PROTOCOL: TAK-620-1020

TITLE:	A Phase 1, Open-label, Randomized, Cross-over Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of a Single Oral Dose of Maribavir Administered in Healthy Japanese Subjects Compared with Matched, Healthy, Non-Hispanic, Caucasian Subjects and to Assess Dose-Proportionality of 3 Doses of Maribavir in the Japanese Subjects
DRUG:	TAK-620 (Maribavir)
IND:	051001
EUDRACT NO.:	Non-EUDRACT
SPONSOR:	Shire ViroPharma LLC (Shire, [and affiliates]); Shire is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 300 Shire Way, Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	[redacted], DO, FACP
PROTOCOL HISTORY:	Protocol Amendment 1: 08 July 2020 Original Protocol: 03 April 2020

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: DocuSigned by: [redacted]	**Date:** 09-Jul-2020 | 11:32:11 JST
[redacted] MD PhD MPH, Medical Monitor Signing Reason: I approve this document Signing Time: 09-Jul-2020 | 11:31:35 JST 553DE151B602454FBEAAC13589A35005	

Investigator's Acknowledgement

I have read this protocol for Study TAK-620-1020.

Title: A Phase 1, Open-label, Randomized, Cross-over Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of a Single Oral Dose of Maribavir Administered in Healthy Japanese Subjects Compared with Matched, Healthy, Non-Hispanic, Caucasian Subjects and to Assess Dose-Proportionality of 3 Doses of Maribavir in the Japanese Subjects

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 Council for Harmonisation guidelines of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

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

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

Investigator Name and Address: (please hand print or type)	[redacted], DO, FACP

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

Since finalization of the Original Protocol on 03 April 2020, additional feedback has been received from the team that necessitates an amendment to the protocol. The purpose of this amendment is to update the site and principal investigator information and provide further clarification on procedures and safety.

Changes in grammar, spelling, punctuation, format, minor editorial changes (including changes for consistency and clarity), and refinements to the introductory text, list of abbreviations, and cross references are not reflected in this change summary.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **08 July 2020**	**Global**
Description of Change	**Rationale**	**Section(s) Affected by Change**
Updated the principal/coordinating investigator information as site changed	Update to site and principal investigator	Cover page; Protocol Signature Page
Updated Medical Monitor information to remove office phone number	Update as office phone is not currently in use	Emergency Contact Information page
Updated e-mail address for reporting product quality complaints	Update contact information for product quality complaints	Product Quality Complaints page
Updated matching criteria for subject enrollment to add sex. Removed statement indicating that there are no gender differences in maribavir PK observed based on historical data, thus subject enrollment is not matched by gender between the Japanese and Caucasian subjects.	Update to control PK variability	Synopsis; Section 3.1, Study Design and Flow Chart; Section 7.2.1, Demographic and Other Baseline Characteristics
Clarified language regarding maribavir PK to indicate that the doses of 200, 400, and 800 mg were selected for evaluating dose proportionality as a more than two-fold differences in systemic exposure to maribavir is not expected in Japanese subjects as compared to Caucasian subjects.	Clarification	Section 3.1, Study Design and Flow Chart;
Removed exclusion criterion 19, current use of antacids, proton pump inhibitors, or H2 antagonists	Update as this criterion is already addressed in other criterion and clarified in Section 4.3, Restrictions	Synopsis; Section 4.2, Exclusion Criteria; Section 4.3, Restrictions
Updated restriction 2 to indicated subjects should refrain from consuming grapefruit or grapefruit juice, oranges, Seville oranges, and products containing these items, vegetables from the mustard green family [eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard], charbroiled meats, and products containing these ingredients).	Update to exclude additional vegetables to align with exclusion criterion 20	Section 4.3, Restrictions

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date 08 July 2020**	**Global**
Description of Change	**Rationale**	**Section(s) Affected by Change**
Added a subsection describing administration of maribavir	Clarification regarding administration process	Section 6.2, Administration of Investigational Product(s)
Added medications taken via injection/infusion	Clarification	Section 7.2.2.1, Medical and Medication History
Removed specific mL volumes for sampling and include only in Table 7, Volume of Blood to be Drawn from Each Subject, updating approximate sample volume, changing HBsAg/HIV/HCV from 5 to 3.5 mL and Biochemistry from 8.5 to 5 mL which are the minimum volumes needed	Update specific volume details recorded in one location, Table 7	Section 7.2.2.6, Clinical Laboratory Tests; Section 7.2.2.9, Serology Screen; Section 7.2.4, Volume of Blood to be Drawn from Each Subject
Clarified that blood sampling assessments should be performed within 30 minutes prior to dose administration. All other Predose assessments should be completed within 60 minutes of dose administration, with the exception of the physical examination which should be completed within 90 minutes of dose administration.	Clarification regarding timing of assessments in the detailed schedule of assessments tables	Table 2, Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 1; Table 3, Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 2; Table 4, Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1'; Table 6, Detailed Schedule of Assessments for Non-Hispanic Caucasian Subjects for Days 1 and 2 of Treatment Period 1
Added that water will be restricted 1 hour before and 1 hour after dosing, and maribavir doses will be administered with a glass (240 mL) of room temperature water	Clarification to be consistent with fasting conditions suggested by FDA guidance (Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations Guidance for Industry, Draft February, 2019)	Synopsis; Table 1, Schedule of Assessments for Subjects of Japanese Descent; Table 2, Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 1; Table 3, Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 2; Table 4, Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 3; Table 5, Schedule of Assessments for Non-Hispanic, Caucasian Subjects; Table 6, Detailed Schedule of Assessments for Non-Hispanic Caucasian Subjects for Days 1 and 2 of Treatment Period 1;

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Description of Change	**Rationale**	**Section(s) Affected by Change**
		Section 3.1, Study Design and Flow Chart; Section 6.2.3 Administration
Added that vomiting will be recorded if it occurs within 4 hours after dosing of the investigational drug (maribavir)	For the purpose of control of PK variability. If vomit happens within the window, PK data from the affected subject in the corresponding treatment period may be excluded from PK data analysis.	Synopsis; Table 1, Schedule of Assessments for Subjects of Japanese Descent; Table 2, Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 1; Table 3, Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 2; Table 4, Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 3; Table 5, Schedule of Assessments for Non-Hispanic, Caucasian Subjects; Table 6, Detailed Schedule of Assessments for Non-Hispanic Caucasian Subjects for Days 1 and 2 of Treatment Period 1; Section 3.1, Study Design and Flow Chart; Section 6.2.3 Administration
Clarified to indicate in footnote that the test for alcohol abuse will be performed on Day -1 using an on-site breathalyzer test.	Clarification	Table 1, Schedule of Assessments for Subjects of Japanese Descent; Table 5, Schedule of Assessments for Non-Hispanic, Caucasian Subjects
Updated to allow randomization will occur in Treatment Period 2, Day -1 or Day 1	Update to allow flexibility to randomize on Day -1 or Day 1	Table 3, Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 2
Corrected table to record weight at Treatment Period 1 Day 1	Correction	Table 6, Detailed Schedule of Assessments for Non-Hispanic Caucasian Subjects for Days 1 and 2 of Treatment Period 1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **08 July 2020**	**Global**
Description of Change	**Rationale**	**Section(s) Affected by Change**
Clarified that rescreening of subjects may be permitted at the discretion of the study Principal Investigator in consultation with the Shire Study Medical Monitor	Clarification	Section 7.1.1.2, Rescreening of Subjects
Removed nonessential details regarding sample size justification	Simplification of sample size text to reduce confusion	Synopsis; Section 8.9, Sample Size Calculation and Power Consideration
Clarified that drugs of abuse, alcohol, and cotinine will be tested at screening and on Day -1 to align with exclusion criterion	Clarification	Table 1, Schedule of Assessments for Subjects of Japanese Descent; Table 5, Schedule of Assessments for Non-Hispanic, Caucasian Subjects
Clarified that all females are required to have a negative pregnancy test	Clarification	Section 4.4.1, Female Contraception; Section 7.2.2.7, Pregnancy Test
Clarified that screen failures will not be captured	Clarification	Section 6.2.1, Allocation of Subjects to Treatment
Corrected dosing for Day 1 of Treatment Period 3 for Japanese subjects. It will be whichever dosage they did not receive on Day 1 of Treatment Period 2 not Day 4	Correction	Section 6.2.2, Dosing
Corrected biochemistry for thyroxine as free T4 will be evaluated not T4 total	Correction	Section 7.2.2.6, Clinical Laboratory Tests
Clarified that populations should be considered sets rather than populations	Clarification to align with Statistical Analysis Plan	Synopsis; Section 8.6, Study Population; Section 8.7.1, Pharmacokinetic Endpoint(s); Section 8.8, Safety Analyses
Corrected PK parameter, changing Vdx/F to Vz/F	Correction	Synopsis; Section 8.7.1, Pharmacokinetic Endpoint(s)
Updated MedDRA version to 23.0 or later	Updated to capture COVID-19 specific terminology	Section 8.8, Safety Analyses

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the "Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious adverse events (AEs) as Required by the Protocol" within 24 hours to the Shire Global Drug Safety Department. The fax number and e-mail address are provided on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO) (as applicable) and Shire Medical Monitor using the details below.

For protocol- or safety-related questions the investigator must contact the Shire Medical Monitor:

[redacted], MD, PhD, MPH

[redacted] Shire Study Medical Monitor

Telephone:

Cell phone: [redacted] (24-hour coverage)

E-mail: [redacted]

For protocol- or safety-related questions or concerns outside of normal business hours, the investigator must contact the Shire Medical Monitor.

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Shire within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis.

A product quality complaint includes any instances where there is an allegation or report relating to Shire licensed or investigational products, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that the product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product quality complaints include, but are not limited to, the following:

Unit issues	• Bottle/vial fill shortage or overage • Tablet damaged/broken • Vial cracked/broken	• Product discoloration
Labeling	• Label missing • Leaflet or Instructions For Use (IFU) missing • Label illegible	• Incomplete, inaccurate, or misleading labeling • Lot number or serial number missing
Packaging	• Damaged packaging (eg, secondary, primary, bag/pouch) • Tampered seals • Inadequate or faulty closure	• Missing components within package
Foreign material	• Contaminated product • Particulate in bottle • Particulate in packaging	

Please report the product quality complaint using the "Product Quality Complaint Data Collection Form" via the email address:

[redacted]

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ABBREVIATIONS

AE	adverse event
AUC	area under the curve
AUC_{last}	area under the curve from the time of dosing to the last measurable concentration
$AUC_{0\text{-}inf}$	area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration
$AUC_{0\text{-}inf}$%extrap	The percent of $AUC_{0\text{-}inf}$ extrapolated, calculated by $(1\text{-}AUC_{last}/AUC_{0\text{-}inf})*100$
β-HCG	beta-human chorionic gonadotropin
BMI	body mass index
BID	twice daily
C_{max}	maximum concentration
CL/F	oral clearance
CMV	cytomegalovirus
CRA	clinical research associate
CRC	clinical research center
CRF	case report form
CRO	contract research organization
CV	coefficient of variation
CV%	percent coefficient of variation
CYP	cytochrome P450
DNA	deoxyribonucleic acid
EC	Ethics Committee
ECG	electrocardiogram
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	hepatitis B surface antibody
HCV	hepatitis C virus
HDPE	high density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplants
IB	Investigator's Brochure

IP	investigational product (investigational drug)
IRB	Institutional Review Board
IV	intravenous
λz	first order rate constant associated with the terminal (log linear) portion of the curve
P-gp	P-glycoprotein
PK	pharmacokinetics
PT	preferred term
QTc	corrected QT interval
QTcF	The corrected QT interval by Fredericia Correction Formula
SAE	serious adverse event
SAP	statistical analysis plan
SOT	solid organ transplant
SUSAR	Suspected Unexpected Serious Adverse Reaction
t1/2	terminal half-life
TEAE	treatment-emergent adverse event
TID	3 times daily
T_{lag}	Delay between the time of dosing and time of appearance of drug (investigational) in plasma in the employed sampling scheme
t_{max}	time of maximum observed concentration sampled during a dosing interval
TSH	thyroid-stimulating hormone
US	United States
US FDA	United States Food and Drug Administration
US CFR	United States Code of Federal Regulations
Vdz/F	Apparent volume of distribution

STUDY SYNOPSIS

Protocol number: TAK-620-1020	**Drug:** Maribavir
Title of the study: A Phase 1, Open-label, Randomized, Cross-over Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of a Single Oral Dose of Maribavir Administered in Healthy, Japanese Subjects Compared with Matched, Healthy, Non-Hispanic, Caucasian Subjects and to Assess Dose-Proportionality of 3 Doses of Maribavir in the Japanese Subjects	
Number of subjects (total and for each treatment arm): A total of 24 healthy, adult, male and/or female subjects will be enrolled into the study, comprising 12 subjects of Japanese descent and 12 matched, non-Hispanic, Caucasian subjects. Subjects who discontinue early without completing all planned pharmacokinetic (PK) assessments in Period 1 may be replaced at the sponsor's discretion to ensure at least 24 subjects (12 subjects of Japanese descent and 12 matching, non-Hispanic Caucasian subjects) with evaluable PK for the statistical analysis of the primary objective (PK comparison between Japanese and non-Hispanic, Caucasian subjects) complete the study. If subjects discontinue early during Period 2 or Period 3, there is no need for replacement. Non-Hispanic, Caucasian subjects will be matched to subjects of Japanese descent based on age (±10 years), sex, and body mass index (BMI) (±15%). • The subjects of Japanese descent will be randomized to receive 3 single oral doses of maribavir at 200 mg, 400 mg, and 800 mg in a crossover study design. • Matched, non-Hispanic, Caucasian subjects will receive a single 400 mg oral dose of maribavir.	
Investigator(s): [redacted], D.O., FACP	
Site(s) and Region(s): [redacted]	
Study period (planned): ~Aug 2020 to ~Nov 2020	**Clinical phase:** 1
Objectives: **Primary:** • To compare the PK profile of maribavir, administered as a single oral dose at 400 mg, between healthy, adult subjects of Japanese descent and matched, healthy, adult, non-Hispanic, Caucasian subjects **Secondary:** • To assess the dose proportionality of maribavir PK following single oral doses of 200, 400, and 800 mg in healthy, adult subjects of Japanese descent • To assess the safety and tolerability of single oral doses of 200, 400, and 800 mg of maribavir in healthy, adult subjects of Japanese descent • To evaluate the safety and tolerability of a single 400 mg oral dose of maribavir in matched, healthy, adult, non-Hispanic, Caucasian subjects **Exploratory:** • [redacted]	

Rationale:

This study is being conducted to compare the PK, safety, and tolerability of maribavir administered as a single oral dose in healthy adult subjects of Japanese descent and matched, healthy, adult non-Hispanic, Caucasian subjects. In addition, this study will assess the dose-proportionality and PK of maribavir in healthy, adult subjects of Japanese descent.

In accordance with the ICH-E5, this study is designed to evaluate whether there is any ethnic difference in PK and safety of maribavir between Japanese and non-Japanese subjects. These data will inform the bridging of safety and efficacy data from non-Japanese subjects to the Japanese population.

The results from this study will be utilized to guide dose selection for a future Phase 3 study in Japanese transplant patients with cytomegalovirus (CMV) infection.

Investigational product, dose, and mode of administration:

Maribavir is the investigational product (IP) for this study and will be administered orally as a single 200 mg (1×200 mg tablet, current Phase 3 formulation), 400 mg (2×200 mg tablets), and 800 mg (4×200 mg tablets) dose.

Methodology:

This is a Phase 1, open-label, randomized, crossover, partially fixed sequence, single-center study to evaluate the PK profile, safety, and tolerability of maribavir administered in healthy, adult subjects of Japanese descent and matched, healthy, adult, non-Hispanic, Caucasian subjects. The non-Hispanic, Caucasian subjects will receive a single oral dose of 400 mg maribavir on Day 1. For this cohort there will be one treatment period (Table 5 and Table 6).The Japanese subjects will receive 3 doses of maribavir separated by a 72-hour washout period between doses: in Treatment Period 1 on Day 1, they will receive a single oral dose of 400 mg of maribavir; in Treatment Period 2 and Treatment Period 3 on Day 1, they will be randomized to receive a single oral dose of either 200 mg followed by 800 mg of maribavir or vice versa (Table 1, Table 2, Table 3, and Table 4). A total of 24 subjects will be enrolled: 12 subjects of Japanese descent and 12 non-Hispanic, Caucasian subjects. Non-Hispanic, Caucasian subjects will be matched to Japanese subjects based on age (±10 years), sex, and BMI (±15%).

The study will comprise a 28-day screening period, Treatment Period 1 for the non-Hispanic, Caucasian cohort, and Treatment Periods 1, 2, and 3 for the subjects of Japanese descent. There will be a post-treatment follow-up telephone call at 7 (±4) days after the last dose of IP for all subjects. Screening will occur within 28 days of the first dose. Subjects will be admitted to the clinical research center (CRC) on Day -1. All subjects (Japanese and Caucasian) can have their typical diet prior to the study; all subjects (Japanese and Caucasian) will receive identical meals on Day 1 (up to 24 hours post dose) in all treatment periods to maintain control. Doses will be administered with a glass (240 mL) of room temperature water after at least a 10-hour overnight fasting, with water restricted 1 hour before and 1 hour after dosing. Food will be provided to subjects approximately 4 hours after study drug administration. Vomiting occurring within 4 hours after dosing will be recorded. There will be at least a 72-hour washout between maribavir doses for the subjects of Japanese descent.

The total number of nights subjects will be expected to stay at the CRC is approximately 2 for the non-Hispanic, Caucasian subjects and approximately 8 for the subjects of Japanese descent. The maximal total duration of study participation for a non-Hispanic, Caucasian subject is approximately 37 days and approximately 47 days for the subjects of Japanese descent, if the maximum screening period, treatment, washout, and follow-up visit durations are used.

Treatment Period:

- In Treatment Period 1, all study subjects (both Japanese and Caucasian) will receive maribavir as a single oral dose of 400 mg.
- In Treatment Periods 2 and 3, all subjects of Japanese descent will receive maribavir as a single oral dose of either 200 mg or 800 mg, depending upon randomization assignment.

Assessments

- Serial blood samples for PK analysis will be collected in each treatment period for the determination of maribavir and [redacted] plasma concentrations at pre-dose and up to approximately 24 hours post dose. These blood samples will be collected according to the Schedules of Assessments (Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6).
- Safety and tolerability will be determined through assessment of treatment-emergent adverse events (TEAEs) from the first dose to the post-treatment follow-up telephone call at 7 (±4) days after the last dose of IP, and vital signs, electrocardiogram (ECG), and clinical laboratory evaluations on Day 1 pre-dose and up to 24 hours post dose in each treatment period.

Follow-up

- A post-treatment follow-up telephone call will occur at 7 (±4) days after the last dose of IP for each subject. Subjects who experience AEs will be followed longer if needed, including an unscheduled clinic visit if appropriate, depending on the nature, severity, and seriousness of the AE.

Inclusion and exclusion criteria:

Inclusion Criteria:

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated (personally or via a legally-authorized representative) informed consent/assent as applicable to participate in the study.
3. Healthy subjects of Japanese descent must have been born in Japan and must not have lived outside of Japan for >10 years; both parents and all 4 grandparents must be of Japanese origin. Healthy, non-Hispanic, Caucasian subjects must have both parents and all 4 grandparents of non-Hispanic, Caucasian origin.
4. Age 18 years to 55 years, inclusive at the time of consent. The date of signature of the informed consent is defined as the beginning of the screening period. This inclusion criterion will only be assessed at the first screening visit.
5. Male, or non-pregnant, non-breastfeeding female who agrees to comply with any applicable contraceptive requirements of the protocol or females of non-childbearing potential.
6. Healthy as determined by the investigator on the basis of screening evaluations. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry (includes thyroid stimulating hormone [TSH] and free T4 at screening only), and urinalysis.
7. Hemoglobin for males ≥135.0 g/L and females ≥120.0 g/L at screening and on Day -1.
8. BMI between 18.5 and 28.0 kg/m^2 inclusive and a body weight >45 kg (99 lbs.). This inclusion criterion will only be assessed at the first screening visit.
9. Ability to swallow a dose of IP.

Exclusion Criteria:

1. History of any hematological, hepatic, respiratory, cardiovascular, renal, neurological, or psychiatric disease, gall bladder removal, or current recurrent disease that could affect the action, absorption, or disposition of the IP, or clinical or laboratory assessments.
2. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the IP or procedures.
3. Known or suspected intolerance or hypersensitivity to maribavir, closely-related compounds, or any of the stated ingredients.
4. Significant illness, as judged by the investigator, within 2 weeks of the first dose of IP.
5. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the first dose of IP.
6. Have taken another IP within 30 days or five half-lives of that IP, whichever is greater, prior to the first dose of maribavir.
7. Have been enrolled in a clinical study (including vaccine studies) within 30 days prior to the first dose

of IP that, in the investigator's opinion, may impact this study.

8. Have had any substantial changes in eating habits within 30 days prior to the first dose of IP, as assessed by the investigator.
9. Confirmed systolic blood pressure >139 mmHg or <89 mmHg, and diastolic blood pressure >89 mmHg or <49 mmHg.
10. Twelve-lead ECG demonstrating corrected QT interval (QTc) >450 msec at screening. If QTc exceeds 450 msec, the ECG should be repeated 2 more times and the average of the 3 QTc values should be used to determine the subject's eligibility.
11. Known history of alcohol or other substance abuse, including synthetic cannabinoids within the last year.
12. Male subjects who consume more than 21 units of alcohol per week or 3 units per day. Female subjects who consume more than 14 units of alcohol per week or 2 units per day. (1 alcohol unit=1 beer or 1 wine [5 oz/150 mL] or 1 liquor [1.5 oz/40 mL] or 0.75 oz alcohol).
13. A positive urine test for drugs of abuse, alcohol, or cotinine at screening or on Day -1.
14. A positive human immunodeficiency virus (HIV), hepatitis B surface antibody (HBsAg), or hepatitis C virus (HCV) antibody screen.
15. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch). Ex-users must report that they have stopped using tobacco for at least 30 days prior to receiving the first dose of IP.
16. Routine consumption of more than 2 units of caffeine per day or subjects who experience caffeine withdrawal headaches. (1 caffeine unit is contained in the following items: one 6 oz [180 mL] cup of coffee, two 12 oz [360 mL] cans of cola, one 12 oz cup of black tea, and three 1 oz [85 g] chocolate bars. (Decaffeinated coffee, herbal tea, or cola are not considered to contain caffeine).
17. Prior screen failure, randomization, enrollment, or participation in this study.
18. Current use of any prescription medication (with the exception of hormonal replacement therapy) within 30 days of the first dose of IP. Current use of any over the counter medication (including herbal preparations like St. John's wort and ginkgo biloba, or homeopathic preparations) within 14 days of the first dose of IP.
19. Ingestion of known cytochrome P450 (CYP)3A modulators within 7 days of Day 1, Period 1 (includes grapefruit or grapefruit juice, oranges, Seville oranges, vegetables from the mustard green family [eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard], charbroiled meats, and products containing these ingredients).
20. History of active or chronic oral/nasal cavity infections, gastroesophageal reflux, asthma treatment with albuterol, zinc supplementation.
21. Subjects with dry mouth syndrome or burning mouth syndrome or menopausal women suffering from dysgeusia.
22. Subjects who have acute gastrointestinal symptoms at screening or admission (eg, nausea, vomiting, diarrhea, and heartburn).

Maximum duration of subject involvement in the study:

- Planned duration of screening period: Subjects will be screened within 28 days prior to the first dose of the IP.
- Planned duration of treatment period: All subjects will be admitted to the CRC on Day -1. Caucasian subjects will be administered a single oral dose of maribavir 400 mg on Day 1 and will be discharged on Day 2. They will spend a total of approximately 3 days and 2 nights at the CRC. Subjects of Japanese descent will receive a single oral dose of 400 mg maribavir on Day 1 in Treatment Period 1, and will be dosed in a crossover fashion with a single dose of maribavir of either 200 mg or 800 mg based on their randomization assignment on Day 1 in Treatment Periods 2, and 3. They will spend in total approximately 9 days and 8 nights at the CRC.
- Planned duration of washout period between single doses of maribavir for the subjects of Japanese descent: There will be a 72-hour washout period from single dose to single dose of maribavir. This is not applicable for Caucasian subjects, as they will receive one single dose of maribavir.
- Planned duration of follow-up: There will be a post-treatment follow-up telephone call at 7 (±4) days after the last dose of IP for each subject. Subjects who experience AEs will be followed longer if needed,

including an unscheduled clinic visit if appropriate, depending on the nature, severity, and seriousness of the AE.

- Planned total duration of study participation: The maximal total duration of study participation for Caucasian subjects will be 37 days, and for Japanese subjects will be 47 days, if the maximum screening, treatment, washout, and follow-up durations are used.

Statistical Analysis:

Subject Populations:

- The Enrolled Set will consist of all subjects who have signed informed consent and also passed inclusion/exclusion criteria.
- The Safety Set will consist of all subjects who receive any amount of IP. Analysis will be performed according to the treatment regimen actually received regardless of the randomized treatment regimen.
- The Pharmacokinetic (PK) Set will consist of subjects who receive at least 1 dose of study drug and have evaluable post-dose maribavir PK data (defined as complete concentration-time profile to obtain meaningful estimates of PK parameters).

Pharmacokinetic Endpoint(s):

A PK evaluation of maribavir concentrations and [redacted] will be performed based on the PK Set. PK parameters will be estimated for maribavir and [redacted] following the administration of maribavir 400 mg for non-Hispanic, Caucasian subjects and of 200, 400, and 800 mg for subjects of Japanese descent.

Maribavir C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ will be the primary endpoints. [redacted]

PK parameters will include, but not be limited to the following:

- C_{max}: Maximum concentration
- t_{max}: Time of maximum observed concentration sampled during a dosing interval
- AUC_{last}: Area under the curve from the time of dosing to the last measurable concentration
- $AUC_{0\text{-}inf}$: Area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration
- $AUC0\text{-}_{inf}$%extrap The percent of AUC0-inf extrapolated, calculated by (1-AUClast/AUC0-inf)*100
- λ_z: First order rate constant associated with the terminal (log linear) portion of the curve
- $t_{½}$: Terminal half-life
- CL/F: Apparent clearance (maribavir only)
- $V_{z/F}$: Apparent volume of distribution (maribavir only)
- T_{lag} Delay between the time of dosing and time of appearance of drug (investigational) in plasma in the employed sampling scheme

In addition, dose-normalized (to 400mg) AUC_{last}, $AUC_{0\text{-}inf}$, and C_{max} will be calculated.

Pharmacokinetic Analysis:

Maribavir C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ will be the primary endpoints. [redacted] Individual concentrations and PK parameters (including dose-normalized) of maribavir and [redacted] will be listed and summarized by maribavir dose with descriptive statistics (number, arithmetic mean, standard deviation [SD], coefficient of variation [CV], median, minimum, maximum, geometric mean, and percent coefficient of variation (CV%) of geometric mean. The 95% CIs of the geometric means of PK

parameters will be presented as well.
Figures of individual and mean (±SD) maribavir concentration-time profiles will be generated on linear and semi-log scales. The mean plots will be generated and presented by overlaying the Japanese cohort and non-Hispanic, Caucasian cohort. Figures of PK parameters and dose-normalized C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ vs. dose in Japanese subjects will be generated. Box-Whisker plots for selected PK parameter will be generated with Japanese cohort and non-Hispanic Caucasian side by side.

In order to compare the PKs of maribavir between subjects of Japanese descent and matched, non-Hispanic, Caucasian subjects, the differences of log-transformed PK parameters (AUC_{last}, $AUC_{0\text{-}inf}$, and C_{max}) from the maribavir 400 mg oral dose will be examined between cohorts using an analysis of variance model. The geometric mean ratio and its 90% CI of PK parameters will be provided from the model. In addition, the difference of log-transformed dose-normalized $AUC_{0\text{-}inf}$, AUC_{last} and C_{max} will be examined between the Japanese cohort estimated at the 200 mg dose and the non-Hispanic, Caucasian cohort estimated at the 400 mg dose, as well as between the Japanese cohort estimated at the 800 mg dose and the non-Hispanic, Caucasian cohort estimated at 400 mg dose, using an analysis of variance model. The geometric mean ratio and its 90% CI of PK parameters will be provided from the model. Forest plots of geometric mean ratios for selected PK parameters between Japanese cohort and the non-Hispanic Caucasian cohort at 400 mg will be generated. [redacted]

Dose proportionality will also be examined for maribavir PK parameters for the Japanese subjects. Dose proportionality will be assessed for C_{max} and AUC (AUC_{last} and $AUC_{0\text{-}inf}$) using the power model. The power model assumes a linear relationship between the natural log transformed PK parameter and the natural log transformed dose.

$\ln(\text{Parameter}) = \alpha + \beta \times \ln(\text{Dose}) + \text{Random error}$

Where α is the intercept, β is the slope, and Random error is a random residual error. Dose proportionality will be assessed by estimating mean slope with the corresponding two-sided 90% CI from the power model. The fold increase in PK parameters and associated 90% CI when doubling the dose will be presented. [redacted]

Safety Endpoints:

Safety will be assessed for the following evaluations:

- Number, severity, seriousness, and causality of TEAEs
- Changes in vital signs, ECGs, and clinical laboratory results (hematology, chemistry, and urinalysis) from baseline to post-baseline time points. Baseline is defined as the last non-missing assessment prior to the first dose.

Statistical Methodology for Safety Endpoints:

Safety data, including TEAEs, laboratory tests, ECGs, and vital signs, will be summarized. Quantitative safety data, as well as the difference from baseline, if applicable, will be summarized by descriptive statistics. Frequency counts will be compiled for classification of qualitative safety data. Direct safety comparisons between the two cohorts will be presented from the maribavir 400 mg dosing data. All other safety data from the 200 mg and 800 mg doses in the subjects of Japanese descent will be summarized and listed.

Sample Size Justification:

The sample size consideration for the primary objective of evaluating the PK profile of maribavir, administered as a single oral dose at 400 mg, between Japanese subjects and matched, healthy, adult, non-Hispanic, Caucasian subjects is based on feasibility and comparable studies. A total of 24 subjects (12 subjects of Japanese descent and 12 matched, non-Hispanic, Caucasian subjects) will be targeted to be enrolled in the study.

Table 1 Schedule of Assessments for Subjects of Japanese Descent

Visit	Screening	Pre-dose Assessments	Treatment Period 1		Washout Period[i]	Treatment Period 2		Washout Period[i]	Treatment Period 3		Early Termination	Follow-up[j]
Study Day	**–28 to -02**	**-1**	**1**	**2**	**3-5**	**1**	**2**	**3-5**	**1**	**2**		**7 (±4)**
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Demography[a]	X											
Medical/medication history	X	X										
Physical examination	X	X[b]	X	X		X	X		X	X	X	
Vital signs (BP, pulse, temperature, and respiratory rate)[c]	X	X	X	X		X	X		X	X	X	
Height and weight[d]	X	X	X			X			X	X	X	
Electrocardiogram (12-lead)	X	X	X	X		X	X		X	X	X	
Biochemistry, hematology, and urinalysis	X	X	X	X		X	X		X	X	X	
HIV, HBsAg, and HCV antibodies	X											
Serum β-HCG pregnancy test (females only)[e]	X	X										
Urine pregnancy test (females only)[e]			X			X			X		X	
Urine drug, alcohol, and cotinine screening[f]	X	X										
IP administration[g]			X			X			X			
PK blood sampling[h]			X	X		X	X		X	X		
Check-in to the CRC		X										
Discharge from the CRC										X		

Table 1 Schedule of Assessments for Subjects of Japanese Descent

Visit	Screening	Pre-dose Assessments	Treatment Period 1		Washout Period[i]	Treatment Period 2		Washout Period[i]	Treatment Period 3		Early Termination	Follow-up[j]
Study Day	**–28 to -02**	**-1**	**1**	**2**	**3-5**	**1**	**2**	**3-5**	**1**	**2**		**7 (±4)**
Adverse events/serious adverse events[i]	X	X	X	X		X	X		X	X	X	X
Concomitant medications	X	X	X	X		X	X		X	X	X	X

β-hCG=β-human chorionic gonadotropin; BP=blood pressure; CRC=clinical research center; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IP=investigational product; PK=pharmacokinetic

a Subjects must have been born in Japan and must not have lived outside of Japan for >10 years; both parents and all 4 grandparents of must be of Japanese origin.

b If more than 2 days have passed since screening, a physical examination should be repeated on Day -1.

c Vital signs will be obtained while subject is in the supine position on study days noted. BP at screening visit is compared on both arms. The same (right or left) arm with the higher blood pressure will be used throughout the study. Temperature will be taken at screening, at predose on Day 1, and on each study day.

d Height will be recorded at the screening visit only.

e Serum β-hCG testing is required at screening and on Day -1 for all female subjects.

f Tests for drugs of abuse, alcohol, and cotinine will be performed at screening and on Day -1. Testing for alcohol on Day -1 will be performed using an on-site breathalyzer test.

g All maribavir doses will be administered with a glass (240 mL) of room temperature water after a 10 hour overnight fasting, with water restricted 1 hour before and 1 hour after dosing. All subjects (Japanese and Caucasian) can have their typical diet prior to the study; all subjects (Japanese and Caucasian) will receive identical meals on Day 1 (up to 24 hours post dose) in all treatment periods to maintain control. Food will be provided to subjects approximately 4 hours after IP administration. Vomiting occurring within 4 hours after dosing will be recorded.

h PK samples will be collected pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, and 24 hours post dosing with the IP on Day 1 of all 3 treatment periods.

i Washout period of a minimum of 72 hours and a maximum of 73 hours after administration of the IP on Day 1. Following the washout period, subjects will be asked regarding concomitant medications and any AEs.

jThere will be a post-treatment follow-up telephone call at 7 (±4) days after the last dose of IP. Subjects who experience AEs will be followed longer if needed, including an unscheduled clinic visit if appropriate, depending on the nature, severity, and seriousness of the AE.

Table 2 Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 1

Study Day	**Day 1[a]**															**Day 2**
Hour (relative to dosing time)	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[b]	X[e]															
Vital signs (BP, pulse, temperature, and respiratory rate)[b,c]	X[e]							X								X
Weight[b]	X[e]															
Electrocardiogram (12-lead)[b,d]	X[e]							X								X
Biochemistry, hematology, and urinalysis[b]	X[e]															X
IP administration[f]		X														
PK blood sampling[g]	X[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events/serious adverse events[b]	X[e]	X						X								X
Concomitant medication[b]	X[e]	X														X

ECG=electrocardiogram; IP=Investigational Product; PK=pharmacokinetic; QTc=corrected QT interval

[a] There will be a minimum of 72 hours and a maximum of 73 hours washout period between administration of the last dose of investigational product in Treatment Period 1 and Treatment Period 2. There will also be a minimum of 72 hours and a maximum of 73 hours washout period between administration of the last dose of investigational product in Treatment Period 2 and Treatment Period 3. Following washout, subjects will be asked regarding concomitant medications and any AEs.

[b] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.

[c] Vital signs will be obtained while subject is in the supine position on study days noted. BP at screening visit is compared on both arms. The same (right or left) arm with the higher blood pressure will be used throughout the study. Temperature will be taken at screening, at predose on Day 1, and on each study day.

[d] If QTc exceeds 450 msec, the ECG should be repeated 2 more times and the average of the 3 QTc values should be used to determine the subject's eligibility. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

[e] Blood sampling assessments should be performed within 30 minutes prior to dose administration. All other predose assessments should be completed within 60 minutes of dose administration, with the exception of the physical examination which should be completed within 90 minutes of dose administration.

[f] All maribavir doses will be administered with a glass (240 mL) of room temperature water after a 10 hour overnight fasting, with water restricted 1 hour before and 1 hour after dosing. All subjects (Japanese and Caucasian) can have their typical diet prior to the study; all subjects (Japanese and Caucasian) will receive identical meals on Day 1 (up to 24 hours post dose) in all treatment periods to maintain control. Food will be provided to subjects approximately 4 hours after IP administration. Vomiting occurring within 4 hours after dosing will be recorded.

[g] The sponsor's expectation is that the investigator will ensure that every effort is made to collect all PK blood samples at the precise protocol scheduled time. PK blood collection must not deviate from the nominal collection time set forth in the protocol by more than ±5 minutes from samples drawn within 4 hours post-dose or by more than ±15 minutes for samples drawn beyond 4 hours post-dose. Samples drawn outside these parameters will be considered a protocol deviation.

Table 3 Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 2

Study Day	**Day 1[a]**															**Day 2**
Hour (relative to dosing time)	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[b]	X[f]															
Randomization[c]	X[f]															
Vital signs (BP, pulse, temperature, and respiratory rate)[b,d]	X[f]							X								X
Weight[b]	X[f]															
Electrocardiogram (12-lead)[b,e]	X[f]							X								X
Biochemistry, hematology, and urinalysis[b]	X[f]															X
IP administration[g]		X														
PK blood sampling[h]	X[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events/serious adverse events[b]	X[f]	X						X								X
Concomitant medication[b]	X[f]	X														X

ECG=electrocardiogram; IP=Investigational Product; PK=pharmacokinetic; QTc=corrected QT interval

[a] There will be a minimum of 72 hours and a maximum of 73 hours washout period between administration of the last dose of investigational product in Treatment Period 1 and Treatment Period 2. There will also be a minimum of 72 hours and a maximum of 73 hours washout period between administration of the last dose of investigational product in Treatment Period 2 and Treatment Period 3. Following washout, subjects will be asked regarding concomitant medications and any AEs.

[b] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.

[c] Randomization will occur in Treatment Period 2, Day -1 or Day 1.

[d] Vital signs will be obtained while subject is in the supine position on study days noted. BP at screening visit is compared on both arms. The same (right or left) arm with the higher blood pressure will be used throughout the study. Temperature will be taken at screening, at predose on Day 1, and on each study day.

[e] If QTc exceeds 450 msec, the ECG should be repeated 2 more times and the average of the 3 QTc values should be used to determine the subject's eligibility. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

[f] Blood sampling assessments should be performed within 30 minutes prior to dose administration. All other predose assessments should be completed within 60 minutes of dose administration, with the exception of the physical examination which should be completed within 90 minutes of dose administration.

[g] All maribavir doses will be administered with a glass (240 mL) of room temperature water after a 10 hour overnight fasting, with water restricted 1 hour before and 1 hour after dosing. All subjects (Japanese and Caucasian) can have their typical diet prior to the study; all subjects (Japanese and Caucasian) will receive identical meals on Day 1 (up to 24 hours post dose) in all treatment periods to maintain control. Food will be provided to subjects approximately 4 hours after IP administration. Vomiting occurring within 4 hours after dosing will be recorded.

[h] The sponsor's expectation is that the investigator will ensure that every effort is made to collect all PK blood samples at the precise protocol scheduled time. PK blood collection must not deviate from the nominal collection time set forth in the protocol by more than ±5 minutes from samples drawn within 4 hours post-dose or by more than ±15 minutes for samples drawn beyond 4 hours post-dose. Samples drawn outside these parameters will be considered a protocol deviation.

Table 4 Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 3

Study Day	**Day 1[a]**															**Day 2**
Hour (relative to dosing time)	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[b]	X[e]															
Vital signs (BP, pulse, temperature, and respiratory rate)[b,c]	X[e]							X								X
Weight[b]	X[e]															X
Electrocardiogram (12-lead)[b,d]	X[e]							X								X
Biochemistry, hematology, and urinalysis[b]	X[e]															X
IP administration[f]		X														
PK blood sampling[g]	X[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events/serious adverse events[b]	X[e]	X						X								X
Concomitant medication[b]	X[e]	X														X

ECG=electrocardiogram; IP=Investigational Product; PK=pharmacokinetic; QTc=corrected QT interval

[a] There will be a minimum of 72 hours and a maximum of 73 hours washout period between administration of the last dose of investigational product in Treatment Period 1 and Treatment Period 2. There will also be a minimum of 72 hours and a maximum of 73 hours washout period between administration of the last dose of investigational product in Treatment Period 2 and Treatment Period 3. Following washout, subjects will be asked regarding concomitant medications and any AEs.

[b] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.

[c] Vital signs will be obtained while subject is in the supine position on study days noted. BP at screening visit is compared on both arms. The same (right or left) arm with the higher blood pressure will be used throughout the study. Temperature will be taken at screening, at predose on Day 1, and on each study day.

[d] If QTc exceeds 450 msec, the ECG should be repeated 2 more times and the average of the 3 QTc values should be used to determine the subject's eligibility. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

[e] Blood sampling assessments should be performed within 30 minutes prior to dose administration. All other predose assessments should be completed within 60 minutes of dose administration, with the exception of the physical examination which should be completed within 90 minutes of dose administration.

[f] All maribavir doses will be administered with a glass (240 mL) of room temperature water after a 10 hour overnight fasting, with water restricted 1 hour before and 1 hour after dosing. All subjects (Japanese and Caucasian) can have their typical diet prior to the study; all subjects (Japanese and Caucasian) will receive identical meals on Day 1 (up to 24 hours post dose) in all treatment periods to maintain control. Food will be provided to subjects approximately 4 hours after IP administration. Vomiting occurring within 4
hours after dosing will be recorded.

[g] The sponsor's expectation is that the investigator will ensure that every effort is made to collect all PK blood samples at the precise protocol scheduled time. PK blood collection must not deviate from the nominal collection time set forth in the protocol by more than ±5 minutes from samples drawn within 4 hours post-dose or by more than ±15 minutes for samples drawn beyond 4 hours post-dose. Samples drawn outside these parameters will be considered a protocol deviation.

Table 5 Schedule of Assessments for Non-Hispanic, Caucasian Subjects

Visit	Screening	Predose Assessments	Treatment Period 1		Early Termination	Follow-up[i]
Study Day	**–28 to -02**	**-1**	**1**	**2**		**7 (±4)**
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demography[a]	X					
Medical/medication history	X	X				
Physical examination	X	X[b]	X	X	X	
Vital signs (BP, pulse, temperature, and respiratory rate)[c]	X	X	X	X	X	
Height and weight[d]	X	X	X	X	X	
Electrocardiogram (12-lead)	X	X	X	X	X	
Biochemistry, hematology, and urinalysis	X	X	X	X	X	
HIV, HBsAg, and HCV antibodies	X					
Serum β-HCG pregnancy test (females only)[e]	X	X				
Urine pregnancy test (females only)[e]			X		X	
Urine drug, alcohol, and cotinine screening[f]	X	X				
IP administration[g]			X			
PK blood sampling[h]			X	X		
Check-in to the CRC		X				
Discharge from the CRC				X		
Adverse events/serious adverse events[i]	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X

β-hCG=β-human chorionic gonadotropin; BP=blood pressure; CRC=clinical research center; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IP=investigational product; PK=pharmacokinetic

[a] Subjects must have both parents and all 4 grandparents of non-Hispanic, Caucasian descent.

[b] If more than 2 days have passed since screening, a physical examination should be repeated on Day -1.

[c] Vital signs will be obtained while subject is in the supine position on study days noted. BP at screening visit is compared on both arms. The same (right or left) arm with the higher blood pressure will be used throughout the study. Temperature will be taken at screening, at predose on Day 1, and on each study day.

[d] Height will be recorded at the screening visit only.

[e] Serum β-hCG testing is required at screening and on Day -1 for all female subjects. Urine pregnancy tests will be performed prior to dosing on Day 1 for all female subjects.

[f] Tests for drugs of abuse, alcohol, and cotinine will be performed at screening and on Day -1. Testing for alcohol on Day -1 will be performed using an on-site breathalyzer test.

[g] All maribavir doses will be administered with a glass (240 mL) of room temperature water after a 10 hour overnight fasting, with water restricted 1 hour before and 1 hour after dosing. Food will be provided to subjects approximately 4 hours after IP administration. Vomiting occurring within 4 hours after dosing will be recorded.

[h] Collection time points for PK sampling will include pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, and 24 hours post dosing with the IP on Day 1.

[i] There will be a post-treatment follow-up telephone call at 7 (±4) days after the last dose of IP. Subjects who experience AEs will be followed longer if needed, including an unscheduled clinic visit if appropriate, depending on the nature, severity, and seriousness of the AE.

Table 6 Detailed Schedule of Assessments for Non-Hispanic Caucasian Subjects for Days 1 and 2 of Treatment Period 1

Study Day	Day 1															Day 2
Hour (relative to dosing time)	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X[d]															
Vital signs (BP, pulse, temperature, and respiratory rate)[a,b]	X[d]							X								X
Weight[a]	X[d]															X
Electrocardiogram (12-lead)[a,c]	X[d]							X								X
Biochemistry, hematology, and urinalysis[a]	X[d]															X
IP administration[e]		X														
PK blood sampling[f]	X[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events/serious adverse events[a]	X[d]	X						X								X
Concomitant medication[a]	X[d]	X														X

ECG=electrocardiogram; IP=Investigational Product; PK=pharmacokinetic; QTc=corrected QT interval

[a] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.

[b] Vital signs will be obtained while subject is in the supine position on study days noted. BP at screening visit is compared on both arms. The same (right or left) arm with the higher blood pressure will be used throughout the study. Temperature will be taken at screening, at predose on Day 1, and on each study day.

[c] If QTc exceeds 450 msec, the ECG should be repeated 2 more times and the average of the 3 QTc values should be used to determine the subject's eligibility. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

[d] Blood sampling assessments should be performed within 30 minutes prior to dose administration. All other predose assessments should be completed within 60 minutes of dose administration, with the exception of the physical examination which should be completed within 90 minutes of dose administration.

[e] All maribavir doses will be administered with a glass (240 mL) of room temperature water after a 10 hour overnight fasting, with water restricted 1 hour before and 1 hour after dosing. Food will be provided to subjects approximately 4 hours after IP administration. Vomiting occurring within 4 hours after dosing will be recorded.

[f] The sponsor's expectation is that the investigator will ensure that every effort is made to collect all PK blood samples at the precise protocol scheduled time. PK blood collection must not deviate from the nominal collection time set forth in the protocol by more than ±5 minutes from samples drawn within 4 hours post-dose or by more than ±15 minutes for samples drawn beyond 4 hours post-dose. Samples drawn outside these parameters will be considered a protocol deviation.

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% to 100% of various adult populations (de la Hoz et al. 2002). However, symptomatic CMV infection or CMV disease occurs almost exclusively in individuals with compromised immune systems. CMV remains a significant problem for patients undergoing various types of transplants that are associated with the use of potent immunosuppressive chemotherapy, including hematopoietic stem cell transplants (HSCT) and solid organ transplants (SOT) (de la Hoz et al. 2002; Razonable and Emery 2004).

It has been found that CMV infection increases incidence of opportunistic infections and graft rejection, and decreased allograft and patient survival (Rubin 1989; Hodson et al. 2005; Ljungman et al. 2006). Organ-specific associations with CMV infection include bronchiolitis obliterans in lung recipients, vanishing bile duct syndrome in liver recipients, accelerated transplant vasculopathy in heart recipients and transplant glomerulopathy, transplant renal artery stenosis or increased risk of transplant rejection (Razonable and Emery 2004; Legendre and Pascual 2008; Richardson et al. 1981; Pouria et al. 1998; Farrugia and Schwab 1992). These effects are believed to be mediated by the ability of the virus to modulate the immune system, either directly or secondary to the host antiviral response through regulation of cytokine, chemokine, and/or growth factor production.

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

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

Development of anti-viral resistance to currently available anti-CMV agents is also an ongoing clinical problem in solid organ and stem cell transplantation leading to graft loss and even mortality for some transplant patients. As described by Limaye et al. 2000, ganciclovir resistance developed in 7% D+/R- kidney, liver, and pancreas recipients who were prophylaxed with 3 months of oral ganciclovir. Ganciclovir resistant disease accounted for 20% of CMV disease,

occurred late (a median of 10 months after transplantation), was associated with higher intensity of immunosuppression, and was considered a clinically serious concern (Avery 2007).

There are no approved therapies for the treatment of CMV infection or CMV disease in transplant recipients, and no approved treatment for CMV infection or disease that is resistant or refractory to currently available therapies in any population. Maribavir is currently in Phase 3 clinical development for the treatment of CMV infection or disease, including those resistant or refractory to ganciclovir, valganciclovir, foscarnet, or cidofovir, in transplant recipients.

1.2 Product Background

1.2.1 Preclinical Information

Refer to the latest version of the maribavir (SHP620/TAK-620) Investigator's brochure (IB).

1.2.2 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 maribavir is 3-fold 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). Maribavir is active in vitro against strains of CMV that are resistant to ganciclovir, foscarnet, or cidofovir.

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.

1.2.3 Pharmacokinetics and metabolism

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

Administration of maribavir in conjunction with food resulted in a 28% decrease in C_{max} without a significant effect on AUC when compared to administration under fasting conditions. Bioavailability of a 100 mg tablet was unaffected by crushing the tablet or changes in gastric pH.

Maribavir was bound to plasma proteins, namely human serum albumin, lipoproteins, and alpha-1-acid-glycoprotein. The fraction of unbound maribavir was estimated at approximately 1.5% in healthy subjects and 0.96% in transplant patients. The apparent plasma elimination half-life for unchanged maribavir was approximately 5-7 hours. Maribavir is metabolized primarily in the liver through cytochrome P450 (CYP)3A4 pathway with the formation of the primary metabolite, VP44469. VP44469 does not have anti-CMV activity and does not affect major CYP enzymes or transporter activity. Renal clearance is a minor route of elimination of maribavir. Data from a Phase 1 study demonstrated no gender differences in maribavir PK. A population PK analysis conducted using pooled PK data from HP620-202 and SHP620-203 did not show apparent PK differences in Asian vs. non-Asian subjects; however, the sample size of Asian subjects was small (n=7).

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

- Concomitant administration of maribavir (400 mg BID) with tacrolimus, a substrate of CYP3A4 and P-glycoprotein (P-gp), resulted in increased tacrolimus C_{max} and AUC by 38% and 51%, respectively.
- Maribavir does not have a clinically significant effect on the activity of CYP1A2, CYP3A, CYP2C9, or CYP2D6; however, it inhibits CYP2C19 activity (based on plasma omeprazole/5-OH omeprazole ratio). A follow-up clinical study indicates maribavir had no effect on the PK of voriconazole (a CYP2C19 substrate).
- In vivo, maribavir 400 mg BID did not affect digoxin AUC; however, it increased C_{max} by 24.8%.
- Concurrent administration of rifampin, an inducer of CYP3A4 and P-gp, and maribavir significantly reduced plasma concentrations of maribavir, resulting in a 61% reduction in AUC, reduced half-life, and significantly increased clearance, most likely due to induction of hepatic and intestinal CYP3A4, and possible enhancement of P-gp transport.
- Concomitant administration of antacid has no effect on maribavir exposure.
- Concomitant administration of ketoconazole increased maribavir AUC and C_{max} by 46% and 10%, respectively.

1.2.4 Efficacy

Two Phase 2 studies were conducted to assess the safety, tolerability, and anti-CMV activity of maribavir for treatment of CMV infections: Study 1262-202 (SHP620-202) in transplant subjects with CMV infections or disease that are resistant or refractory to treatment with anti-CMV agents conducted in the US and Study 1262-203 (SHP620-203) in transplant recipients with wild-type CMV infections who do not have CMV organ disease (asymptomatic) conducted in Europe. In both these studies subjects received maribavir at 1 of 3 dose strengths, 400, 800, or 1200 mg BID, and both studies demonstrated favorable anti-CMV activity for maribavir, besides showing that maribavir was well tolerated with no safety concerns at all doses evaluated.

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

1.2.5 Safety

Maribavir has been administered across a broad range of oral doses from 50 mg/day to 2400 mg/day. Clinical safety experience has been obtained from 16 Phase 1 studies in adult, healthy volunteers, special populations (subjects with renal and hepatic impairment, and stable renal transplant recipients), and human immunodeficiency virus (HIV)-infected subjects. These studies included adult subjects only. Maribavir has been administered across a broad range of oral doses from 50 mg/day to 2400 mg/day. The most common TEAE in single- and multiple-dose Phase 1 studies was taste disturbance (dysgeusia). A definitive corrected QT interval (QTc) study demonstrated no clinically significant repolarization effect of maribavir administered orally at single doses of 100 mg and 1200 mg in healthy subjects. In addition, no other significant electrocardiographic effects of maribavir were found.

Maribavir was safe and well tolerated in Phase 1 studies. The most common treatment-emergent adverse event (TEAE) in single- and multiple-dose Phase 1 studies was taste disturbance (dysgeusia). Among maribavir-treated subjects, dysgeusia was reported by up to 80% of subjects across the single-dose studies (dose range, 50 mg to 600 mg) and by 64% to 92% of subjects across the multiple-dose studies (dose range, 300 mg/day to 2400 mg/day). Of the 259 cases of dysgeusia reported by maribavir-treated subjects in Phase 1, 252 were mild or moderate and 7 were of severe intensity. Dysgeusia was generally reported as a bitter or metallic taste that was considered related to maribavir administration. In a few cases, the taste disturbance was reported as more noticeable with liquids, especially cold beverages. Dysgeusia usually started within 1 hour after maribavir dosing and resolved within approximately 8 hours after dosing in the single-dose studies (range, 0.5 hours to 25 hours) and within 1 day after the last dose in the multiple-dose studies. No subjects were withdrawn from treatment because of taste disturbance. Among maribavir-treated subjects, 94% (778/831) of TEAEs were of mild or moderate intensity; 62% (517/831) of TEAEs were considered by the investigator to be related to maribavir.

Maribavir had a favorable safety and tolerability profile in both the Phase 2 and Phase 3 trials for CMV prophylaxis. The most common TEAEs that appeared to be associated with maribavir treatment were dysgeusia and gastrointestinal (GI)-related events (eg, diarrhea, 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 SHP620-203), subjects received maribavir at 1 of 3 dose strengths: 400, 800, or 1200 mg BID, and both studies demonstrated that maribavir was well-tolerated with no safety concerns at all doses evaluated. In Study SHP620-202, 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 cohorts.

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.

Refer to the latest version of the maribavir IB for the most detailed and most current information regarding the drug metabolism, PK, efficacy and safety of maribavir.

1.3 Risk/Benefit and Ethical Assessment

To date, maribavir has been safe and well tolerated 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 stem cell transplant 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 continuation of maribavir development in the Phase 3 treatment studies.

Always refer to the latest version of the maribavir IB for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, PK, efficacy, and safety of maribavir.

1.4 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, 1996; E6 R2, 2017), Title 21 of the US Code of Federal Regulations (US CFR), the European Union (EU) Directives (2001/20/EC; 2005/28/EC), and applicable national and local regulatory requirements.

The responsibilities of the study sponsor and investigator(s) are described fully in Appendix 1.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

This study is being conducted to compare the PK, safety, and tolerability of maribavir administered as a single oral dose in healthy, adult subjects of Japanese descent and matched, healthy, adult, non-Hispanic, Caucasian subjects. In addition, this study will assess the dose-proportionality of PK of maribavir in healthy, adult subjects of Japanese descent.

In accordance with the ICH-E5, this study is designed to evaluate whether there is any ethnic difference in PK and safety of maribavir between Japanese and non-Japanese subjects. These data will inform the bridging of safety and efficacy data from non-Japanese subjects to the Japanese population.

The results from this study will be utilized to guide dose selection for a future Phase 3 study in Japanese transplant patients with CMV infection.

2.2 Study Objectives

2.2.1 Primary Objective

- To compare the PK profile of maribavir, administered as a single oral dose at 400 mg, between healthy, adult subjects of Japanese descent and matched, healthy, adult, non-Hispanic, Caucasian subjects

2.2.2 Secondary Objectives

- To assess the dose proportionality of maribavir PK following single oral doses of 200, 400, and 800 mg in healthy, adult subjects of Japanese descent
- To assess the safety and tolerability of single oral doses of 200, 400, and 800 mg of maribavir in healthy, adult subjects of Japanese descent
- To evaluate the safety and tolerability of a single 400 mg oral dose of maribavir in matched, healthy, adult, non-Hispanic, Caucasian subjects

2.2.3 Exploratory Objective

- [redacted]

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 1, open-label, randomized, crossover, partially fixed sequence, single-center study to evaluate the PK profile, safety, and tolerability of maribavir administered in healthy, adult subjects of Japanese descent and matched, healthy, adult, non-Hispanic, Caucasian subjects. A total of 24 subjects will be enrolled: 12 subjects of Japanese descent and 12 non-Hispanic, Caucasian subjects. Non-Hispanic, Caucasian subjects will be matched to Japanese subjects based on age (±10 years), sex, and body mass index (BMI) (±15%).

The study design flow chart is presented in Figure 1.

Subjects will be screened within 28 days prior to the first dose of the investigational product (IP). Subjects will be admitted to the Clinical Research Center (CRC) on Day -1.

For the non-Hispanic, Caucasian group, the study will comprise a 28-day Screening Period and Treatment Period 1. These subjects will receive a single oral dose of 400 mg maribavir on Day 1 and will be discharged on Day 2. For this cohort there will be one treatment period (Table 5 and Table 6).

For the subjects of Japanese descent, the study will comprise a 28-day Screening Period and 3 treatment periods. These subjects will receive 3 doses of maribavir separated by a least a 72-hour washout period between doses: in Treatment Period 1 on Day 1, they will receive a single oral dose of 400 mg of maribavir; in Treatment Period 2 and Treatment Period 3 on Day 1, they will be randomized to receive a single oral dose of 200 mg followed by 800 mg of maribavir or a single oral dose of 800 mg followed by 200 mg maribavir (Table 1, Table 2, Table 3, and Table 4).

All subjects (Japanese and Caucasian) can have their typical diet prior to the study; all subjects (Japanese and Caucasian) will receive identical meals on Day 1 (up to 24 hours post dose) in all treatment periods to maintain control. All maribavir doses will be administered with a glass (240 mL) of room temperature water after at least a 10-hour overnight fasting, with water restricted 1 hour before and 1 hour after dosing. Food will be provided to subjects approximately 4 hours after study drug administration. (Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations, 2019). Vomiting occurring within 4 hours after dosing will be recorded. There will be at least a 72-hour washout between maribavir doses for the subjects of Japanese descent.

The study duration for the non-Hispanic, Caucasian cohort will comprise a 28-day screening period and Treatment Period 1. For the subjects of Japanese descent, the study duration will comprise a 28-day screening period and Treatment Periods 1, 2, and 3. For both groups (Japanese and Caucasian subjects), there will be a post-treatment follow-up telephone call at 7 (±4) days after the last dose of IP.

The total number of nights subjects will be expected to stay at the CRC is approximately 2 for the non-Hispanic, Caucasian subjects and approximately 8 for the subjects of Japanese descent.

The maximal total duration of study participation for a non-Hispanic, Caucasian subject is approximately 37 days and approximately 47 days for the subjects of Japanese descent, if the screening, treatment, washout, and follow-up visit durations are used.

Treatment Period:

- In Treatment Period 1, all study subjects (both Japanese and Caucasian) will receive maribavir as a single 400 mg oral dose. For the non-Hispanic, Caucasian group there will be only one treatment period.
- In Treatment Periods 2 and 3, all subjects of Japanese descent will receive maribavir as a single oral dose of either 200 mg or 800 mg, depending upon randomization assignment.

Pharmacokinetic Assessments

- Serial blood samples for PK analysis will be collected in each treatment period for the determination of maribavir and [redacted] plasma concentrations at pre-dose and up to approximately 24 hours post dose. These blood samples will be collected according to the Schedules of Assessments (Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6).

Safety Assessments

- Safety and tolerability will be determined through assessment of TEAEs from the first dose to the post-treatment follow-up telephone call at 7 (±4) days after the last dose of IP, and vital signs, ECG, and clinical laboratory evaluations on Day 1 pre-dose and up to 24 hours post dose in each treatment period.

Follow-up

- A post-treatment follow-up telephone call will occur at 7 (±4) days after the last dose of IP for each subject. Subjects who experience AEs will be followed longer if needed, including an unscheduled clinic visit if appropriate, depending on the nature, severity, and seriousness of the AE.

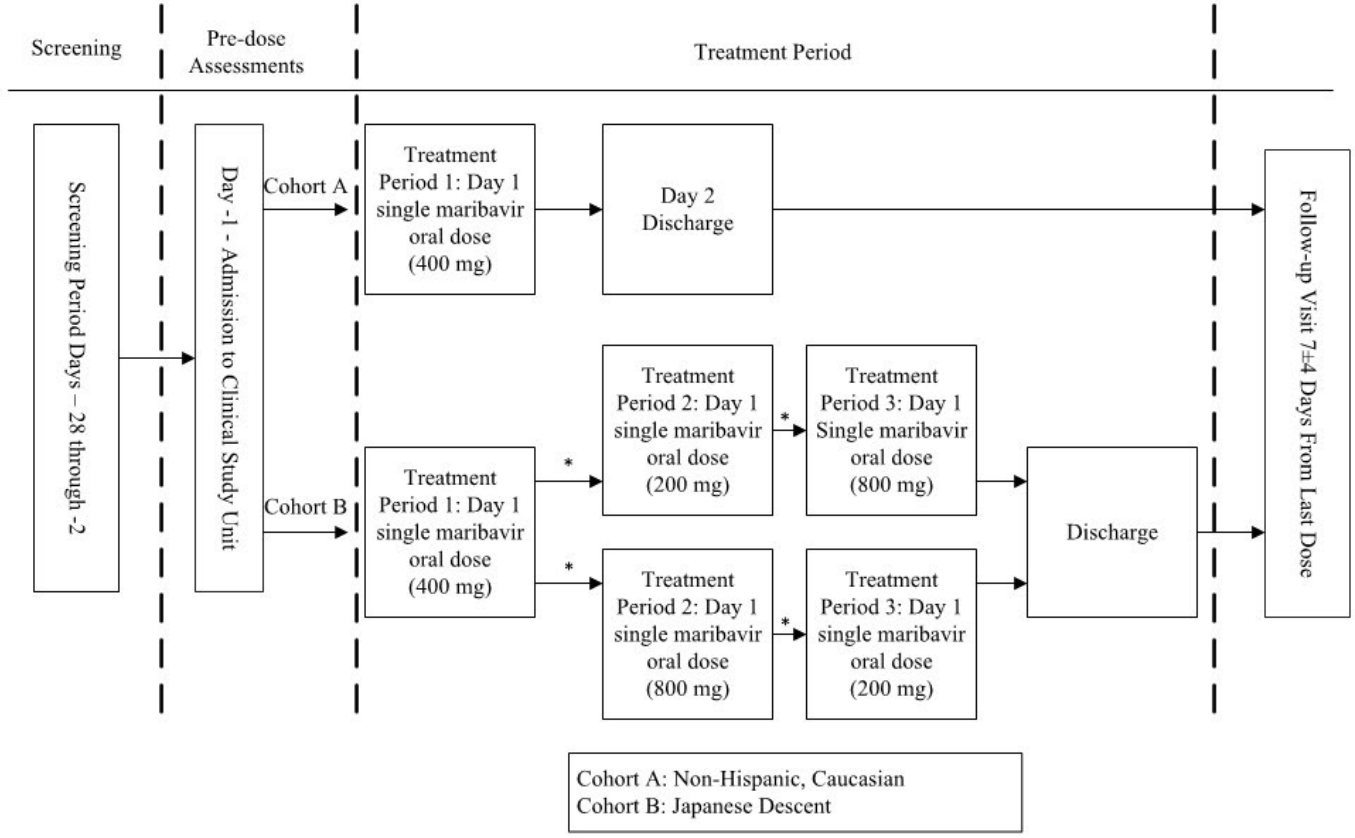
Rationale for Study Design and Dose Selection

- Maribavir 400 mg BID is the clinical dose currently being evaluated in the ongoing pivotal Phase 3 studies; therefore, a single oral dose of 400 mg maribavir was selected for evaluating the primary objective of this study – to compare maribavir PK between Japanese and Caucasian subjects. Maribavir has demonstrated time-independent PK and a favorable safety profile in previous Phase 1 studies. Therefore, evaluating PK following repeated dosing, eg, 400 mg BID, is not necessary in this study. Although dose proportionality of PK for doses from 50 mg up to 900 mg was demonstrated in previous studies in Caucasian subjects, to explore the appropriate clinical dosage in Japanese subjects the lower and higher dosages were also selected to assess dose proportionality and to support the future Phase 3 clinical

development of maribavir in Japanese subjects. Therefore, the secondary objective of the study was to evaluate dose proportionality of maribavir PK in subjects of Japanese descent. The doses of 200, 400, and 800 mg were selected for evaluating dose proportionality as a more than two-fold differences in systemic exposure to maribavir is not expected in Japanese subjects as compared to Caucasian subjects. As the primary objective is to compare maribavir PK at 400 mg, the 400 mg dose is to be evaluated in Treatment Period 1 in both Japanese and Caucasian subjects to avoid treatment period effects on this comparison.

Figure 1 Study Design Flow Chart

This is an open-label study to evaluate the PK, safety, and tolerability of single doses of maribavir in healthy, adult subjects of Japanese descent and matched, healthy, adult, non-Hispanic, Caucasian subjects. These cohorts of healthy, non-Hispanic, Caucasian subjects and healthy Japanese subjects need not be dosed at the same time.



*Washout period of 72 to 73 hours after treatment on Day 1.

3.2 Maximum Duration of Participation and Study Completion

The maximum duration of participation for non-Hispanic, Caucasian subjects is expected to be approximately 37 days, and the maximum duration of participation for subjects of Japanese descent is expected to be approximately 47 days, if the maximum screening, treatment, washout, and follow-up durations are used. The study will be completed in approximately 1 month to 2 months.

The Study Completion Date is defined as the date on which the last subject in the study completes the final protocol-defined assessment(s). Please note that this includes the follow-up visit or contact, whichever is later (refer to Section 7.1.4 for the defined follow-up period for this protocol).

3.3 Sites and Regions

This study will be conducted at a single site in the United States (US).

4. STUDY POPULATION

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 screening period starts with the signing of the informed consent. During the screening period, inclusion/exclusion criteria for study participation will be checked/tested. The subject will not be considered eligible for the study without meeting all of the criteria below.

Subjects cannot be enrolled or randomized before all inclusion criteria (including test results) are confirmed.

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated (personally or via a legally-authorized representative) informed consent/assent as applicable to participate in the study.
3. Healthy subjects of Japanese descent must have been born in Japan and must not have lived outside of Japan for >10 years; both parents and all 4 grandparents must be of Japanese origin. Healthy, non-Hispanic, Caucasian subjects must have both parents and all 4 grandparents of non-Hispanic, Caucasian origin.
4. Age 18 to 55 years inclusive, at the time of consent. The date of signature of the informed consent is defined as the beginning of the screening period. This inclusion criterion will only be assessed at the first screening visit.
5. Male, or non-pregnant, non-breastfeeding female who agrees to comply with any applicable contraceptive requirements of the protocol or females of non-childbearing potential.
6. Healthy as determined by the investigator on the basis of screening evaluations. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry (includes thyroid stimulating hormone [TSH] and free T4 at screening only), and urinalysis.
7. Hemoglobin for males ≥135.0 g/L and females ≥120.0 g/L at screening and on Day -1.
8. BMI between 18.5 and 28.0 kg/m^2 inclusive with a body weight >45 kg (99 lbs.). This inclusion criterion will only be assessed at the first screening visit.
9. Ability to swallow a dose of IP.

4.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met.

1. History of any hematological, hepatic, respiratory, cardiovascular, renal, neurological, or psychiatric disease, gall bladder removal, or current recurrent disease that could affect the action, absorption, or disposition of the IP, or clinical or laboratory assessments.
2. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the IP or procedures.
3. Known or suspected intolerance or hypersensitivity to maribavir, closely-related compounds, or any of the stated ingredients.
4. Significant illness, as judged by the investigator, within 2 weeks of the first dose of IP.
5. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the first dose of IP.
6. Have taken another IP within 30 days or five half-lives of that IP, whichever is greater, prior to the first dose of maribavir.
7. Have been enrolled in a clinical study (including vaccine studies) within 30 days prior to the first dose of IP that, in the investigator's opinion, may impact this study.
8. Have had any substantial changes in eating habits within 30 days prior to the first dose of IP, as assessed by the investigator.
9. Confirmed systolic blood pressure >139 mmHg or <89 mmHg, and diastolic blood pressure >89 mmHg or <49 mmHg.
10. Twelve-lead ECG demonstrating QTc >450 msec at screening. If QTc exceeds 450 msec, the ECG should be repeated 2 more times and the average of the 3 QTc values should be used to determine the subject’s eligibility.
11. Known history of alcohol or other substance abuse, including synthetic cannabinoids within the last year.
12. Male subjects who consume more than 21 units of alcohol per week or 3 units per day. Female subjects who consume more than 14 units of alcohol per week or 2 units per day. (1 alcohol unit=1 beer or 1 wine [5 oz/150 mL] or 1 liquor [1.5 oz/40 mL] or 0.75 oz alcohol).
13. A positive urine test for drugs of abuse, alcohol, or cotinine at screening or on Day -1.
14. A positive HIV, hepatitis B surface antibody (HBsAg), or hepatitis C virus (HCV) antibody screen.
15. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch). Ex-users must report that they have stopped using tobacco for at least 30 days prior to receiving the first dose of IP.
16. Routine consumption of more than 2 units of caffeine per day or subjects who experience caffeine withdrawal headaches. (1 caffeine unit is contained in the following items: one 6 oz [180 mL] cup of coffee, two 12 oz [360 mL] cans of cola, one 12 oz cup of black tea, and three 1 oz [85 g] chocolate bars. (Decaffeinated coffee, herbal tea, or cola are not considered to contain caffeine).
17. Prior screen failure, randomization, enrollment, or participation in this study.
18. Current use of any prescription medication (with the exception of hormonal replacement therapy, hormonal contraceptives, and occasional use of ibuprofen and/or acetaminophen) within 30 days of the first dose of IP. Current use of any over the counter medication (including herbal preparations like St. John’s wort and ginkgo biloba, or homeopathic preparations) within 14 days of the first dose of IP.

19. Ingestion of known CYP 3A modulators within 7 days of Day 1, Period 1 (includes grapefruit or grapefruit juice, oranges, Seville oranges, vegetables from the mustard green family [eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard], charbroiled meats, and products containing these ingredients).
20. History of active or chronic oral/nasal cavity infections, gastroesophageal reflux, asthma treatment with albuterol, zinc supplementation.
21. Subjects with dry mouth syndrome or burning mouth syndrome or menopausal women suffering from dysgeusia.
22. Subjects who have acute GI symptoms at screening or admission (eg, nausea, vomiting, diarrhea, and heartburn).

4.3 Restrictions

All subjects (Japanese and Caucasian) can have their typical diet prior to the study; all subjects (Japanese and Caucasian) will receive identical meals on Day 1 (up to 24 hours post dose) in all treatment periods to maintain control.

Subjects should refrain from the following:

1. Strenuous physical exercise 48 hours prior to admission to the CRC and during the in-house stays at the CRC.
2. Consuming grapefruit or grapefruit juice, oranges, Seville oranges, and products containing these items, vegetables from the mustard green family [eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard], charbroiled meats, and products containing these ingredients) and products containing these items from 7 days prior to Day 1 of the first treatment period through the completion of the last treatment period.
3. Consuming pine nuts 7 days prior to Day 1 of the first treatment period through the completion of the last treatment period.
4. Consuming alcohol 48 hours prior to admission to the CRC and during the in-house stay at the CRC.
5. Use of tobacco or any products containing nicotine within 30 days of Day 1 of the first treatment period through the completion of the last treatment period.
6. Taking or regularly using any prescription medication with the exception of those listed in Section 5.2.1 from 30 days prior to receiving the first dose of the IP through the completion of the discharge assessments and procedures, and over the counter medications (including over-the counter multi-vitamin, herbal, or homeopathic preparations) from 14 days prior to receiving the first dose of the IP through the completion of the discharge assessments and procedures. Subjects should not use antacids, proton pump inhibitors, H2 antagonists, or zinc supplementation.
7. Foods or beverages containing caffeine/xanthine 48 hours prior to admission to the CRC and during the in-house stay at the CRC.

4.4 Reproductive Potential

4.4.1 Female Contraception

There is no clinical experience with maribavir in pregnant subjects.

Sexually active females of child-bearing potential must be advised to use an acceptable method of contraception throughout the study period and for 30 days following the last dose of IP. 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 30 days following the last dose of IP.

Female subjects should be either:

- Post-menopausal (12 consecutive months of spontaneous amenorrhea and ≥age 50 years), or
- Surgically sterile (having undergone one of the following surgical procedures: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- All females of child-bearing potential-with a negative serum beta-human chorionic gonadotropin (β-HCG) pregnancy test at the screening visit and prior to randomization or enrollment. Females of child-bearing potential-must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the first dose of IP, plus condoms. Note: if subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days. If hormonal contraceptives are used they should be administered according to the package insert.

4.4.2 Male Contraception

Male subjects will be required to use a condom in conjunction with spermicidal gel, foam, cream, film, or suppository from time of dosing until 3 months after the last dose of IP. Childbearing female partners of male study participants will be required to follow the acceptable methods of contraception for this study (described in Section 4.4.1) from the time of first dosing until 3 months after the last dose of IP. 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 of the first dose until 3 months after the last dose of IP. Male subjects must not donate sperm until 3 months after the last dose of IP.

4.5 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution, or may be withdrawn at any time at the

discretion of the investigator or sponsor (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject with the medical monitor when possible.

If IP is discontinued, regardless of the reason, the early withdrawal evaluations listed in Table 1 and Table 5 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo follow-up evaluations. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for discontinuation, date of discontinuation of the IP, and the total amount of IP administered must be recorded in the source documents and the case report form (CRF).

Subjects who discontinue early without completing all planned PK assessments for Treatment Period 1 may be replaced at the sponsors discretion to ensure at least 24 subjects (12 subjects of Japanese descent and 12 matching, non-Hispanic, Caucasian subjects) with evaluable PK for the statistical analysis of the primary objective (PK comparison between Japanese and non-Hispanic, Caucasian subjects). If subjects discontinue early during Treatment Period 2 or 3, there is no need for replacement.

4.5.1 Reasons for Discontinuation

The reason for discontinuation must be determined by the investigator and recorded in the subject's source document. If a subject discontinued for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be indicated.

Reasons for discontinuation include but are not limited to:

- AE
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Other (The investigator must specify on 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 IP.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal treatments, vitamins non-pharmacological treatments such as psychotherapy as appropriate) received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) of the date of first dose of IP. Prior treatment information must be recorded on the appropriate CRF page.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of IP and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded on the appropriate CRF page.

5.2.1 Permitted Treatment

Subjects should refrain from taking any medications (excluding those medications listed below) during the course of the study. Any medication which is considered necessary for the subject's safety and wellbeing may be given at the discretion of the investigator. The administration of all medications (including IPs) must be listed on the appropriate CRF page.

Medications permitted during the study are listed below:

- Hormonal contraceptives for females of child-bearing potential administered according to the package insert (Section 4.4.1)
- Hormone replacement therapy
- Occasional use of ibuprofen and/or acetaminophen

5.2.2 Prohibited Treatment

Refer to Section 4.3 on restrictions for prohibited treatments.

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The IP is maribavir, which will be provided in tablet form.

Maribavir tablets are blue, film-coated tablets containing 200 mg of maribavir. The tablets are packaged in a 60 cc, white, high-density polyethylene (HDPE) bottle containing 40 tablets.

Additional information and detailed instructions are provided in the maribavir IB, and in a Pharmacy Manual that will be provided.

The sponsor will provide the IP.

6.1.1 Blinding the Treatment Assignment

Not applicable. This is an open-label study.

6.1.2 Unblinding the Treatment Assignment

Not Applicable. This is an open-label study.

6.2 Administration of Investigational Product(s)

6.2.1 Allocation of Subjects to Treatment

This is an open-label, randomized study. The actual treatment given to individual subjects is determined by a randomization schedule.

The subjects of Japanese descent will receive 3 doses of maribavir separated by a 72-hour washout period between doses: in Treatment Period 1 on Day 1, they will receive a single oral dose of 400 mg of maribavir; in Treatment Period 2 and Treatment Period 3 on Day 1, they will be randomized to receive a single oral dose of either 200 mg followed by 800 mg of maribavir in a crossover study design.

Subject numbers are assigned to all subjects as they consent to take part in the study. The subject number is assigned to subjects according to the sequence of presentation for study participation.

A 4-digit randomization number, [redacted], will be allocated immediately prior to dosing after eligibility has been determined. Once a randomization number has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. For randomized subjects, the randomization number will be the identifying number used throughout CRF. 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.

Screen failures will not be captured for this study.

The randomization number represents a unique number corresponding to IP allocated to the subject prior to dosing after eligibility has been determined.

6.2.2 Dosing

The non-Hispanic, Caucasian subjects will receive a single oral dose of 400 mg maribavir (2×200 mg maribavir tablets) on Day 1. The Japanese subjects will receive 3 doses of maribavir: on Day 1 of Treatment Period 1, they will receive a single oral dose of 400 mg of maribavir (2×200 mg maribavir tablets); on Day 1 of Treatment Period 2, they will be randomized to receive a single oral dose of either 200 mg (1×200 mg tablets) or 800 mg of maribavir (4×200 mg maribavir tablets); and on Day 1 of Treatment Period 3, they will receive a single oral dose of whichever dosage they did not receive on Day 1 of Treatment Period 2 (200 mg or 800 mg).

6.2.3 Administration

All subjects (Japanese and Caucasian) can have their typical diet prior to the study; all subjects (Japanese and Caucasian) will receive identical meals on Day 1 (up to 24 hours post dose) in all treatment periods to maintain control. All maribavir doses will be administered with a glass (240 mL) of room temperature water after at least a 10-hour overnight fasting, with water restricted 1 hour before and 1 hour after dosing. Food will be provided to subjects approximately 4 hours after study drug administration. Vomiting occurring within 4 hours after dosing will be recorded. There will be at least a 72-hour washout between maribavir doses for the subjects of Japanese descent (Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations, 2019).

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification are applied to the IP container.

All IP (maribavir) is labeled with a minimum of the protocol number, medication identification number (if applicable), dosage form (including product name and quantity in pack), directions for use, storage conditions, batch number and/or packaging reference, the statements “For clinical trial use only” and/or “CAUTION: New Drug – Limited by Federal (or US) Law to Investigational Use” and “Keep out of reach of children,” and the sponsor’s name and address.

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the IP in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name

Additional labels may not be added without the sponsor’s prior full agreement.

6.3.2 Packaging

Investigational product is packaged in the following labeled container:

- Maribavir tablet: 60 cc, white, square, HDPE bottle

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

6.3.3 Storage

The investigator has overall responsibility for ensuring that IP is stored in a secure, limited access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier (if allowed by law/regulations) on the IP bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the IP 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 IP 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 IP 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 IP to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the IP, documenting shipment content and condition. Accurate records of all IP dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing IP. 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 IP only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the IP carrying his/her treatment assignment. All dispensed medication will be documented in the subject's source and/or other IP record.

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

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

With the written agreement of the sponsor, at the end of the study all unused stock and empty/used IP packaging may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of IP 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 IP delivered with those used and returned. All IP must be accounted for and all discrepancies investigated and documented to the sponsor’s satisfaction.

6.5 Subject Compliance

Compliance must be assessed by observation of dosing by the investigator or designee. In addition, the CRC personnel should perform a hand and mouth check of the subject to assure the IP has been ingested. The investigator/nominated person will record details on the drug accountability log(s) and/or source documents. In addition, details of the dosing time (time, date, dose level) will be captured in the appropriate CRF.

6.6 Retention of Bioavailability and Bioequivalence Testing Samples

Not applicable.

7. STUDY PROCEDURES

7.1 Study Schedule

See Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6 for study procedures.

The following "priority order" will be in effect when more than 1 procedure or assessment is required at a particular time point.

- Spontaneous or solicited AE reporting
- ECG
- Vital signs
- PK blood sampling
- Clinical laboratory tests
- Physical examination.

NOTE: Blood sampling for PK evaluation must be performed at the precise protocol-scheduled time. Actual sampling time(s) must be accurately recorded in the source document and appropriate CRF.

7.1.1 Screening Period

Written, signed, and dated informed consent from the subject prior to the performance of any study-related procedures must be obtained by the principal investigator or a designee. A copy of the signed informed consent and assent form must be given to the subject for their records.

Screening procedures must be completed within 28 days of Day 1 as appropriate, prior to receiving the first dose of IP. All screening assessments and procedures are to be performed by the principal investigator or a qualified designee. See Table 1 and Table 5 for a complete list of screening procedures to be performed.

7.1.1.1 Screening Failure

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 IP.

For purposes of data collection, all subjects who give consent to the study, but are not enrolled and/or randomized will be reported as screen failures even if they were otherwise fully eligible for the study, for example alternates/reserve subjects.

7.1.1.2 Rescreening of Subjects

Subjects who fail to meet all inclusion/exclusion criteria may be permitted to be rescreened for the study at the discretion of the study Principal Investigator in consultation with the Shire Study Medical Monitor.

Eligible subjects who meet all inclusion/exclusion criteria, but are unable to participate in the study due to scheduling conflicts/timing, may be rescreened based on investigator discretion and Sponsor approval should their availability to participate fall outside the screening window. In these cases, a new screening number must be assigned for each subject who is rescreened and a new informed consent form must be signed.

7.1.2 Predose Assessments

Following the screening visit, eligible subjects will return to the CRC on Day -1 of the study. Predose assessments, including check-in to the CRC will be performed on Day -1, as described in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6.

7.1.3 Treatment Periods

The non-Hispanic, Caucasian subjects will have one Treatment Period. The Japanese subjects will have Treatment Periods 1, 2, and 3.

7.1.3.1 Treatment Period 1 (Non-Hispanic, Caucasian Subjects)

Study assessments for non-Hispanic, Caucasian Subjects Days 1 and 2 in Treatment Period 1 are outlined in Table 5 and Table 6. Administration of maribavir will occur on Day 1 as described in Section 6.2.2. Non-Hispanic, Caucasian subjects will be discharged from the CRC on Day 2.

7.1.3.2 Treatment Period 1 (Japanese Subjects)

Study assessments for Japanese subjects on Days 1 and 2 in Treatment Period 1 are outlined in Table 1 and Table 2. Administration of maribavir will occur on Day 1, as described in Section 6.2.2. There will be a 72-hour washout period after administration of the IP on Day 1.

7.1.3.3 Treatment Period 2 (Japanese Subjects)

Study assessments for Japanese subjects on Days 1 and 2 in Treatment Period 2 are outlined in Table 1 and Table 3. Administration of maribavir will occur on Day 1, as described in Section 6.2.2. There will be a 72-hour washout period after administration of the IP on Day 1.

7.1.3.4 Treatment Period 3 (Japanese Subjects)

Study assessments for Japanese subjects on Days 1 and 2 in Treatment Period 3 are outlined in Table 1 and Table 4. Administration of maribavir will occur on Day 1, as described in Section 6.2.2. Japanese subjects will be discharged from the CRC on Day 2.

7.1.4 Follow-up Period (All Subjects)

There will be a follow-up telephone call at 7 (±4) days after the last dose of IP to query for SAEs, AEs, and concomitant treatments. Subjects who experience AEs will be followed longer if needed, including an unscheduled clinic visit if appropriate, depending on the nature, severity, and seriousness of the AE. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (Appendix 2.2).

7.1.5 Additional Care of Subjects After the Study

No after care is planned for this study.

7.2 Study Evaluations and Procedures

7.2.1 Demographic and Other Baseline Characteristics

Subject demographic information including date of birth, sex, age, race, and ethnicity will be collected at the initial screening visit, prior to the subject receiving the first dose of IP.

7.2.1.1 Height and Weight

Height and weight will be measured and recorded in the subject's source documents.

7.2.2 Safety

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

Actual safety assessment times will be monitored and recorded. The sponsor's expectation is that the investigator will ensure that every effort is made to perform all assessments at the protocol-scheduled time. Any safety assessment that deviates from the scheduled assessment time set forth in the protocol by more than ±15 minutes will be considered a protocol deviation.

Adverse events (defined as AEs occurring from the time of informed consent signature to first dose of IP), TEAEs (all AEs occurring after the first treatment or worsening after the first treatment), prior medication, and concomitant medication use will be assessed and monitored from the time the subject signs the informed consent form to completion of study (including to time of screen failure or dropout/discontinuation). While confined in the CRC, subject safety will also be closely monitored through blood pressure measurements, ECG measurement, clinical safety labs, and physician oversight.

7.2.2.1 Medical and Medication History

A complete medical and medication history, as well as demographic information, will be performed at the Screening Visit/time points described in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6 by a qualified licensed physician, physician's assistant, or a nurse practitioner. The medical and medication history will be collected and recorded in the subject's source documents. The medical history will include:

- History of respiratory, cardiovascular, renal, GI, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases
- Recent ingestion of medication (30 days prior to entering the Screening Period)
  Record medications taken via Injection/Infusion (IV, IM, SQ) ie, insulin, vaccine, etc.

7.2.2.2 Physical Examination (Including Height and Weight)

A complete physical examination will be performed at the time points described in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6 by a qualified licensed physician, physician's assistant, or a nurse practitioner.

The physical examination will include a review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose, and throat
- Spine/neck/thyroid
- Musculoskeletal
- Respiratory
- Cardiovascular
- Neurological
- Abdomen (including liver and kidneys).

If more than 2 days have passed since screening, a physical examination should be repeated on Day -1. Abnormalities identified at the Screening Visit will be documented in the subject's source documents and on the medical history CRF. Changes after the Screening Visit will be captured as AEs on the AE CRF page, as deemed appropriate by the investigator.

7.2.2.3 Adverse Event Collection

At each study visit and at the post-treatment follow-up telephone call, 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?"). Adverse events are collected from the time informed consent is signed. (Refer to Appendix 2 for AE definitions, assessment, collection time frame, and reporting procedures.)

7.2.2.4 Vital Signs

Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6. Additional blood pressure and pulse rate measurements may be performed, as determined by the investigator, in order to ensure appropriate monitoring of subject safety and accurate recording of vital sign measurements. Any changes from baseline which are deemed clinically significant by the investigator are to be recorded as an AE.

The same method for obtaining blood pressure measurement (auscultatory or oscillometric) should be used throughout the study (and documented) for all subjects. In addition, the conditions of vital sign measurements should be controlled and as consistent as possible during

the study, in order to minimize external variability of the readings. It is advised that measurements be collected at a comfortable room temperature with little to no background noise, using the same (appropriately sized) cuff placed at the same location of the same arm during the study. The bladder should be deflated (calibrated for oscillometric method or manually by auscultatory method) at a rate of 2-3 mmHg/s (and the first and last audible sounds recorded as systolic and diastolic pressure) after at least 5 minutes of rest in the supine position.

The cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1).

The subject should be asked to remove all clothing that covers the location of cuff placement. The subject should not have exercised or consumed coffee, black tea, cola, chocolate, alcohol, or nicotine within 30 minutes of collection. The subject should be instructed to relax as much as possible for at least 5 minutes prior to collection. The subject should remain quiet during this time and through the measurement.

The subject should be lying comfortably, with the legs uncrossed. The arm should be supported with a pillow, such that the middle of the cuff on the upper arm is at the level of the right atrium (approximately halfway between the bed and the level of the sternum).

At the Screening Visit, blood pressure should be compared between both arms.

One reading in a supine position should be taken. When there is a consistent inter-arm difference in either SBP/DBP confirmed over 3 consecutive measurements (>10mmHg), the arm with the higher blood pressure should be used for inclusion at screening and the last measurement recorded in the CRF. The same (right or left) arm with the higher blood pressure will be used throughout the study.

The use of automated devices for measuring pulse rate is acceptable although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

Respiratory Rate

The subject should be in a comfortable position. The observer should hold the extremity of the subject as a distraction for the patient (ie, pretending he/she is taking the subject's radial pulse) and count the respiration for 1 minute.

Body Temperature

Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used.

7.2.2.5 Electrocardiogram

Twelve-lead ECGs will be performed at the times specified in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6. All ECGs will be performed using the equipment supplied by the CRC.

The following parameters will be recorded on the appropriate CRF page: heart rate, PR, RR, QRS, and QT intervals. The Fridericia's correction for QT interval (QTcF) will be derived from the data in the database. The investigator's assessment of the ECG tracing as normal or abnormal must be documented, and if abnormal, his/her determination of whether the abnormality is clinically significant or not, will be documented on the tracing and recorded in the CRF.

The subject should be asked to remove all clothing that covers the location of lead placement. The subject should not have exercised or consumed coffee, black tea, cola, chocolate, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings.

Electrocardiogram recording, including a 10 second rhythm strip, will be obtained approximately 2 minutes to 4 minutes apart for all assessments. The recordings should be immediately assessed and if not valid, should be repeated in order to obtain a valid recording.

If QTc exceeds 450 msec, the ECG should be repeated 2 more times and the average of the 3 QTc values and the average of other triplicate ECG measurements should be used and recorded in the CRF. Invalid recordings will not be entered in the CRF.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements.

If the QTcF interval (calculated online on site) is increased by >45 msec from the baseline, or an absolute QTcF value is >500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2 minutes to 4 minutes apart, to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>45 msec from the baseline; or is >500 msec), then a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. When triplicate ECGs are collected, the mean of the triplicate measurements should be used to trigger the decision to collect follow-up ECGs.

If QTcF values remain above 500 msec (or >45 msec from the baseline) for >4 hours (or sooner at the discretion of the investigator); or QTcF intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to <500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the investigator).

If a machine-read QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTcF values are in the acceptable range.

7.2.2.6 Clinical Laboratory Tests

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

All clinical laboratory tests will be performed according to the laboratory's standard procedures.

The subject should not eat or drink anything for at least 8 hours to 10 hours before having clinical laboratory tests.

Reference ranges will be supplied by the laboratory and used to assess the results for clinical significance and out-of-range changes which may be associated with, or constitute, an AE. 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. Abnormal clinical laboratory values, which 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:

Biochemistry

Blood samples for serum biochemistry will be collected into a serum separator tube at the time points described in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6. The following parameters will be assessed:

Sodium	Phosphate	β-HCG [a]
Potassium	Protein	
Glucose(fasting)	Carbon dioxide	
Urea nitrogen	Albumin	
Creatinine	Aspartate transaminase	
Calcium	Alanine transaminase	
Chloride	Gamma glutamyl transferase	
Thyroid stimulating hormone (TSH)[a]	Alkaline phosphatase	
Thyroxine (free T4)	Total bilirubin	
Triiodothyronine (T3)	Uric acid	

[a] Females only.

Hematology

Blood samples for hematology will be collected into a K_2EDTA tube at the time points described in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6. The following parameters will be assessed:

Hemoglobin	Total neutrophils (absolute)
Hematocrit	Eosinophils (absolute)
Red blood cells	Monocytes (absolute)
Platelet count	Basophils (absolute)
White blood cell count; total and differential	Lymphocytes (absolute)

Urinalysis

A urine sample for urinalysis will be collected at the time points described in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6. The following parameters will be assessed:

pH	Blood	Nitrites
Glucose	Ketones	Leukocyte esterase
Protein	Bilirubin	Specific gravity

Microscopic examination will be conducted if protein and/or blood is/are detected during urinalysis. At a minimum the microscopic examination will consist of red blood cells, white blood cells, casts, and bacteria.

7.2.2.7 Pregnancy Test

A pregnancy test is performed on all females as outlined in Table 1 and Table 5, or if pregnancy is suspected, or on withdrawal of the subject from the study.

7.2.2.8 Drug and Alcohol Screen

A urine screen for drugs of abuse and alcohol will be performed at the time points described in Table 1 and Table 5. Additional drug and alcohol screens may be performed at the investigator's discretion.

Urine samples are to be tested for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiate metabolite, and phencyclidine.

Results of urine drug and alcohol screens will be reviewed and verified by the study monitor, but will not be collected in the CRF database.

Any positive result for drugs of abuse, cotinine, or alcohol at screening or on Day -1 will exclude the subject from further participation in the study.

7.2.2.9 Serology Screen

At the Screening Visit, a blood sample will be drawn into a serum separator tube to test for the presence of HIV, HBsAg, and HCV antibody.

The test results must be confirmed negative prior to enrollment in the study. If a test result is positive, the subject will be excluded from entering the study. Results of the virology screen will be reviewed and verified by the study monitor, but will not be collected in the CRF database.

7.2.3 Pharmacokinetic Procedures

The name and address of the bioanalytical laboratory(ies) for this study will be maintained in the investigator's files at the/each site and in the Trial Master File with the sponsor.

Actual PK blood sample collection times versus time of dosing will be recorded. The sponsor's expectation is that the investigator will ensure that every effort is made to collect all PK blood samples at the precise protocol scheduled time. Pharmacokinetic blood collection must not deviate from the nominal collection time set forth in the protocol by more than ±5 minutes from samples drawn within 4 hours post-dose or by more than ±15 minutes for samples drawn beyond 4 hours post-dose. Samples drawn outside these parameters will be considered a protocol deviation.

7.2.3.1 Blood Sample Collection and Handling Procedures

Blood samples will be collected at the time specified in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6 to measure plasma concentrations of maribavir and [redacted].

Blood sample collection, processing and handling instructions are provided in the Laboratory Manual.

7.2.3.2 Plasma Drug Assay Methodology

Plasma concentrations of maribavir and [redacted] will be measured using the most current validated bioanalytical method. In addition, selected plasma samples may be used to investigate incurred sample reproducibility (full details will be described in the bioanalytical study plan). The presence of other metabolites or artifacts may be monitored or quantified as appropriate. Raw data will be stored in the archive of the designated bioanalytical contract laboratory.

7.2.4 Volume of Blood to be Drawn from Each Subject

The volume of blood intended to be drawn from each subject is presented in Table 7.

Table 7 Volume of Blood to be Drawn from Each Subject

Assessment		Approximate Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic samples [a]		4	42 (Japanese) 14 (Caucasian)	168 mL (Japanese) 56 mL (Caucasian)
HBsAg, HIV, HCV		3.5	1 (Japanese) 1 (Caucasian)	3.5 mL (Japanese) 3.5 mL (Caucasian)
Safety	Biochemistry and β-HCG [b]	5	8 (Japanese) 4 (Caucasian)	68 mL (Japanese) 34 mL (Caucasian)
	Hematology	4	8 (Japanese) 4 (Caucasian)	32 mL (Japanese) 16 mL (Caucasian)
Total mL				271.5 mL (Japanese) 109.5 mL (Caucasian)

β-HCG=beta-human chorionic gonadotropin; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus

[a] If a catheter is used, the first 1mL is to be discarded; then take 2mL into appropriate tube for pharmacokinetic sample. A total of 3mL of blood drawn has been used in determination of sample volume.

[b] β-HCG testing for females only.

During this study, it is expected that approximately 271.5 mL of blood will be drawn from Japanese subjects and approximately 109.5 mL of blood will be drawn from Caucasian subjects regardless of sex.

Note: The amount of blood to be drawn for each assessment 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. DATA MANAGEMENT AND STATISTICAL METHODS

8.1 Data Collection

The investigators' authorized site personnel must enter the information required by the study CRF Completion Guidelines or similar for all data requiring transcription of the source. 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. It is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

8.2 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.

8.3 Data Handling

Not applicable to this study.

8.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The Statistical Analysis Plan (SAP) will provide the statistical methods and definitions for the analysis of the PK 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, IP exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513).

8.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There is no planned interim analysis, adaptive design, or Data Monitoring Committee in this study.

8.6 Study Population

The **Enrolled Set** will consist of all subjects who have signed informed consent and also passed inclusion/exclusion criteria.

The **Safety Set** will consist of all subjects who receive any amount of IP. Analysis will be performed according to the treatment regimen actually received regardless of the randomized treatment regimen.

The Pharmacokinetic (**PK) Set** will consist of subjects who receive at least 1 dose of study drug and have evaluable post-dose maribavir PK data (defined as complete concentration-time profile to obtain meaningful estimates of PK parameters). The PK analyses will be based on this analysis population.

Subjects who do not provide reliable concentration-time profile (in 1 or more periods) may be excluded from PK analysis (for the corresponding treatment period).

8.7 Pharmacokinetic Analyses

8.7.1 Pharmacokinetic Endpoint(s)

A PK evaluation of maribavir concentrations and [redacted] will be performed based on the PK Set. Pharmacokinetics parameters will be estimated for maribavir and [redacted] following the administration of maribavir 400 mg for non-Hispanic, Caucasian subjects and of 200, 400, and 800 mg for subjects of Japanese descent.

Maribavir C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ will be the primary endpoints. [redacted]

PK parameters will include, but not be limited to the following:

- C_{max} Maximum observed plasma concentration
- t_{max} Time of maximum observed concentration sampled during a dosing interval
- AUC_{last} Area under the curve from the time of dosing to the last measurable concentration
- $AUC_{0\text{-}inf}$ Area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration

- $AUC_{0\text{-}inf}$%extrap The percent of $AUC_{0\text{-}inf}$ extrapolated, calculated by $(1\text{-}AUC_{last}/AUC_{0\text{-}inf})*100$
- λz elimination rate in the terminal phase
- $t_{1/2}$ Terminal half-life
- CL/F Apparent total body clearance following extravascular administration calculated as dose divided by $AUC_{0\text{-}inf}$
- Vz/F Apparent volume of distribution following extravascular administration calculated as CL/F divided by λz
- T_{lag} Delay between the time of dosing and time of appearance of drug (investigational) in plasma in the employed sampling scheme

In addition, dose-normalized (to 400 mg) AUC_{last}, $AUC_{0\text{-}inf}$, and C_{max} will be calculated for Japanese subjects.

8.7.1.1 Statistical Analysis of Pharmacokinetic Parameters

Maribavir C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ will be the primary endpoints. [redacted] Individual concentrations and PK parameters (including dose-normalized) of maribavir and [redacted] will be listed and summarized by maribavir dose with descriptive statistics (number, arithmetic mean, standard deviation [SD], coefficient of variation [CV], median, minimum, maximum, geometric mean, and percent coefficient of variation (CV%) of geometric mean. The 95% CIs of the geometric means of C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ parameters will be presented as well. Figures of individual and mean (±SD) maribavir concentration-time profiles will be generated on linear and semi-log scales. The mean concentration-time profiles will be generated and displayed by overlaying the Japanese cohort and Non-Hispanic Caucasian cohort. Figures of PK parameters and dose-normalized PK parameters vs. dose in Japanese subjects will be generated. Box-Whisker plots for selected PK parameter will be generated with Japanese cohort and Non-Hispanic Caucasian side by side.

In order to compare the PKs of maribavir between subjects of Japanese descent and matched non-Hispanic, Caucasian subjects, the differences of log-transformed PK parameters (AUC_{last}, $AUC_{0\text{-}inf}$, and C_{max}) from the maribavir 400 mg oral dose will be examined between cohorts using an analysis of variance model. The geometric mean ratio and its 90% CI of PK parameters for Japanese descent vs. Caucasian will be provided from the model. In addition, the difference of log-transformed dose-normalized AUC_{last}, $AUC_{0\text{-}inf}$, and C_{max} will be examined between the Japanese cohort estimated at the 200 mg dose and the Non-Hispanic Caucasian cohort estimated at the 400 mg dose, as well as between the Japanese cohort estimated at the 800 mg dose and the Non-Hispanic Caucasian cohort estimated at 400 mg dose, using an analysis of variance model. The geometric mean ratio and its 90% CI will be provided from the model. Forest plots of geometric mean ratios for selected PK parameters between Japanese cohort vs. the Non-Hispanic Caucasian cohort at 400 mg will be generated. [redacted]

Dose proportionality will also be examined for maribavir PK parameters for the Japanese subjects. Dose proportionality will be assessed for C_{max} and AUC (AUC_{last} and $AUC_{0\text{-}inf}$) using the power model. The power model assumes a linear relationship between the natural log transformed parameter and the natural log transformed dose.

$\ln(\text{Parameter}) = \alpha + \beta \times \ln(\text{Dose}) + \text{Random error}$

Where α is the intercept, β is the slope, and Random error is a random residual error. Dose proportionality will be assessed by estimating mean slope with the corresponding two-sided 90% CI from the power model. The fold increase in PK parameters and associated 90% CI when doubling the dose will be presented. [redacted]

8.8 Safety Analyses

The Safety Set will be used to summarize safety data. Safety will be assessed for the following evaluations:

- Number, severity, seriousness, and causality of TEAEs
- Changes in vital signs ECGs, and clinical laboratory results (hematology, chemistry, and urinalysis) from baseline to post-baseline time points. Baseline is defined as the last non-missing assessment prior to the first dose.

Safety data, including TEAEs, 12-lead ECGs, vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate), and clinical laboratory data (biochemistry, hematology, and urinalysis, will be summarized with the descriptive statistics. Potentially clinically important findings will also be summarized or listed. The potentially clinically important values will be defined in the SAP.

Quantitative safety data as well as the difference from baseline, if applicable, will be summarized by descriptive statistics. Frequency counts will be compiled for classification of qualitative safety data. Direct safety comparisons between the two cohorts (the subjects of Japanese descent and Non-Hispanic Caucasian subjects) will be presented from the maribavir 400 mg dosing data. All other safety data from the 200 mg and 800 mg in the subjects of Japanese descent will be summarized and listed.

For each safety variable, the last value collected before the first dose of investigational product in that treatment period will be used as baseline for all analyses of that safety variable in that treatment period.

An AE (classified by preferred term [PT]) that occurred during the study will be considered a TEAE if it had a start date on or after the first dose of investigational product or if it had a start date before the date of the first dose of investigational product, but increased in intensity on or after the date of the first dose of investigational product. An AE that occurred after the follow-up phone call will not be counted as a TEAE.

Adverse events will be coded using the agreed-upon version of Medical Dictionary for Regulatory Activities, Version 23.0. or later. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, and by PT. Treatment emergent adverse events will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

8.9 Sample Size Calculation and Power Considerations

The sample size consideration for the primary objective of evaluating the PK profile of maribavir, administered as a single oral dose at 400 mg, between Japanese subjects and matched, healthy, adult, non-Hispanic, Caucasian subjects is based on feasibility and comparable studies.

A total of 24 subjects (12 subjects of Japanese descent and 12 matched, non-Hispanic, Caucasian subjects) will be targeted to be enrolled in the study.

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10. PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	30 April 2020	Global
Amendment 1.0	08 July 2020	Global

Appendix 1 Regulatory, Ethical, and Study Oversight Considerations

Appendix 1.1 Regulatory and Ethical Considerations

This study is conducted in accordance with current applicable regulations including ICH E6, EU Directive 2001/20/EC, and all updates, as well as local ethical and legal requirements.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

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.

Appendix 1.2 Sponsor's Responsibilities

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, current ICH GCP guideline E6 (1996), EU Directive 2001/20/EC Guidelines, as well as all applicable national and local laws and regulations.

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

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

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.

The timing for study registration and results summary posting must be in accordance with applicable local and national requirements.

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 study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

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 Institutional Review Boards (IRBs)/Ethics committees (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.

Appendix 1.3 Investigator's Responsibilities

Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

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

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curricula 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.

Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

Protocol Adherence and Investigator Agreement

The investigator and any sub-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 IP, 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.

Documentation and Retention of Records

Case Report Forms

Case report forms are supplied by the 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 will have separate source documentation; no data will be recorded directly onto the CRF.

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.

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

Once the CRA/study monitor has verified the contents of the completed CRF pages against the source data, the duplicate pages are retrieved and forwarded to the study sponsor (or designee) for data entry. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

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 and original clinical laboratory reports

All key data must be recorded in the subject's source documents.

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

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc.).

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 United States Food and Drug Administration [US FDA], European Medicines Agency [EMA], United Kingdom Medicines and Healthcare products Regulatory Agency UKMHRA) or an auditor.

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

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.

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 IP; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

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.

Appendix 1.4 Ethical Considerations

Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally-authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent 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.

The principal investigator provides the sponsor with a copy of the consent form which was reviewed by the IRB/EC and which received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

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

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

Investigational product supplied will not be released until the sponsor has received written IRB/EC approval.

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. If required by local law, substantial amendments to the protocol must also be approved by the appropriate regulatory agency prior to implementation.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC appraised of the progress of the study and of any changes made to the protocol, at least annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. This can be the responsibility of the sponsor or investigator for sites within the EU; or for multicenter studies, the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs as required by IRB/EC procedures.

Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the 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 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/EC 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 identifying number.

The results of studies containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth, where allowed per local law, 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.

Study Results / Publication Policy

The term "Publication" shall mean any paper, article, manuscript, report, poster, internet posting, presentation slides, abstract, outline, video, instructional material, presentation (in the form of a written summary), or other public disclosure of the study results, in printed, electronic, oral, or other form. The parties understand and agree that participation in the study may involve a commitment to publish the data from all sites participating in the study in a cooperative publication with other investigators prior to publication or oral presentations of the study results on an individual basis. The site agrees not to publish or present the site's study results until such time as either the aggregate multi-site study results are published in a cooperative publication or for a period of one (1) year after termination or completion of the study at all participating sites, whichever shall first occur. After that time, the site may publish the site's study results in scientific journals or present the study results at symposia or other professional meetings in accordance with the following provisions:

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.

At least sixty (60) days prior to submitting an abstract, manuscript, or other document for publication, a copy of the proposed publication will be provided to the sponsor by the site for review. Upon the sponsor's request, the site agrees to remove any and all confidential information (expressly excluding study results) identified in the publication and to delay such submission or presentation for an additional sixty (60) day period in order to allow the sponsor time to file any patent application(s). All publications of the study results shall appropriately reference the multi-site study publication, if any, or the fact that the study results are a subset of data resulting from a larger multi-site study.

Shire is committed to transparent dissemination of all scientific, technical and medical manuscripts generated from Shire-supported research. Therefore, after January 1, 2018, Shire will require the submission of all Shire-supported research manuscripts to journals that offer public availability via Open Access (including publisher platforms/repositories and self-archiving). Open Access refers to the free at point of entry, online availability of published research output with, where available, rights of re-use according to an End User License.

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) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals. Participation as an investigator does not confer any rights to authorship of publications.

Appendix 2 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

Appendix 2.1 Adverse Event Definitions

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 IP or medicinal product. 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).

Treatment-emergent Adverse Event

A TEAE is defined as any event emerging or manifesting at or after the initiation of treatment with an IP or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the IP or medicinal product.

Serious Adverse Event

An SAE is any untoward medical occurrence (whether considered to be related to IP 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, that are the result of elective or previously scheduled investigations procedures or surgery for pre-existing conditions and 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
- Results in 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 bronchospasm associated with anaphylaxis 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.

Unexpected Adverse Event

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the IB. "Unexpected" also refers to the AEs that are mentioned in the maribavir IB and/or prescribing information as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IB and/or prescribing information as the Reference Safety Information. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any suspected adverse reaction to study treatment (ie, including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Unanticipated Adverse Device Effect

An unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study protocol or product labeling; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Clinical Laboratory and Other Safety Assessment

A change in the value of a clinical laboratory parameter, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of IP, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the IP, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, or ECG values which were not present at the pretreatment evaluation 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 or expected disease evolution) is found for the abnormal values.

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

Appendix 2.2 Collection of Adverse Events

All AEs/SAEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.4. This includes events occurring during the screening phase of the study, regardless of whether or not IP is administered.

All AEs/SAEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to baseline), 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.

Appendix 2.3 Assessment of Adverse Events

Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity is captured as a new event. Worsening medical conditions, signs or symptoms present prior to initiation of IP, must be recorded as new AEs.

For example, if a subject reports mild intermittent dyspepsia prior to initiation of dosing with the IP, and the dyspepsia becomes severe and more frequent after first dose of a new AE of severe dyspepsia (with the appropriate date of onset) should be documented in the source.

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.

Relationship Categorization

A physician/investigator must make the assessment of relationship to IP 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 IP. 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 IP and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the IP 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 IP and the event.

Outcome Categorization

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

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown.

If applicable, action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF.

Appendix 2.4 Safety Reporting

Reference Safety Information

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

Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department, the CRO, and Shire Medical Monitor within 24 hours of becoming aware of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (Appendix 2.9) unless they result in an SAE.

The investigator must complete, sign, and date the Shire "Clinical Study Serious Adverse Event for SAEs and Non-serious AEs as Required by Protocol" Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested), and fax or e-mail the form to the Shire Global Drug Safety Department. A copy of the Shire Clinical Study Serious Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the CRO and Shire Medical Monitor using the details specified in the emergency contact information section of the protocol.

Appendix 2.5 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to IP) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.4, and must be reported to the Shire Global Drug Safety Department and the CRO and Shire Medical Monitor within 24 hours of the first awareness of the event.

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

Appendix 2.6 Serious Adverse Event Onset and Resolution Dates

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

In addition, any signs or symptoms reported 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.

Appendix 2.7 Fatal Outcome

Any SAE that results in the subject's death (eg, 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 IP action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the IP should be recorded as "dose not changed" or "not applicable" (if the subject never received IP or it is a single dose study). The IP action of withdrawn should not be selected solely as a result of the subject's death.

Appendix 2.8 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.4.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Shire Global Drug Safety Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO and Shire Medical Monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form.

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 post-partum.

Appendix 2.9 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 Appendix 2.4.

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 IP when used for a non-medical 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 IP other than as directed or indicated at any dose (Note: this includes a situation where the IP is not used as directed at the dose prescribed by the protocol)

- **Overdose** – Intentional or unintentional intake of a dose of IP higher than the protocol-prescribed dose

- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an IP. Medication errors should be collected/reported for all products under investigation. The administration and/or use of the unassigned treatment, or the administration and/or use of an expired IP is/are always reportable as a medication error.

Cases of subjects missing doses of the IP should be reported as missed dose.

Appendix 2.10 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm, these do not constitute de facto deviation from the protocol. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may implement urgent safety measures to protect study subjects from immediate hazard to their health or safety. The measures should implement immediately and does not require prior authorization from the sponsor. In the event(s) of an apparent direct hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, and within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible IRB(s)/EC(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

Appendix 2.11 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor is responsible for notifying the relevant regulatory authorities, IRBs and ECs of related, unexpected SAEs.

In addition, the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the TAK-620 program.

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