maribavir PK data obtained from the study subjects will be performed. ~~by an independent unblinded team/CRO.~~ Interim population PK analysis will be performed by an independent unblinded team or CRO who will have no involvement in the conduct of the study. Results from this analysis will not be shared with any members of the study team until after database lock. Rules governing this process are detailed in the sponsor's (or designee's) standard operating procedures.		Section 9.10.3

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Amendment 1 to Protocol SHP620-302 incorporated the following major changes:

- Modification of primary, key secondary, and secondary objectives to include subjects who discontinue study treatment early and meet the criteria of confirmed CMV viremia clearance as responders in the primary efficacy analysis.
- Modified Inclusion Criterion 5 to indicate that the current CMV infection must be the first episode of CMV viremia after HSCT, either primary or reactivation.
- Clarified Inclusion Criterion 8 to indicate that urine pregnancy tests may be done per institutional requirements in addition to serum; however, they are not sufficient for eligibility determination.
- Added a new Exclusion Criterion 3 to exclude subjects with recurrent CMV infection.
- Amended Exclusion Criterion 6 to indicate that subjects must not be on treatment with anti-CMV agents (ganciclovir, valganciclovir, foscarnet or cidofovir) for the current CMV infection for longer than 72 hours.

Note: A subject who is receiving these anti-CMV agents must discontinue their use before the first dose of study treatment. A subject who may be receiving cidofovir must discontinue this antiviral at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment.

Note: Subjects who were administered these anti-CMV agents for prophylaxis should have these treatments completed at least 2 weeks prior to the study entry or start of the treatment for current infection, whichever comes first, and have undetectable CMV DNA (based on local laboratory) for at least 2 weeks between the completion of the anti-CMV prophylaxis and onset of the current infection.

- 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.
- Clarified Exclusion Criterion 16 indicating that known (previously documented) HIV historical results will be accepted and no additional study testing will be required.
- Added an intensive PK sampling schedule for adolescents.
- An additional pregnancy test at 4 weeks (Visit 6/Week 4) to obtain a monthly testing 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).
- 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 CYP2C19 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.

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.

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Protocol Amendment		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **02 Mar 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated signatory to Obiamiwe Umeh, MD, MSc.		Protocol Signature Page
Added "FU = follow-up" to the abbreviations list.		Abbreviations
Created a list of definitions pertaining to evaluations/analysis for the study for easy access and convenience.		Definitions
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
Modification of 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
Modification of 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 at Study Week 8 will be considered as responders in the efficacy analysis.		Synopsis, Section, 2.4.2, Section 9.8.2
Modification of secondary objectives and corresponding endpoints and analyses as follows. Added the former primary and key secondary objectives as secondary objectives: • "To compare the efficacy of maribavir to valganciclovir in CMV viremia clearance after 8 weeks of treatment of asymptomatic CMV infection in HSCT recipients." • "To compare the efficacy of maribavir and valganciclovir on maintenance of CMV viremia clearance, achieved after completion of 8 weeks of treatment, through Study Weeks 12 (4 weeks post-treatment period), 16 (8 weeks of post-treatment/follow-up phase), and 20 (12 weeks post-treatment)." Added the secondary objectives: • "To assess the maintenance of CMV viremia clearance achieved at the end of Study Week 8, through Weeks 12 (4 weeks post-treatment) and 20 (12 weeks post-treatment)." • "To evaluate the incidence of recurrence of confirmed CMV viremia in the 2 study treatment arms during the first 8 weeks of the study, during the 12 weeks of the follow-up study phase, and at any time during the study." • "To evaluate the incidence of recurrence of confirmed CMV viremia in the 2 study treatment arms when subjects are on treatment and off treatment."		Synopsis, Section 2.4.3, Section 9.8.5

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Amendment Number **1**	**Amendment Date** **02 Mar 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Deleted the following objective and the corresponding endpoint since it became redundant with the modified primary objective: • ~~"To assess the two study treatment arms for maintenance of CMV viremia clearance achieved while on study treatment, irrespective of its duration, at 8 weeks of study"~~		
[redacted]		[redacted]
Updated the published article Ljungman 2002 with Ljungman 2016 where relevant.		Section 1.1, Section 3.1, Section 7.2.23
Modified Inclusion Criterion 5 to exclude subjects with recurrent CMV infection: "The current CMV infection must be the first episode of CMV viremia after HSCT, either primary or reactivation."		Synopsis, Section 4.1
Clarified Inclusion Criterion 8 to indicate that urine pregnancy tests may be done per institutional requirements; however, they are not sufficient for eligibility determination.		Synopsis, Section 4.1
Added a new Exclusion Criterion 3 to exclude subjects with recurrent CMV infection: "Be presenting with recurrent CMV infection (defined as a new detection of CMV infection) in a subject who had at least one previously documented episode of CMV infection post-transplant, and who has had at least 2 weeks of undetectable CMV DNA between the episodes (during active surveillance, based on same local laboratory and same sample type). The subject must also have been off any anti-CMV treatment between the current and prior infection. Otherwise, the current infection may be considered continuation of the prior infection."		Synopsis, Section 4.2
Amended Exclusion Criterion 6 to indicate that subjects must not "be on treatment" with anti-CMV agents (ganciclovir, valganciclovir, foscarnet or cidofovir) for the current CMV infection for longer than 72 hours. **Note**: A subject who is receiving these anti-CMV agents must discontinue their use before the first dose of study treatment. A subjects who may be receiving cidofovir must discontinue this antiviral at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment.		Synopsis, Section 4.2

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Description and Rationale for Change		**Section(s) Affected by Change**
Note: Subjects who were administered these anti-CMV agents for prophylaxis should have these treatments completed at least 2 weeks prior to the study entry or start of the treatment for current infection, whichever comes first, and have undetectable CMV DNA (based on local laboratory) for at least 2 weeks between the completion of the anti-CMV prophylaxis and onset of the current infection."		
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 (Table 4)
Clarified Exclusion Criterion 16 indicating that known historical results will be accepted and no additional study testing will be required. "Have known (previously documented) positive results for human immunodeficiency virus (HIV)."		Synopsis, Table 1 (footnote "i"), Section 3.1, Section 4.2, Section 7.1.1, Section 7.2.3.5 (Virology)
Removed text indicating that PK samples collected from subjects receiving valganciclovir would be discarded: "~~Pharmacokinetic samples collected from subjects receiving valganciclovir will be discarded prior to analysis.~~"		Synopsis, Section 7.2.4.1
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 Table 11 and Table 12 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 ≥16 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
Per CTFG requirements, added an additional pregnancy test at 4 weeks (Visit 6/ Week 4) so that tests are performed at a regular interval.		Table 1, Section 7.1.2
Added intensive PK sampling schedule for adolescents.		Table 1 (footnote "o"), Section 7.2.4.1
Added text for the study rationale regarding pediatric subjects.		Section 2.2

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Amendment Number **1**	**Amendment Date** **02 Mar 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
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 childbearing potential participating in the study. Added that 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 childbearing potential and that the vasectomized partner has received medical assessment of the surgical success.		Section 4.4.1
Added the following to male contraception per the Clinical Trial Facilitation Group requirements (CTFG): "Male subjects will be required to use a condom in conjunction with a highly effective method of birth control for their female partners of childbearing age. 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 or valganciclovir). 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. Male subjects must not donate sperm until 90 days after the last dose of study treatment".		Section 4.4.2
Added caution and recommendation for careful monitoring of concentration levels of concomitant medications that are substrates of CYP2C19 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
Corrected error in cited week number for end of study visit.		Section 7.1.3
Added additional clinical laboratory evaluations for: Hematology: manual differential results for band neutrophils, basophils, eosinophils, lymphocytes, monocytes, segmented neutrophils, and total neutrophils. Urinalysis: leukocyte esterase in the microscopic evaluation. Other: immunoglobulins IgG and immunoglobulins total (a total of IgG + IgA + IgM) with no reference ranges associated with the immunoglobulins total value.		Section 7.2.3.5
[redacted]		[redacted]

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Amendment Number **1**	**Amendment Date** **02 Mar 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Added the additional blood draw volume required for intensive PK sampling for adolescents: "Subjects between the ages of 12 to <18 years will have an additional 24 mL of blood drawn for intensive PK visits."		Section 7.2.5, Table 8
Amended Section 8.2.7 to include fatal outcomes: "The study population is HSCT recipients with CMV infections. The following SAEs are common in this study population and are anticipated to occur, hence these SAEs (including fatal outcome) 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, [redacted] • Any other viral, bacterial, or fungal infection • Acute and chronic GVHD" • Reactivation/progression of the malignancy or other disease, which is an underlying disease, that led to the transplant This includes fatal outcomes of the aforementioned SAEs. *Maribavir Phase 2 (studies 1263-202 and 1263-203) data will be used as reference.		Section 8.2.7
Added reference to updated industry regulation: Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2) Current Step 4 version dated 09 November 2016.		Section 10.1.1, Section 10.2.1
Updated the table in Appendix 3 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 Sections, as needed

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APPENDIX 2 CHILD-PUGH CLASSIFICATION OF CHRONIC LIVER DISEASE

Table A1 Child-Pugh Classification of Chronic Liver Disease

Score	Bilirubin (mg/dL)	Albumin (gm/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

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APPENDIX 3 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.

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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.

The following mutations have been determined to confer resistance to ganciclovir/valganciclovir or cross-resistance to foscarnet, cidofovir or maribavir (Campanini et al., 2012; Cherrier et al., 2018; Chou, 2020; Chou and Bowlin, 2011; Fischer et al., 2016; Gilbert et al., 2011; Harada et al., 1997; Van Leer Buter et al., 2019; Viracor, n.d.; Wong et al., 2019). The PRS and MRS populations will be defined by the presence of one or more of these mutations at study baseline genotypic results performed by the central specialty laboratory.

Table A2 Known Ganciclovir/Valganciclovir Resistance Mutations

UL97 Mutation	Ganciclovir/Valganciclovir
F342S	R (also MBV-R)
F342Y	R (also MBV-R)
V356G	R (also MBV-R)
K359E	R
K359Q	R
L405P	R
D456N	R (also MBV-R)
M460I	R
M460T	R
M460V	R
M460L	R*
V466G	R (also MBV-R)
C480F	R (also MBV-R)
C480R	R (also MBV-R)
C518Y	R
H520Q	R
P521L	R (also MBV-R)
A590T	R[a]
del590 to 600	R[a]
del590 to 603	R[a]
del591 to 594	R
del591 to 607	R
A591D	R[a]
A591V	R
C592G	R[b]
C592F	R[a]
del594 to 601	R[a]
A594E	R
A594G	R
A594P	R
A594S	R
A594T	R
A594V	R

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Table A2 Known Ganciclovir/Valganciclovir Resistance Mutations

UL97 Mutation	Ganciclovir/Valganciclovir
L595F	R
L595S	R
L595W	R
L595T	R[a]
del595	R
del595 to 603	R
del596	R
E596G	R
E596Y	R
del597 to 598	R
del597 to 599	R
del597 to 600	R[a]
del597 to 603	R[a]
N597I	R[a]
G598S	R
G598V	R[a]
del599	R
K599M	R[a]
K599T	R
del599 to 603	R[a]
del600	R
del601	R
del600 to 601	R
del601 to 602	R
del601 to 603	R
C603R	R
C603S	R
C603W	R
C603Y	R[a]
A606D	R[a]
C607F	R
C607S	R[a]
C607Y	R

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Table A2 Known Ganciclovir/Valganciclovir Resistance Mutations

UL97 Mutation	Ganciclovir/Valganciclovir
I610T	R
A613V	R
del617	R (also MBV-R)

MBV=maribavir; R=resistance
[a] Clinical isolates but unconfirmed by Marker transfer.
[b] Alone confers modest resistance. When found in conjunction with UL54 del 981 to 982, there is a much higher level of resistance.
Note: Mutations in bold letters are the most common mutations.

Table A3 UL54 Resistance Mutations, Including Cross-resistance

UL54 Mutation	Cidofovir	Foscarnet	Ganciclovir
S290R	S	R	S
D301N	R	S	R
E303D[a]	R	S	R
E303G[a]	R	S	R
N408D	R	S	R
N408K	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[a]	R	S	R
P488R	R	S	R
K493N	R	R	R
N495K	S	R	R
P497S	R	S	R
K500N	R	S	R
L501F	R	S	R
L501I	R	S	R

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Table A3 UL54 Resistance Mutations, Including Cross-resistance

UL54 Mutation	Cidofovir	Foscarnet	Ganciclovir
T503I	R	S	R
A505V[a]	R	S	R
K513N	R	S	R
K513E	R	S	R
K513R	R	S	R
K513T	R	S	R
D515E	S	S	R
D515Y	R	S	R
L516R	R	S	R
L516P	R	S	R
L516W	R	S	R
I521T	R	S	R
P522A	R	S	R
P522S	R	S	R
del524	R	S	R
V526L	R	S	R
C539G	R	S	R
C539R	R	S	R
D542E[a]	R	S	S
A543P	R	S	R
L545S	R	S	R
L545W	R	S	R
T552N	S	R	R
L565V	R	R	R
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
V715A	S	R	S
V715M	S	R	S

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Table A3 UL54 Resistance Mutations, Including Cross-resistance

UL54 Mutation	Cidofovir	Foscarnet	Ganciclovir
I726T	S	S	R
I726V[b]	R	S	R
E756K	R or S[b]	R	R
E756D	S	R	S
E756Q	S	R	S
L773V	R	R	R
L776M	S	R	R
V781I	S	R	R[b]
V787A	S	R	R
V787E	R	R	R
V787L	S	R	R
L802M	S	R	R or S[b]
K805Q	R	S	S
A809V	S	R	R
V812L[a]	R	R	R
T813S	R	R	R
T821I	S	R	R
V823A	R	S	R
P829S	S	S	R
A834P	R	R	R
T838A	S	R	S
G841A	R	R	R
G841S	S	R	R
M844T	S	R	S
M844V	S	R	R
V946L	S	R	S
E951D	S	R	R
L957F	S	S	R
del981 to 982	R	R	R
A987G	R	S	R
A987V	S	R	S

R=resistant; S=sensitive
[a] Also confers resistance to brincidofovir.
[b] Low grade or variable resistance.

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APPENDIX 4 DEFINITIONS OF TISSUE INVASIVE CMV 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., 2017; please refer to the citation for full details on the definitions of CMV disease). 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 polymerase chain reaction (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.

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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 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 or retina taken during ophthalmological exam should be provided.

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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.

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APPENDIX 5 KARNOFSKY PERFORMANCE STATUS SCALE

The Karnofsky Performance Scale Index (Table A4) 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.

Table A4 Karnofsky Performance Scale Index

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

Sources:

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: M139-44.

de Haan R, Aaronson A, et al. Measuring quality of life in stroke. Stroke. 1993; 24:320-7.

Hollen PJ, Gralla RJ, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. Cancer. 1994; 73: 2087-98.

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APPENDIX 6 [redacted]

[redacted]

APPENDIX 7 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).

Table A6 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)

BSA=body surface area; GI=gastrointestinal; GVHD=graft-versus-host disease

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.

Source: Table 1, Harris et al., 2016

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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.

Table A7 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

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APPENDIX 8 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).

Figure A-1. Organ Scoring of Chronic GVHD

	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, capable of self-care, >50% of waking hours out 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):*_____				

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Figure A-1. Organ Scoring of Chronic GVHD (continued)

	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):*_____				

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Figure A-1. Organ Scoring of Chronic GVHD (continued)

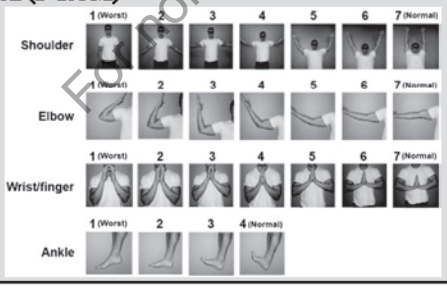
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	☐ Tightness of arms or legs OR joint 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)



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ADL=activities of daily living; ALT=alanine aminotransferase; AP=alkaline phosphatase; BSA=body surface area; ECOG=Eastern Cooperative Oncology Group; FEV1=forced expiratory volume in 1 second; GVHD=graft-versus-host-disease; KPS=Karnofsky Performance Status; LFTs=liver function tests; LPS=Lansky Performance Status; 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 Supplementary Figure: Figure A-2).

** 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.

Figure A-2. Supplemental Genital Tract Chronic GVHD Scoring and Supplemental Skin GVHD Scoring (supplemental material for Jagasia et al. [2015], Figure 1.)

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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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 (Table 2 in the supplemental material for Jagasia et al. [2015])

Table A8 NIH Global Severity of Chronic GVHD

Mild chronic GVHD 1 or 2 organs involved with no more than score 1 plus Lung score 0
Moderate chronic GVHD 3 or more organs 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 At least 1 organ with a score of 3 OR Lung score of 2 or 3
Key points: In skin: higher 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

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APPENDIX 9 DIAGNOSTIC CRITERIA FOR CHRONIC GVHD

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

Table A9 Signs and Symptoms of Chronic GVHD

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive[a] (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities[b]	Common[c] (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)	

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Table A9 Signs and Symptoms of Chronic GVHD

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive[a] (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities[b]	Common[c] (Seen with Both Acute and Chronic GVHD)
Genitalia	Lichen planus–like features Lichen sclerosus–like features	Erosions Fissures Ulcers		
Females	Vaginal scarring or clitoral/labial agglutination			
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[d]	Air trapping and bronchiectasis on chest CT	Cryptogenic organizing pneumonia Restrictive lung disease[e]	
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to fasciitis or sclerosis	Myositis or polymyositis[f]	Edema Muscle cramps Arthralgia or arthritis	

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Table A9 Signs and Symptoms of Chronic GVHD

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive[a] (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities[b]	Common[c] (Seen with Both Acute and Chronic GVHD)
Hematopoietic and Immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hyper-gammaglobulinemia Autoantibodies (AIHA, ITP) Raynaud's phenomenon	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

AIHA=autoimmune hemolytic anemia; ALT=alanine aminotransferase; BOS=bronchiolitis obliterans syndrome; GVHD=graft-versus-host disease; ITP=idiopathic thrombocytopenic purpura.

[a] In all cases, infection, drug effect, malignancy, or other causes must be excluded.

[b] Can be acknowledged as part of the chronic GVHD manifestations if diagnosis is confirmed.

[c] Common refers to shared features by both acute and chronic GVHD.

[d] Bronchiolitis obliterans syndrome can be diagnostic for lung chronic GVHD only if distinctive sign or symptom present in another organ (see text).

[e] Pulmonary entities under investigation or unclassified.

[f] Diagnosis of chronic GVHD requires biopsy.

Source: Table 1, Jagasia et al., 2015

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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.

Table A10 Histological Criteria for GVHD by Organ System

Organ or System	Minimal Criteria for Acute/Active GVHD[a]	Specific Criteria for Chronic GVHD[b]
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

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Table A10 Histological Criteria for GVHD by Organ System

Organ or System	Minimal Criteria for Acute/Active GVHD[a]	Specific Criteria for Chronic GVHD[b]
Oral/oropharyngeal mucosa and conjunctiva	Lichenoid interface lymphocytes with infiltration of mucosa (exocytosis) and variable apoptosis[c]	
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[d]
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[e]
Kidney		Membranous nephropathy, minimal change disease
Lesions of Uncertain Pathogenesis		
Lung		COP
Skeletal Muscle		Myositis

CBO=constrictive bronchiolitis obliterans; COP=cryptogenic organizing pneumonia; GVHD=graft-versus-host-disease

[a] 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.

[b] 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.

[c] 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.

[d] 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.

[e] Constrictive bronchiolitis obliterans 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

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C. Recommendations for Final Diagnosis Categories of GVHD (Table 2 in Shulman et al., 2015)

Table A11 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

CMV=cytomegalovirus; GVHD=graft-versus-host-disease; MMF=mycophenolate mofetil

Source: Table 2, Shulman et al., 2015

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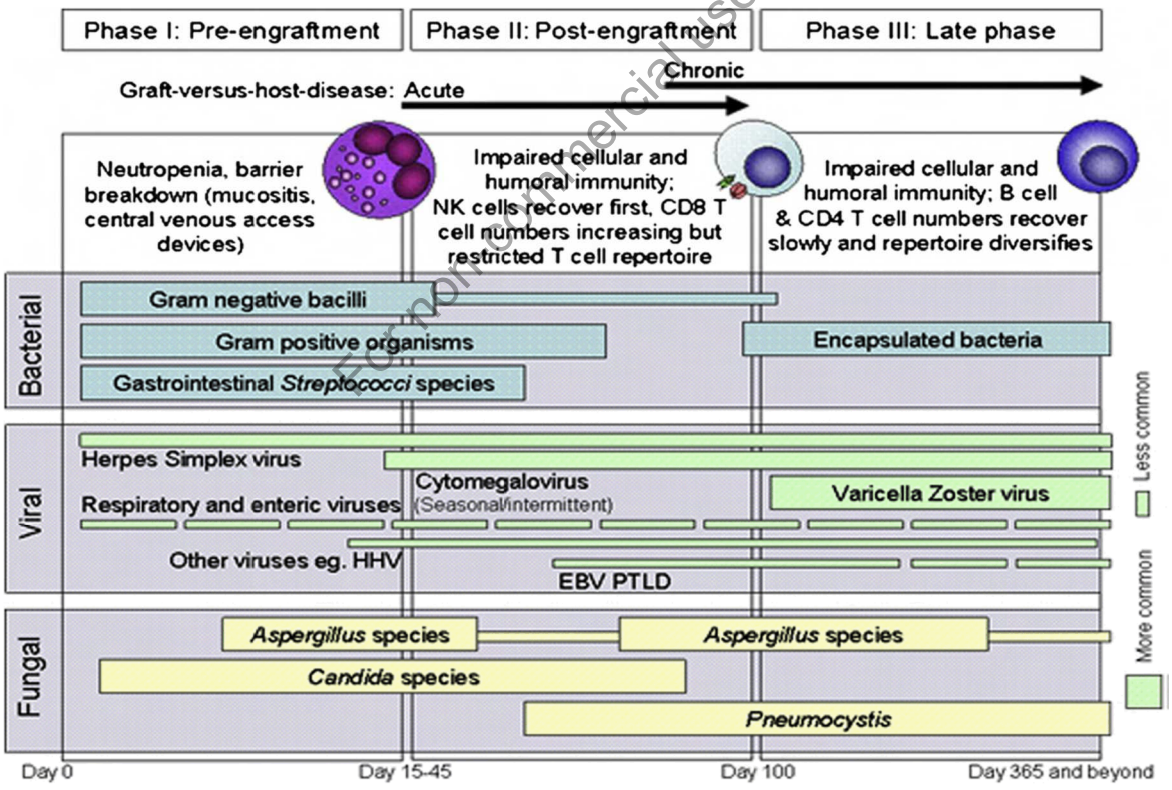
APPENDIX 10 BACTERIAL AND FUNGAL INFECTIONS ASSESSMENT

In Hematopoietic Stem Cell Transplant (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 comorbidities, 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).

Figure A-3. Phases of Opportunistic Infections Among Allogeneic HSCT Recipients



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EBV=Epstein-Barr virus; HHV=human herpes virus; HSCT=Hematopoietic Stem Cell Transplant; PTLD=post-transplant lympho-proliferative disease

Phase I: <15-45 days post-transplant; Phase II: 30-100 days post-transplant; Phase III: >100 days after HSCT.

Source: 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 postengraftment 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 postengraftment 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.

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Table A12 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 bacterial and fungal infections diagnosed as possible/probable or proven per the criteria described by Boeckh et al. (2015) are reported.

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 (eg, 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

A. 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.

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B. 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.

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