CLINICAL STUDY PROTOCOL

NCT Number: NCT04131556

Study Title: A Phase 1, Open-label, Randomized, Crossover, Bioavailability, Dose Proportionality, and Food Effect Study Comparing the Pharmacokinetics and Palatability of Two Candidate Pediatric Powder-for-Oral-Suspension Formulations of Maribavir to the Current Maribavir Tablet Formulation Administered in Healthy Adult Subjects

Study Number: TAK-620-1019

Protocol Version and Date:

Original Protocol: 28 Aug 2019
Amendment 1: 05 Nov 2019

PROTOCOL: TAK-620-1019

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DRUG: TAK620 (SHP620), Maribavir

IND: 051001

EUDRACT NO.: 2015-004725-13

SPONSOR: Shire Human Genetic Therapies, Inc. (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], MD
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PROTOCOL HISTORY: Original Protocol: 28-Aug-2019

Protocol Signature Page

Sponsor's (Shire) Approval

Signature: [redacted]	Date: [redacted]
[redacted], MD, PhD, MPH	

Investigator's Acknowledgement

I have read this protocol for Study TAK-620-1019.

Title: A Phase 1, Open-label, Randomized, Crossover, Bioavailability, Dose Proportionality, and Food Effect Study Comparing the Pharmacokinetics and Palatability of Two Candidate Pediatric Powder-for-Oral-Suspension Formulations of Maribavir to the Current Maribavir Tablet Formulation Administered in Healthy Adult 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 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], MD [redacted] [redacted] [redacted]

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of an SAE, the investigator must fax or e-mail the "Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by 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)/Shire Medical Monitor using the details below.

For protocol- or safety-related questions or concerns <u>during normal business hours 8:00 am-5:00pm (local time per region),</u> the investigator must contact the Shire Medical Monitor:

[redacted], MD, PhD, MPH

Clinical Pharmacology Medical Leader/ Shire Study Medical Monitor

Telephone: [redacted] (business hours)

[redacted] (24-hour coverage)

E-mail: [redacted]

For protocol- or safety-related questions or concerns <u>outside of normal business hours</u>, 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 according to procedures.

This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination); or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products); or a product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but did not result in an AE, which include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, eg, reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (eg, potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

For instructions on reporting AEs related to product complaints, see Appendix 4.4.

Please use the information below as applicable to report the Product Quality Complaint or Non-Medical Complaint:

Origin of Product Quality Complaint	E-mail Address
North and South America	[redacted]
European Union and Rest of World	[redacted]

Telephone number (provided for reference if needed):

Shire, Lexington, MA (USA)

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
AUC	area under the curve
$AUC_{0\text{-last}}$	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
β-HCG	beta-human chorionic gonadotropin
BCS	Biopharmaceutics Classification System
BMI	body mass index
CI	confidence interval
C_{max}	maximum concentration occurring at t_{max}
CL/F	oral clearance
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSU	clinical study unit
CV%	coefficient of variation
EC	ethics committee
ECG	electrocardiogram
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antibody
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HSA	serum albumin
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
PK	pharmacokinetics
PCI	potentially clinically important
QTc	corrected QT interval
SAE	serious adverse event

SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
TID	3 times daily
T_{lag}	delay between the time of dosing and time of appearance of concentration in the sampling
t_{max}	time of maximum observed concentration sampled during a dosing interval
TSH	thyroid-stimulating hormone
$t_{1/2}$	terminal half-life
US	United States

STUDY SYNOPSIS

Protocol number: TAK-620-1019	**Drug:** Maribavir

Title of the study: A Phase 1, Open-label, Randomized, Crossover, Bioavailability, Dose Proportionality, and Food Effect Study Comparing the Pharmacokinetics and Palatability of Two Candidate Pediatric Powder-for-Oral-Suspension Formulations of Maribavir to the Current Maribavir Tablet Formulation Administered in Healthy Adult Subjects

Number of subjects (total and for each treatment arm): 38 subjects (18 in Part 1 and 20 in Part 2)

Investigator: [redacted], MD

Site(s) and Region(s):
[redacted]

Study period (planned): 2019-2020	**Clinical phase:** 1

Objectives:

Part 1:

- To assess the relative bioavailability of 2 candidate pediatric formulations of maribavir given as a single oral dose at 200 mg as compared to the Phase 3 adult maribavir 200 mg tablet formulation in healthy adult subjects (Primary)
- To assess the palatability of the candidate pediatric formulations measured by a questionnaire (Primary)
- To assess the safety and tolerability of 2 candidate pediatric formulations and the adult tablet formulation of maribavir given as a single oral dose at 200 mg in healthy adult subjects (Secondary)

Part 2:

- To assess the dose proportionality of 50 mg, 100 mg, and 200 mg of the selected pediatric formulation (Primary)
- To assess the impact of food on the rate and extent of absorption of the selected maribavir pediatric formulation given as 200 mg under fasted and fed conditions (Primary)
- To assess the palatability of maribavir formulations at various doses and with food (Primary)
- To assess the safety and tolerability of 2 candidate pediatric formulations and the adult tablet formulation of maribavir given as a single oral dose up to 200 mg in healthy adult subjects (Secondary)

Rationale:

In order to provide a palatable formulation for pediatric use, a taste-masking strategy that minimizes the availability of maribavir in the oral cavity is being explored. As the coating polymer has the potential to hinder drug release and absorption, 2 prototype formulations, each containing the same coating polymer but at different levels, are being evaluated in this study for their impact on palatability and rate and extent of absorption of maribavir. There were no significant effects of food on the rate and extent of absorption of maribavir from the adult tablet formulation, however, since maribavir is a Biopharmaceutics Classification System (BCS) II drug (ie, low solubility-high permeability drug) and the coating polymer may affect the rate and extent of absorption of maribavir, it is necessary to evaluate dose proportionality of the pediatric formulation and effects of food.

Investigational product, dose, and mode of administration:
Treatment A: maribavir 200 mg tablet- current Phase 3 formulation
Treatment B: maribavir 200 mg powder for oral suspension, 32.5% drug loading
Treatment C: maribavir 200 mg powder for oral suspension, 36.1% drug loading
Treatment D: maribavir powder for oral suspension (50 mg fasted)
Treatment E: maribavir powder for oral suspension (100 mg fasted)

Treatment F: maribavir powder for oral suspension (200 mg fasted)
Treatment G: maribavir powder for oral suspension (200 mg fed with a high-fat meal)

Methodology:

This is a single-center (United States), open-label, randomized study. The study will be conducted sequentially in 2 parts. A total of 18 subjects will be enrolled in Part 1 of the study and a total of 20 subjects will be enrolled in Part 2. The study duration will comprise of a 28-day screening period for Part 1 and a 28-day screening period for Part 2. Part 1 will have 3 treatment periods with a 3-day washout period between each of the 3 periods and a follow-up phone call. Part 2 will have 4 treatment periods with a 3-day washout period between each of the 4 treatment periods and a follow-up phone call.

Subjects will be admitted to the clinical study unit (CSU) on Day -1.

In Part 1 2 pediatric candidate powder formulations will be compared with maribavir 200 mg tablet under fasted conditions in regards to their bioavailability and palatability to select 1 pediatric powder formulation for further evaluation in Part 2. In Part 2 dose proportionality of 50, 100 and 200 mg dose of the selected pediatric powder formulation of maribavir will be assessed, as well as the impact of food (a high-fat meal) on the rate and extent of absorption of the selected pediatric formulation. The pediatric formulation of maribavir which will be evaluated in Part 2 will be chosen based on the results of interim analysis of Part 1 pharmacokinetic (PK) and palatability data from 2 candidate pediatric formulations.

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/and assent as applicable to participate in the study.
3. Age 18-50 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.
4. 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. Additional details will be outlined in the protocol.
5. 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 electrocardiogram (ECG), hematology, blood chemistry (includes TSH and free T_4 [FT_4] at screening only), and urinalysis.
6. Hemoglobin for males ≥135.0 g/L and females ≥120.0 g/L at screening and on Day -1.
7. Body mass index (BMI) between 18.0 and 30.0 kg/m^2 inclusive with a body weight >50 kg (110 lbs). This inclusion criterion will only be assessed at the first screening visit.
8. Ability to swallow a dose of investigational product.

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 investigational product, 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 investigational product or procedures.
3. Known or suspected intolerance or hypersensitivity to the investigational product(s), 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 investigational product.
5. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the first dose of investigational product.
6. Within 30 days prior to the first dose of investigational product:
   a. Have used an IP (if elimination half-life is <6 days, otherwise 5 half-lives).
   b. Have been enrolled in a clinical study (including vaccine studies) that, in the investigator's opinion, may impact this Shire-sponsored study.
   c. Have had any substantial changes in eating habits, as assessed by the investigator.
7. Confirmed systolic blood pressure >139 mmHg or <89 mmHg, and diastolic blood pressure >89 mmHg or <49 mmHg.
8. 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.
9. Known history of alcohol or other substance abuse within the last year.
10. 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).
11. A positive screen for alcohol or drugs of abuse at screening or on Day -1 of Treatment Period 1.
12. A positive human immunodeficiency virus (HIV), hepatitis B surface antibody (HBsAg), or hepatitis C virus (HCV) antibody screen.

13. 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 investigational product (maribavir).
14. 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 tea, three 1 oz [85 g] chocolate bars. (Decaffeinated coffee, tea, or cola are not considered to contain caffeine).
15. Prior screen failure randomization, participation, enrollment in this study or participation in Part 1 of this study.
16. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations) with the exception of hormonal replacement therapy. Current use of antacids and H2 antagonists. Current use is defined as use within 30 days of the first dose of investigational product.
17. Ingestion of known CYP3A modulators within 7 days of Day 1, Period 1 (includes grapefruit or grapefruit juice, oranges, Seville oranges, apples or apple juice, vegetables from the mustard green family [eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard], charbroiled meats, and products containing these ingredients).
18. Inability or unwillingness to consume 100 percent of high-fat meal in Part 2 (including subjects with lactose or gluten intolerance)..
19. History of oral/nasal cavity infections, gastroesophageal reflux, asthma treatment with albuterol, zinc supplementation.
20. Subjects with dry mouth syndrome or burning mouth syndrome or menopausal women suffering from dysgeusia.

Maximum duration of subject involvement in the study:

The maximum total duration of study participation for a subject in Part 1 is 46 days. The maximum total duration of study participation for a subject in Part 2 is 49 days.

- Planned duration of screening period Part 1: 28 days
- Planned duration of screening period Part 2: 28 days
- Planned duration of treatment period Part 1: 7 days
- Planned duration of treatment period Part 2: 10 days
- Planned duration of follow-up Part 1: 7±2 days after the last dose of investigational product.
- Planned duration of follow-up Part 2: 7±2 days after the last dose of investigational product.

Endpoints and statistical analysis:

Two analysis populations are defined for this study in Part 1 and in Part 2: pharmacokinetic and safety.

For Part 1:

- The pharmacokinetic population consists of subjects who received at least 1 dose of maribavir, did not vomit within 4 hours of dosing, and have at least 1 evaluable post-dose maribavir concentration value in Part 1.
- The safety population includes subjects who have received at least 1 dose of maribavir in Part 1.

For Part 2:

- The pharmacokinetic population consists of subjects who received at least 1 dose of maribavir, did not vomit within 4 hours of dosing, and have at least 1 evaluable post-dose maribavir concentration value in Part 2.
- The safety population includes subjects who have received at least 1 dose of maribavir in Part 2.

Pharmacokinetic endpoint:

The PK analysis will be based on the PK analysis dataset. Pharmacokinetic parameters will be calculated from maribavir concentration-time data using non-compartmental analysis (NCA) and all calculations will be based

on actual sampling times. Pharmacokinetic parameters will include, but not be limited to, the following:

Part 1 (Day 1, Day 4, and Day 7)

- C_{max}: Maximum concentration occurring at t_{max}
- t_{max}: Time of maximum observed concentration sampled during a dosing interval
- $AUC_{0\text{-}last}$: 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
- $t_{1/2}$ Terminal half-life
- CL/F Apparent total body clearance following extravascular administration calculated as dose divided by $AUC_{0\text{-}inf}$
- T_{lag} Delay between the time of dosing and time of appearance of plasma concentration in the employed sampling scheme

Part 2 (Day 1, Day 4, Day 7, and Day 10)

- C_{max} Maximum concentration occurring at t_{max}
- t_{max} Time of maximum observed concentration sampled during a dosing interval
- $AUC_{0\text{-}last}$ 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
- $t_{1/2}$ Terminal half-life
- CL/F Apparent total body clearance following extravascular administration divided by the fraction of dose absorbed calculated as dose divided by $AUC_{0\text{-}inf}$
- T_{lag} Delay between the time of dosing and time of appearance of concentration in the sampling

In addition, dose-normalized C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ will be calculated for Treatments D, E, and F.

Safety endpoint:

Safety will be assessed for the following evaluations for both Part 1 and Part 2:

- Number, severity, seriousness, and causality of treatment-emergent adverse events (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.

Palatability endpoint:

The palatability will be evaluated to identify, characterize and quantify the sensory attributes of products, eg, basic tastes, texture and mouth feel and to assess the overall acceptability.

Sample Size Justification:

A sample size of 18 subjects in Part 1 and 20 subjects in Part 2 is calculated assuming a true mean ratio of 1.0 with intra-subject coefficient of variation of 0.218, a total of 18 completers is required to have 80% power to show that the 90% confidence intervals of the ratios of the geometric means of the two formulations/treatment lie within the range of 0.80 to 1.25.

The table below indicates the number of subjects required based on the following data:

- The intra-subject coefficient of variation is assumed at 0.166 and 0.218 respectively for $AUC_{0\text{-}inf}$ and C_{max}, which are estimated from the 90% confidence intervals (CIs) of the geometric mean ratio of $AUC_{0\text{-}inf}$, and C_{max} in Study 1263-104.

- Sample size estimation is performed using nQuery's two one-sided test (TOST) of equivalence in ratio of mean for crossover design study.
- True mean ratio: 1.00, 1.05
- Power: 80%, 90%
- One-sided α-level: 0.05 (corresponding to 90% CI)
- Bioequivalence range: 0.8-1.25

	Number of Subjects Required		
		Intra-subject coefficient of variation	
True Ratio	**Power**	0.166	0.218
1.0	80%	12	18
	90%	14	22
1.05	80%	14	22
	90%	18	28

Note sample size estimation is performed using nQuery's TOST of equivalence in ratio of mean for crossover design study.

Statistical Methodology for Pharmacokinetic Endpoint(s):

Part 1

Individual concentrations and PK parameters of maribavir will be listed and summarized by treatment with descriptive statistics (number, arithmetic mean, standard deviation [SD], coefficient of variation [CV%], median, minimum, maximum, geometric mean, and %CV of geometric mean). Figures of individual and mean (+/-SD) concentration-time profiles of plasma maribavir by treatment will be generated on both linear and semi-log scales.

Following the $\log_e$-transformation, the PK parameters including AUC_{last}, $AUC_{0\text{-}inf}$, and C_{max} will be analyzed using a mixed effect model to include sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Analysis of variance will be performed using SAS mixed linear models procedure. Point estimates and their associated 90% CIs will be constructed for the differences in the log-transformed parameters. The point estimates and their associated 90% CIs will be then back-transformed to provide point estimates for the ratio of geometric least squares means and associated 90% CIs on the original scale. Analysis of t_{max} and tlag will be performed by nonparametric t-test.

Part 2

Dose proportionality analysis

The dose proportionality will be first assessed using the Power Model for 50-200 mg (fasted) dose range. The Power Model: $\log(Y_{ijk})=S_i + P_j + \beta x\log(D_k) + \varepsilon_{ijk}$ where D is the total number of doses, N are the total number of subjects and P the total number of periods and i=1,…..,N, j=1,…..,P and k=1,……,D. Y_{ijk} is the log-transformed response variable, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, or C_{max} on the kth dose, in the jth period, for the ith subject. S_i is the random subject effect for the ith subject, P_j is the fixed period effect for the jth period, β was the slope and ε_{ijk} is the error. If the 90% confidence interval for the model estimated mean slope falls within 0.8 and 1.25 limits, then dose proportionality will be concluded. The estimate and 90% confidence interval for the slope and fold increase in PK exposure when doubling the dose will be presented. The corresponding graphical display from the powermodel (back transformed to raw linear scale) with the 90% CI overlaid on the observed data will be provided.

Additionally, a mixed effect analysis of variance (ANOVA) model will be performed with the log-transformed dose normalized response variable, $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, or C_{max}. The geometric mean ratios and 90% CI for each dose compared to the reference dose (50 mg dose) will be provided.

Analysis of Effect of Food

A mixed effect ANOVA model will be performed with log transformed $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, or C_{max}. Point estimates and 90% CI for geometric mean ratios will be computed for treatments (maribavir 200 mg fed vs. 200 mg fasted). If the 90% CI for the geometric mean ratios of treatments (maribavir 200 mg fed vs. 200 mg fasted) falls within 0.8 and 1.25 limits, then equivalence will be concluded. Analysis of t_{max} and tlag will be performed by nonparametric t-test.

Statistical Methodology for Palatability Endpoint:

Data collected from the palatability questionnaire will be summarized descriptively.

STUDY SCHEDULE(S)

Table 1: Schedule of Assessments Part 1

Visit[a]	Screening	Treatment Period 1				Treatment Period 2			Treatment Period 3		Follow-up[l]
Study Day	**-28 to -2**	**-1**	**1[j]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demography	X										
Medical/medication history	X	X									
Physical examination[b]	X	X	X			X			X	X	
Randomization			X[k]								
Vital signs (blood pressure, pulse)[b,c]	X	X	X	X	X	X	X	X	X	X	
Oral temperature	X	X	X			X			X	X	
Height and weight[d]	X	X	X			X			X	X	
Electrocardiogram (12-lead)[b,e]	X	X	X	X		X	X		X	X	
Biochemistry, hematology, and urinalysis[b, f, m]	X	X		X			X			X	
HIV, HBsAg, and HCV antibodies	X										
Beta HCG Pregnancy test (females only)[b, g]	X	X								X	
FSH[h] test in perimenopausal women	X										
Urine drug and alcohol screening[i]	X	X									
Investigational Drug Administration			X			X			X		
Pharmacokinetic blood sampling[j, n]			X	X		X	X		X	X	
Palatability Assessment			X			X			X		
Admit to the CSU (Day -1)		X									
Discharge from the CSU (Day 8 after last assessment)										X	
Washout between treatment periods			X	X	X	X	X	X			
Adverse events/serious adverse events[b]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X

β-hCG=beta-human chorionic gonadotropin; CSU-clinical study unit; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PK=pharmacokinetic; SAE=serious adverse event; TSH=thyroid-stimulating hormone

[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. Treatment Period 1 includes washout (Days 1 through 3), Treatment Period 2 includes washout (Days 4 through 6), and Treatment Period 3 is from Days 7 through 8.

[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. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

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

[e] Twelve-lead ECGs will be measured in the supine position. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

[f] Clinical laboratory assessments include serum biochemistry, TSH and FT_4, at (screening only), hematology, and urinalysis.

[g] Serum β-HCG test at Screening is required for all females. Urine pregnancy test is required for all females at subsequent scheduled time points.

[h] Females only, to confirm menopausal status.

[i] Drugs of abuse and alcohol at screening and Day-1

[j] See Table 2, Table 3, and Table 4 for detailed collection time points.

[k] Randomization is for Treatment Period 1, Day 1 only.

[l] There will be a follow-up telephone call approximately 7±2 days following the last dose of investigational product in Treatment Period 3 (Day 7). AEs/SAEs occurring up to the time of the follow-up telephone call will be captured. The follow-up telephone call should be completed for all subjects including those who withdraw or are removed from the study prior to Day 8 of Treatment Period 3.

[m] If screening occurs on Day -2, biochemistry, hematology and urinalysis is not required on Day -1

[n] 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.

Table 2: Detailed Schedule of Assessments for Treatment Period 1 (Day 1), Part 1

Study Day	**Day 1**																**Day 2**
Hour (relative to dosing time)	**Predose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																
Randomization[b]	X																
Vital signs (blood pressure, pulse) [a, c]	X[e]								X								X
Oral Temperature[a]	X[e]																
Weight	X[e]																
Electrocardiogram (12-lead)[a,d]	X[e]																X
Biochemistry, hematology, and urinalysis[a]	X[e]																X
Investigational drug administration		X															
Pharmacokinetic blood sampling[g]	X[e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[f]														

ECG=electrocardiogram; 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] Randomization will occur in Treatment Period 1, Day 1 only.

[c] Vital signs will be obtained while subject is in the supine position on study days noted. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

[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] These assessments should be performed within 30 minutes prior to dose administration.

[f] Palatability questionnaire should be given within 5 minutes of receiving dose.

[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. 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.

Table 3: Detailed Schedule of Assessments for Treatment Period 2 (Day 4), Part 1

Study Day	Day 4																Day 5
Hour (relative to dosing time)	**Pre-dose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Oral Temperature[a]	X[d]																
Weight	X[d]																
Electrocardiogram (12-lead)[a,c]	X[d]								X								X
Biochemistry, hematology, and urinalysis[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[f]	X[d]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

ECG=electrocardiogram; 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. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

[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] These assessments should be performed within 30 minutes prior to dose administration.

[e] Palatability questionnaire should be given within 5 minutes of receiving dose

[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. 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.

Table 4: Detailed Schedule of Assessments for Treatment Period 3 (Day 7), Part 1

Study Day	Day 7																Day 8
Hour (relative to dosing time)	**Pre-dose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																X
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Electrocardiogram (12-lead)[a,c]	X[d]																X
Oral Temperature[a]	X[d]																X
Weight	X[d]																X
Biochemistry, hematology, and urinalysis[a]																	X
Pregnancy (females only)[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[f]	X[d]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

ECG=electrocardiogram; 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. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

[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] These assessments should be performed within 30 minutes prior to dose administration.

[e] Palatability questionnaire should be given within 5 minutes of receiving dose

[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. 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.

Table 5: Schedule of Assessments Part 2

Visit[a]	Screening	Treatment Period 1				Treatment Period 2			Treatment Period 3			Treatment Period 4		Follow-up[l]
Study Day	**-28 to -2**	**-1**	**1[j]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Informed consent	X													
Inclusion/ exclusion criteria	X	X												
Demography	X													
Medical/medication history	X	X												
Physical examination[b]	X	X	X			X			X			X	X	
Randomization			X[k]											
High-fat meal prior to dose administration			X[n]			X[n]			X[n]			X[n]		
Vital signs (blood pressure, pulse)[b,c]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Oral temperature	X	X	X			X			X			X	X	
Height and weight[d]	X	X	X			X			X			X	X	
Electrocardiogram (12-lead)[b,e]	X	X	X	X		X	X		X	X		X	X	
Biochemistry, hematology, and urinalysis[b, f, m]	X	X		X			X			X			X	
HIV, HBsAg, and HCV antibodies	X													
Pregnancy (females only)[b, g]	X	X											X	
FSH[h] test in perimenopausal women	X													
Urine drug and alcohol screening[i]	X	X												
Investigational Drug Administration			X			X			X			X		
Pharmacokinetic blood sampling[j, o]			X	X		X	X		X	X		X	X	
Palatability Assessment			X			X			X			X		
Admit to the CSU (Day -1)		X												
Discharge from the CSU (Day 11 after last assessment)													X	
Washout between treatment periods			X	X	X	X	X	X	X	X	X			
Adverse events/serious adverse events[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

β-hCG=beta-human chorionic gonadotropin; CSU=clinical study unit; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PK=pharmacokinetic; SAE=serious adverse event; TSH=thyroid-stimulating

Table 5: Schedule of Assessments Part 2

Visit[a]	Screening	Treatment Period 1				Treatment Period 2			Treatment Period 3			Treatment Period 4		Follow-up[l]
Study Day	-28 to -2	-1	1[j]	2	3	4	5	6	7	8	9	10	11	

hormone

[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 3-day washout period between administration of the last dose of investigational product in Treatment Period 2 and Treatment Period 3 and between administration of the last dose in Treatment 4. Treatment Period 1 includes washout (Days 1 through 3), Treatment Period 2 includes washout (Days 4 through 6), and Treatment Period 3 is from Days 7 through 9.

[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. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

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

[e] Twelve-lead ECGs will be measured in the supine position. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

[f] Clinical laboratory assessments include serum biochemistry, (TSH and FT_4 at screening only), hematology, and urinalysis.

[g] Serum β-HCG test at Screening is required for all females. Urine pregnancy test is required for all females at subsequent scheduled time points

[h] Females only, to confirm menopausal status

[i] Drugs of abuse and alcohol at screening, and drugs of abuse and alcohol Day -1.

[j] See Table 6, Table 7, Table 8, and Table 9 for detailed collection time points

[k] Randomization is for Treatment Period 1, Day 1 only.

[l] There will be a follow-up telephone call approximately 7±2 days following the last dose of investigational product in Treatment Period 43 (Day 10). Adverse events/SAEs occurring up to the time of the follow-up telephone call will be captured. The follow-up telephone call should be completed for all subjects including those who withdraw or are removed from the study prior to Day 11 of Treatment Period 4.

[m] If screening occurs on Day -2, biochemistry, hematology and urinalysis is not required on Day -1.

[n] Subjects in Part 2 will receive maribavir depending on his/her randomized assignment to treatment sequence following an overnight fast of at least 10 hours. The study subjects should start the high-fat meal 30 minutes before administration of the drug product. Trial subjects should eat this meal in 30 minutes or less and consume 100 percent of the meal.

[o] 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.

Table 6: Detailed Schedule of Assessments for Treatment Period 1 (Day 1), Part 2

Study Day	Day 1																Day 2
Hour (relative to dosing time)	**Predose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																
Randomization[b]	X																
Vital signs (blood pressure, pulse)[a, c]	X[e]								X								X
Oral Temperature[a]	X																
Weight	X[e]																
Electrocardiogram (12-lead)[a,d]	X[e]																X
Biochemistry, hematology, and urinalysis[a]	X[e]																X
Investigational drug administration		X															
Pharmacokinetic blood sampling[g]	X[e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[f]														

ECG=electrocarodiogram; 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] Randomization will occur in Treatment Period 1, Day 1 only.

[c] Vital signs will be obtained while subject is in the supine position on study days noted. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

[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] These assessments should be performed within 30 minutes prior to dose administration.

[f] Palatability questionnaire should be given within 5 minutes of receiving dose

[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. 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.

Table 7: Detailed Schedule of Assessments for Treatment Period 2 (Day 4), Part 2

Study Day	Day 4																Day 5
Hour (relative to dosing time)	**Pre-dose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Oral Temperature[a]	X[d]																
Weight	X[d]																
Electrocardiogram (12-lead)[a,c]	X[d]																X
Biochemistry, hematology, and urinalysis[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[f]	X [d, e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

ECG=electrocarodiogram; 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. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

[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] These assessments should be performed within 30 minutes prior to dose administration.

[e] Palatability questionnaire should be given within 5 minutes of receiving dose

[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. 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.

Table 8: Detailed Schedule of Assessments for Treatment Period 3 (Day 7), Part 2

Study Day	Day 7																Day 8
Hour (relative to dosing time)	**Pre-dose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination [a]	X																
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Electrocardiogram (12-lead)[a,c]	X[d]																X
Oral Temperature[a]	X[d]																
Weight	X[d]																
Biochemistry, hematology, and urinalysis[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[f]	X[d, e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

[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. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.
[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] These assessments should be performed within 30 minutes prior to dose administration.
[e] Palatability questionnaire should be given within 5 minutes of receiving dose.
[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. 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.

Table 9: Detailed Schedule of Assessments for Treatment Period 4 (Day 10), Part 2

Study Day	Day 10																Day 11
Hour (relative to dosing time)	**Pre-dose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																X
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Electrocardiogram (12-lead)[a,c]	X[d]																X
Oral Temperature[a]	X[d]																X
Weight	X[d]																X
Biochemistry, hematology, and urinalysis[a]																	X
Pregnancy (females only)[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[f]	X[d]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

ECG=electrocardiogram; 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. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

[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] These assessments should be performed within 30 minutes prior to dose administration.

[e] Palatability questionnaire should be given within 5 minutes of receiving dose

[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. 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.

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

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

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 virus's ability to modulate the immune system, either directly or secondary to the host antiviral response through regulation of cytokine, chemokine, and/or growth factor production.

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

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

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

with 3 months of oral ganciclovir. Ganciclovir-resistant disease accounted for 20% of CMV disease, occurred late (a median of 10 months after transplantation), was associated with higher intensity of immunosuppression, and was considered a clinically serious concern (Avery, 2007).

There are no approved therapies for the treatment of CMV infection or CMV disease in transplant recipients, and no approved treatment for CMV infection or disease that is resistant or refractory to currently available therapies in any population. Maribavir is currently 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 Investigator's Brochure.

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- 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, metabolism and drug-drug interactions

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). Pharmacokinetic data obtained in Phase 2 studies was similar to the data observed in healthy volunteers.

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

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

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-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 pharmacokinetics 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 50-2400 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. A definitive QT study demonstrated no clinically significant repolarization effect of maribavir administered orally at single doses of 100 mg and 1200 mg in healthy subjects. In addition, no other significant electrocardiographic effects of maribavir were found.

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

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

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 investigator's brochure for the most detailed and most current information regarding the drug metabolism, pharmacokinetics, 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 SCT 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 investigator's brochure (IB) for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, pharmacokinetics, 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 3.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

In the previous study SHP620-118, taste assessment study of maribavir, maribavir taste was characterized as a strong and lingering bitter taste at clinically-relevant doses, posing a taste-masking challenge.

In order to provide a palatable formulation for pediatric use, a taste-masking strategy that minimizes the availability of maribavir in the oral cavity is being explored. The taste-masking relies on the use of a coating polymer that is insoluble at neutral pH (ie, of saliva) but soluble at acidic pH (ie, of gastric fluid). By encapsulating maribavir inside the coating polymer, maribavir would be unavailable for taste perception in the mouth but, released in the stomach for absorption. As the coating polymer has the potential to hinder drug release and absorption, 2 prototype formulations, each containing the same coating polymer, but with different amounts, are being evaluated in this study for their impact on palatability and rate and extent of absorption of maribavir.

There were no significant effects of food on the rate and extent of absorption of maribavir from the adult tablet formulation; however, since maribavir is a Biopharmaceutics Classification System (BCS) II drug and the coating polymer may affect the rate and extent of absorption of maribavir, it is necessary to evaluate the dose proportionality of the pediatric formulation and the effects of food. This study will be conducted in 2 parts and a planned analysis will be conducted after Part 1 to decide if 1 of the 2 candidate pediatric formulations can be selected based on palatability and relative bioavailability and will be further evaluated for dose proportionality and effects of food in Part 2. The results from this study may be used for further optimization of the pediatric formulation and will provide guidance on dose selection of the pediatric formulation in clinical development for pediatric patients.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objectives of Part 1 of this study are to assess the relative bioavailability of 2 candidate pediatric formulations of maribavir given as a single oral dose at 200 mg as compared to the Phase 3 adult maribavir 200 mg tablet formulation in healthy adult subjects. In addition, the palatability of the candidate pediatric formulations will be assessed by a questionnaire.

The primary objectives of Part 2 of this study are to assess the dose proportionality of 50 mg, 100 mg, and 200 mg of the selected pediatric formulation, to assess the impact of food on the rate and extent of absorption of the selected pediatric formulation given as 200 mg under fasted and fed conditions and to assess the palatability at various doses and with food.

2.2.2 Secondary Objectives

The secondary objective of Part 1 and Part 2 of this study is to assess the safety and tolerability of 2 candidate pediatric formulations and the adult tablet formulation of maribavir given as a single oral dose up to 200 mg in healthy adult subjects.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

The study will be conducted sequentially in 2 parts. In Part 1, two pediatric candidate powder formulations will be compared with maribavir 200 mg tablet under fasted conditions in regards to their bioavailability and palatability. In Part 2 dose proportionality of 50, 100, and 200 mg dose of the selected pediatric powder formulation will be assessed, as well as the impact of food (a high-fat meal) on the rate and extent of absorption of the selected pediatric formulation. The pediatric formulation which will be evaluated in Part 2 will be chosen based on the results of interim analysis of Part 1 PK and palatability data from two candidate pediatric formulations.

Part 1: Relative Bioavailability and Palatability

A total of 18 healthy male and female subjects, 18-50 years of age, inclusive, will be enrolled and expected to complete Part 1 of this study. Subjects who withdraw early will be replaced; the replacement subjects will receive the same treatment sequence assigned to subject who withdraw early. The study will be comprised of the following periods: a screening lasting up to 28 days, 3 treatment periods in which subjects will receive a single dose of the study drug on the first day of each period after a 10-hour overnight fasting, a drug washout of a minimum of 72 hours and maximum of 73 hours between dosing in periods 1 and 2 and periods 2 and 3, and a follow-up phone call (7±2 days) after the last dose of investigational drug (maribavir) is administered (Figure 1). The maximal total duration of study participation for a subject in Part 1 is 46 days, if the maximum screening, washout and follow-up durations are used.

Screening will occur within 28 days prior to randomization to assess eligibility of subjects to participate in the study. Subjects will be admitted to the clinical study unit (CSU) on Day -1. On the morning of Day 1, subjects will be randomized to 1 of 6 sequences in a 1:1:1:1:1:1 treatment allocation. Subjects will receive assigned treatment under fasted conditions in each treatment period. The treatment sequences to be used in the study is shown in Table 10:

Table 10: Treatment Sequence Part 1: N=18

Sequence number (number of subjects per sequence)	Treatment Sequence
1 (n=3)	ABC
2 (n=3)	BCA
3 (n=3)	CAB
4 (n=3)	CBA
5 (n=3)	ACB
6 (n=3)	BAC

Treatment A: maribavir 200 mg tablet- current Phase 3 formulation

Treatment B: maribavir 200 mg powder for oral suspension, 32.5% drug loading

Treatment C: maribavir 200 mg powder for oral suspension, 36.1% drug loading

Treatment Period 1

- On Day 1, subjects in each cohort will receive 200 mg maribavir depending on his/her randomized assignment to the treatment sequence as presented in Table 10.

Washout Period

- There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4).

Treatment Period 2

- On Day 4, subjects in each cohort will receive 200 mg maribavir depending on his/her randomized assignment to treatment sequence (Table 10).

Washout Period

- There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7).

Treatment Period 3

- On Day 7, subjects in each cohort will receive 200 mg maribavir depending on his/her randomized assignment to treatment sequence (Table 10).

Assessments

- **Pharmacokinetic (PK) Assessment**
  Serial blood samples for PK analysis of maribavir concentrations will be collected over 24 hours on Day 1, Day 4, and Day 7. These blood samples will be collected according to the Detailed Schedule of Assessments (Table 2, Table 3, and Table 4).

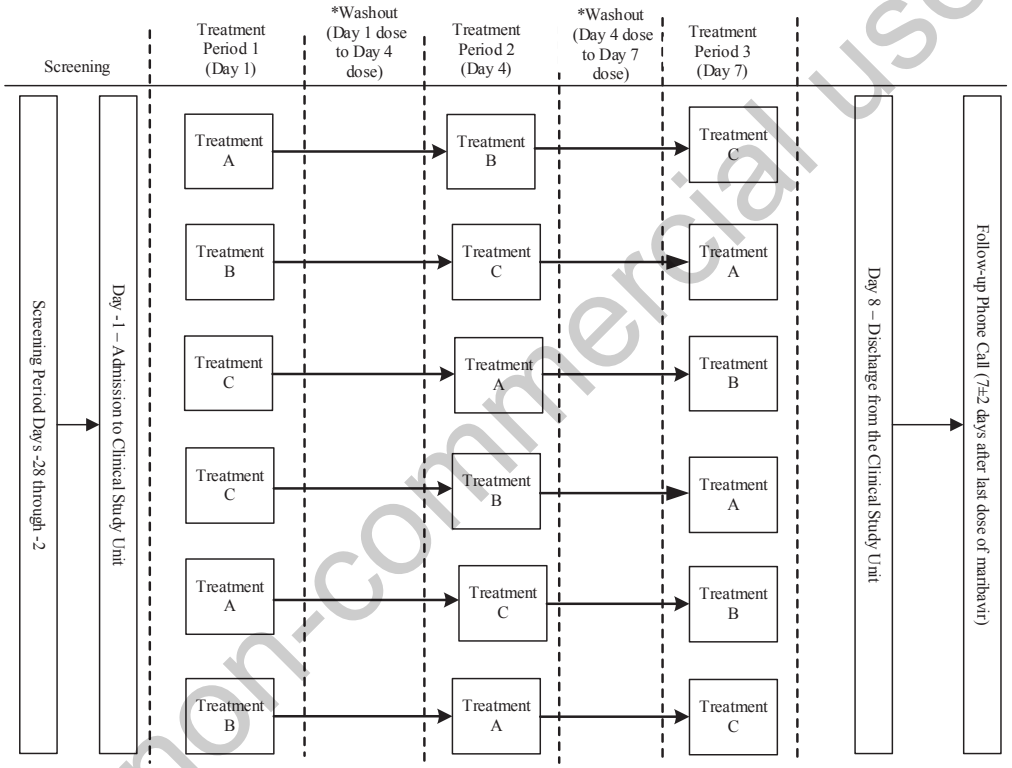
- **Safety and Tolerability Assessment**
  Safety and tolerability will be assessed based on treatment-emergent adverse events (TEAEs), vital signs, laboratory values, electrocardiogram (ECG) findings, and evaluation of clinical signs.

- **Palatability Assessment**
  Palatability will be assessed based on subjects' responses to a questionnaire that will be completed following each dose administration on Day 1, Day 4 and Day 7.

Follow-up

- Subjects will remain in the CSU until completion of the last post dose assessment on Day 8. A post-treatment follow-up telephone call will be performed 7 (±2) days after the last dose of investigational product.

Figure 1: Study Design Flow Chart Part 1



Treatment A: Maribavir 200mg tablet
Treatment B: Maribavir powder for oral suspension, 32.5% drug loading
Treatment C: Maribavir powder for oral suspension, 36.1% drug loading
*NOTE: Treatment will be dependent on randomization sequence.
*NOTE: There will be a drug washout of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4) and between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7)

Part 2: Dose Proportionality and Food Effect

A total of 20 healthy male and female subjects, 18-50 years of age, inclusive, will be enrolled and expected to complete Part 2 of this study. Subjects who withdraw early will be replaced and the replacement subjects will receive the same treatment sequence assigned to subject who withdraw early. The study will be comprised of the following periods: a screening lasting up to 28 days, 4 treatment periods in which subjects will receive a single dose of the study drug on the

first day of each period after a 10-hour overnight fasting, one treatment period in which subjects will receive a single dose of the study drug on the first day of the period after consuming a high-fat meal, a drug washout of a minimum of 72 hours and maximum of 73 hours between dosing in periods 1 and 2, periods 2 and 3, and periods 3 and 4, and a follow-up phone call (7±2 days) after the last dose of investigational drug (maribavir) is administered (Figure 2). The maximal total duration of study participation for a subject in Part 2 is 49 days, if the maximum screening, washout and follow-up durations are used.

An interim analysis is planned after the completion of Part I to evaluate the PK and palatability data from the formulations investigated. Based on the results of the interim analysis of Part 1 data, 1 pediatric formulation may be chosen to be assessed in Part 2.

Screening will occur within 28 days prior to randomization to assess eligibility of subjects to participate in the study. Subjects will be admitted to the CSU on Day -1. On the morning of Day 1, subjects will be randomized to 1 of 4 sequences in a 1:1:1:1 treatment allocation. The treatment sequences to be used in the study is shown in Table 11:

Table 11: Treatment Sequence Part 2: N=20

Sequence number (number of subjects per sequence)	Treatment Sequence
1 (n=5)	DEGF
2 (n=5)	EFDG
3 (n=5)	FGED
4 (n=5)	GDFE

Treatment D: maribavir powder for oral suspension (50 mg fasted)

Treatment E: maribavir powder for oral suspension (100 mg fasted)

Treatment F: maribavir powder for oral suspension (200 mg fasted)

Treatment G: maribavir powder for oral suspension (200 mg fed with a high-fat meal)

Treatment Period 1

- On Day 1, subjects in each cohort will receive maribavir depending on his/her randomized assignment to the treatment sequence as presented in Table 11.

Washout Period

- There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4).

Treatment Period 2

- On Day 4, subjects in each cohort will receive maribavir depending on his/her randomized assignment to treatment sequence (Table 11).

Washout Period

- There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7).

Treatment Period 3

- On Day 7, subjects in each cohort will receive maribavir depending on his/her randomized assignment to treatment sequence (Table 11).

Washout Period

- There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 3 (Day 7) and the administration of maribavir in Period 4 (Day 10).

Treatment Period 4

- On Day 10, subjects in each cohort will receive maribavir depending on his/her randomized assignment to treatment sequence (Table 11).

Assessments

- **Pharmacokinetic (PK) Assessment**
  Serial blood samples for PK analysis of maribavir concentrations will be collected over 24 hours on Day 1, Day 4, Day 7 and Day 10. These blood samples will be collected according to the Detailed Schedule of Assessments (Table 6, Table 7, Table 8, and Table 9).

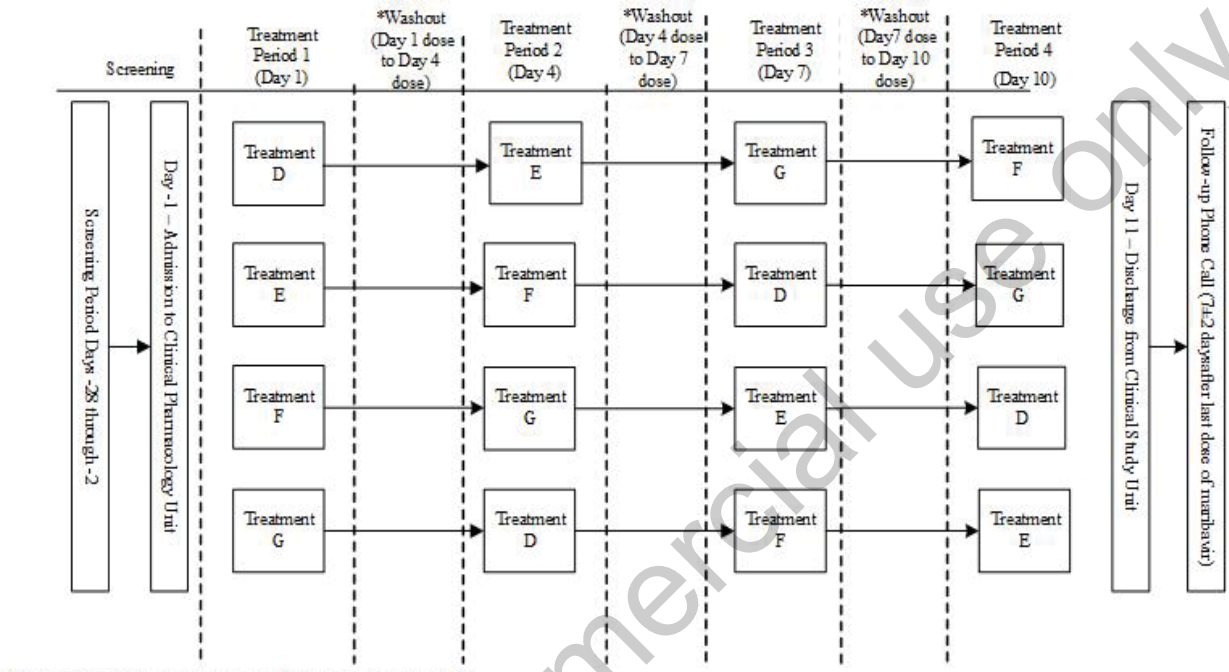
- **Safety and Tolerability Assessment**
  Safety and tolerability will be assessed based on treatment-emergent adverse events (TEAEs), vital signs, laboratory values, electrocardiogram (ECG) findings, and evaluation of clinical signs.

- **Palatability Assessment**
  Palatability will be assessed based on subjects' responses to a questionnaire that will be completed following each dose administration on Day 1, Day 4, Day 7, and Day 10.

Follow-up

- Subjects will remain in the CSU until completion of the last post dose assessment on Day 11. A post-treatment follow-up telephone call will be performed 7 (±2) days after the last dose of investigational product.

Figure 2: Study Design Flow Chart Part 2



Treatment D: Maribavir powder for oral suspension (50 mg fasted)
Treatment E: Maribavir powder for oral suspension (100 mg fasted)
Treatment F: Maribavir powder for oral suspension (200 mg fasted)
Treatment G: Maribavir powder for oral suspension (200 mg fed with a high-fat meal)
*NOTE: Treatment will be dependent on randomization sequence.
*NOTE: There will be a drug washout of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4) between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7), and between the administration of maribavir in Period 3 (Day 7) and the administration of maribavir in Period 4 (Day 10)

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 46 days for Part 1 and 49 days for Part 2. The study will be completed in approximately 12 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 phone call, 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 1 clinical site in the 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 subject will not be considered eligible for the study without meeting all of the inclusion and exclusion criteria.

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/and assent as applicable to participate in the study.
3. Age 18-50 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.
4. 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. Additional details will be outlined in the protocol.
5. 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 TSH and free T_4 (FT_4) at screening only), and urinalysis.
6. Hemoglobin for males ≥135.0 g/L and females ≥120.0 g/L at screening and on Day -1.
7. Body mass index (BMI) between 18.0 and 30.0 kg/m^2 inclusive with a body weight >50 kg (110 lbs). This inclusion criterion will only be assessed at the first screening visit.
8. Ability to swallow a dose of investigational product.

4.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met at the screening visit or Day -1 (if reassessed):

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 investigational product, 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 investigational product or procedures.
3. Known or suspected intolerance or hypersensitivity to the investigational product(s), 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 investigational product.
5. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the first dose of investigational product.
6. Within 30 days prior to the first dose of investigational product:
    - Have used an investigational product (if elimination half-life is <6 days, otherwise 5 half-lives).
    - Have been enrolled in a clinical study (including vaccine studies) that, in the investigator's opinion, may impact this Shire-sponsored study.
    - Have had any substantial changes in eating habits, as assessed by the investigator.
7. Confirmed systolic blood pressure >139 mmHg or <89 mmHg, and diastolic blood pressure >89 mmHg or <49 mmHg.
8. 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.
9. Known history of alcohol or other substance abuse within the last year.
10. 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).
11. A positive screen for alcohol or drugs of abuse at screening or on Day -1 of Treatment Period 1.
12. A positive HIV, hepatitis B surface antibody (HBsAg), or hepatitis C virus (HCV) antibody screen.
13. 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 investigational product (maribavir).
14. 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 tea, three 1 oz [85 g] chocolate bars. (Decaffeinated coffee, tea, or cola are not considered to contain caffeine).
15. Prior screen failure, randomization, participation, or enrollment in this study or participation in Part 1 of this study.

16. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations) with the exception of hormonal replacement therapy. Current use of antacids and H2 antagonists. Current use is defined as use within 30 days of the first dose of investigational product.
17. Ingestion of known CYP3A modulators within 7 days of Day 1, Period 1 (includes grapefruit or grapefruit juice, oranges, Seville oranges, apples or apple juice, vegetables from the mustard green family [eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard], charbroiled meats, and products containing these ingredients).
18. Inability or unwillingness to consume 100 percent of high-fat meal in Part 2 (including subjects with lactose or gluten intolerance).
19. History of oral/nasal cavity infections, gastroesophageal reflux, asthma treatment with albuterol, zinc supplementation.
20. Subjects with dry mouth syndrome or burning mouth syndrome or menopausal women suffering from dysgeusia.

4.3 Restrictions

1. Subjects should refrain from strenuous physical exercise 48 hours prior to admission to the CRU and during the in-house stays at the CRU.
2. Subjects should refrain from consuming grapefruit, Seville oranges, 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. Subjects should refrain from consuming pine nuts 7 days prior to Day 1 of the first treatment period through the completion of the last treatment period.
4. Subjects should refrain from alcohol 48 hours prior to admission to the CRU and during the in-house stay at the CRU.
5. Subjects should refrain from 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. Subjects should refrain from taking or regularly using any medication (including over-the counter multi-vitamin, herbal, or homeopathic preparations) with the exception of those listed in Section 5.2 from 14 days prior to receiving the first dose of the investigational product through the completion of the discharge assessments and procedures. Subjects should not use antacids or zinc supplementation.
7. Subjects should refrain from foods or beverages containing caffeine/xanthine 48 hours prior to admission to the CRU and during the in-house stay at the CRU.
8. Subjects will be required to follow standardized meal schedules and eat the meals provided by the site while housed in the CRU. No outside food or beverages (including gum, mints, etc) will be permitted. Menus will be identical for all subjects at the CRU. Copies of the menus will be provided to the sponsor for approval prior to the start of the study. While confined, the total daily nutritional composition should be approximately 50% carbohydrate, 35% fat, and 15% protein. The daily caloric intake per subject should not exceed

approximately 3200 kcal. For Treatment G in Part 2, a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is to taken within 30 minutes prior to maribavir doses. This high-fat meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.
(An example of a High Fat Breakfast: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, 8 ounces of whole milk.
*50 percent of calories are derived from fat. Substitutions can be made to this meal, if the content, volume, and viscosity are maintained.)

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 should be using an acceptable form of contraception. Females of child-bearing potential must be advised to use acceptable contraceptives throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. 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 investigational product.

Female subjects should be either:

- Post-menopausal (12 consecutive months of spontaneous amenorrhea and ≥ age 50 years)
- 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
- Females of child-bearing potential with a negative urine and/or 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 investigational product, 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.

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 investigational product. 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 investigational product. 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 investigational product. Male subjects must not donate sperm until 3 months after the last dose of investigational product.

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 investigational product is discontinued, regardless of the reason, the early withdrawal evaluations listed in Table 3 and Table 7 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 investigational product, and the total amount of investigational product administered must be recorded in the source documents and the case report form (CRF).

Subjects who discontinue from the study may be replaced at the sponsor's discretion to ensure that 18 subjects complete Part 1 of the study and 20 subjects complete Part 2 of the study.

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:

- Adverse event
- 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 investigational product.

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 pharmacokinetic equivalent of 5 half-lives, whichever is longer) of the date of first dose of investigational product. 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 investigational product 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 investigational products) 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 (see Section 4.4.1)
- Hormone replacement therapy

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 test product is maribavir, which will be provided in tablet and powder form.

Maribavir tablet is a blue, film-coated tablet containing 200 mg of maribavir. The tablets are packaged in a 60 cc, white, HDPE bottle containing 40 tablets.

Maribavir powder for oral suspension is a white to off-white granular powder. The 32.5% w/w powder contains 325 mg of maribavir for every 1 g of powder; the 36.1% w/w powder contains 361 mg of maribavir for every 1 g of powder. The powders are packaged in a 150 cc, white, HDPE bottle containing 40 g of powder. The powders are to be compounded to form unit dose oral suspensions. Additional information and detailed instructions are provided in the maribavir investigator's brochure, and in a Pharmacy Manual that will be provided.

The sponsor will provide the test product, maribavir.

6.1.1 Blinding 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.

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.

Once a randomization number/unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a randomization number/unique identifier is allocated incorrectly, the clinical research associate (CRA)/study monitor must be notified as soon as the error is discovered.

6.2.2 Dosing

6.2.2.1 Part 1, Treatment Period 1

On Day 1, subjects will receive either a single 200 mg dose of maribavir, either in tablet form or as an oral suspension, depending on his/her randomized assignment to the treatment sequence. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 1. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration

6.2.2.2 Washout Period

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4).

6.2.2.3 Part 1, Treatment Period 2

On Day 4, subjects in each cohort will receive 200 mg maribavir depending on his/her randomized assignment to treatment sequence. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 4. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration

6.2.2.4 Washout Period

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7).

6.2.2.5 Part 1, Treatment Period 3

On Day 7, subjects in each cohort will receive 200 mg maribavir depending on his/her randomized assignment to treatment sequence. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 7. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration.

6.2.2.6 Part 2, Treatment Period 1

On Day 1, subjects in each cohort will receive maribavir depending on his/her randomized assignment to the treatment sequence. For treatments D, E, and F, subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 1. For treatment G, subjects will go through an overnight fast of at least 10 hours, receive the high-fat meal 30 minutes before administration of the drug product, and fast for 4 hours after dosing on Day 1. Trial subjects should eat this meal in 30 minutes or less and consume 100 percent of the meal. Refer to Section 4.3, Number 9 for specific information about the high-fat meal. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration. Subjects will fast for 4 hours after dosing on Day 1.

6.2.2.7 Washout Period

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4).

6.2.2.8 Part 2, Treatment Period 2

On Day 4, subjects in each cohort will receive maribavir depending on his/her randomized assignment to treatment sequence. For treatments D, E, and F, subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 4. For treatment G, subjects will go through an overnight fast of at least 10 hours, receive the high-fat meal 30 minutes before administration of the drug product, and fast for 4 hours after dosing on Day 4. Refer to Section 4.3, Number 9 for specific information about the high-fat meal. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration. Subjects will fast for 4 hours after dosing on Day 4.

6.2.2.9 Washout Period

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7).

6.2.2.10 Part 2, Treatment Period 3

On Day 7, subjects in each cohort will receive maribavir depending on his/her randomized assignment to treatment sequence. For treatments D, E, and F, subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 7. For treatment G, subjects will go through an overnight fast of at least 10 hours, receive the high-fat meal 30 minutes before administration of the drug product, and fast for 4 hours after dosing on Day 7. Refer to Section 4.3, Number 9 for specific information about the high-fat meal. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration. Subjects will fast for 4 hours after dosing on Day 7.

6.2.2.11 Washout Period

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 3 (Day 7) and the administration of maribavir in Period 4 (Day 10).

6.2.2.12 Part 2, Treatment Period 4

On Day 10, subjects in each cohort will receive maribavir depending on his/her randomized assignment to treatment sequence. For treatments D, E, and F, subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 10. For treatment G, subjects will go through an overnight fast of at least 10 hours, receive the high-fat meal 30 minutes before administration of the drug product, and fast for 4 hours after dosing on Day 10. Refer to Section 4.3, Number 9 for specific information about the high-fat meal. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration. Subjects will fast for 4 hours after dosing on Day 10.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container.

All investigational product (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 investigational product 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 containers:

- Maribavir tablet: 60 cc, white, square, HDPE bottle
- Maribavir powder for oral suspension: 150 cc, white, round, 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 investigational product 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 investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that

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

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

6.4 Drug Accountability

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

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

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All dispensed medication will be documented in the subject's source and/or other investigational product record.

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

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

With the written agreement of the sponsor, at the end of the study all unused stock and empty/used investigational product 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 investigational products must be in accordance with local, state, and national laws.

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

6.5 Subject Compliance

Compliance must be assessed by observation of dosing by the investigator or designee. In addition, the CRU personnel should perform a hand and mouth check (mouth check is only required for oral dosing) of the subject to assure the investigational product 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 Testing Samples

In compliance with 21 CFR 320.38 (1999), and as recommended in the Center for Drug Evaluation and Research Guidance for Industry dated May 2004 regarding retention of relevant reserve (BA and BE test samples), CROs, site management organizations, or clinical investigators must retain samples when relevant BA/BE testing has been performed under contract by the sponsor. Retained samples must meet 21 CFR 320.38 (1999) and 320.63 (1999) requirements for reserve samples of test article and reference standards according to the following:

- Reserve samples must be representative of the test batches provided and therefore must be randomly selected from identical test article and/or reference standards provided to the site
- The quantity should be sufficient optimally to permit the Food and Drug Administration (FDA) to perform all release testing identified in the application 5 times
- Are adequately identified so that the reserve sample can be positively identified as having come from the same batches as used in the BA/BE studies
- Be stored under conditions that maintain the samples identity, integrity, strength, quality, and purity
- Be retained for at least 5 years following the date of New Drug Application or supplemental New Drug Application approval or, if the Investigational New Drug is discontinued, at least 5 years following the date of completion of the BA/BE study
- Samples must be annually inspected and documented to confirm integrity.

7. STUDY PROCEDURES

Details regarding scheduled assessments and procedures to be conducted in this study are provided below and in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9.

7.1 Study Schedule

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
- Pharmacokinetic blood sampling
- Palatability Questionnaire
- Clinical laboratory tests
- Physical examination.

NOTE: Blood sampling for pharmacokinetic 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

Screening procedures must be completed within 28 days of Day 1 as appropriate prior to receiving the first dose of investigational product. 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 enrolled or administered investigational product(s).

7.1.1.2 Rescreening of Subjects

Subjects who fail to meet all inclusion/exclusion criteria will not be permitted to be rescreened for the study at any point.

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 Treatment Period Part 1

7.1.2.1 Admission to the Clinical Study Unit (CSU) (Day -1)

Following the screening visit, eligible subjects will return to the CSU on Day -1 of the study. See Table 1 for a list of procedures to be completed upon admission to the CSU.

Subjects who successfully complete the pre-admission assessments and procedures will be admitted to the CSU on Day -1 and assigned a subject number on Day 1 as described in Section 6.2. Eligible subjects will be confined to the CSU from the morning of Day -1 until Day 8.

7.1.2.2 Day 1 to Day 3 (Part 1, Period 1)

Study Assessments for Day 1 to Day 3 are outlined in Table 1 and Table 2. Administration of maribavir will occur on Day 1. Subjects will be given a palatability questionnaire immediately following medication administration. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 1.

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4).

7.1.2.3 Day 4 to Day 6 (Part 1, Period 2)

Study Assessments for Day 4 to Day 6 are outlined in Table 1 and Table 3. Administration of maribavir will occur on Day 4. Subjects will be given a palatability questionnaire immediately following medication administration. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 4.

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7).

7.1.2.4 Day 7 to Day 8 (Part 1, Period 3)

Study Assessments for Day 7 to Day 8 are outlined in Table 1 and Table 4. Administration of maribavir will occur on Day 7. Subjects will be given a palatability questionnaire immediately following medication administration. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 7.

7.1.2.5 Final Visit

Subjects will remain in-house for the entire study. Final evaluation will be on Day 8. For any subject who discontinues prematurely, the final visit will be the day they discontinue.

7.1.3 Treatment Period Part 2

7.1.3.1 Admission to the Clinical Pharmacology Unit (Day -1)

Following the screening visit, eligible subjects will return to the CSU on Day -1 of the study. See Table 5 for a list of procedures to be completed upon admission to the CSU.

Subjects who successfully complete the pre-admission assessments and procedures will be admitted to the CSU on Day -1 and assigned a subject number on Day 1 as described in Section 6.2. Eligible subjects will be confined to the CSU from the morning of Day -1 until Day 11.

7.1.3.2 Day 1 to Day 3 (Part 2, Period 1)

Study Assessments for Day 1 to Day 3 are outlined in Table 5 and Table 6. Administration of maribavir will occur on Day 1. Subjects will be given a palatability questionnaire immediately following medication administration. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 1.

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4).

7.1.3.3 Day 4 to Day 6 (Part 2, Period 2)

Study Assessments for Day 4 to Day 6 are outlined in Table 5 and Table 7. Administration of maribavir will occur on Day 4. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 4.

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7).

7.1.3.4 Day 7 to Day 9 (Part 2, Period 3)

Study Assessments for Day 7 to Day 9 are outlined in Table 5 and Table 8. Administration of maribavir will occur on Day 7. Subjects will be given a palatability questionnaire immediately following medication administration. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 7.

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 3 (Day 7) and the administration of maribavir in Period 4 (Day 10).

7.1.3.5 Day 10 to Day 11 (Part 2, Period 4)

Study Assessments for Day 10 to Day 11 are outlined in Table 5 and Table 9. Administration of maribavir will occur on Day 10. Subjects will be given a palatability questionnaire immediately following medication administration. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 10.

7.1.3.6 Final Visit

Subjects will remain in-house for the entire study. Final evaluation will be on Day 11. For any subject who discontinues prematurely, the final visit will be the day they discontinue.

7.1.4 Follow-up Period

The follow-up period for this protocol is 7±2 days for Part 1 and Part 2.

At the end of this period there will be a telephone call initiated by staff to query for serious adverse events (SAEs), AEs, and concomitant treatments. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Appendix 4.2)

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

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 precise 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 investigational product), TEAEs (all AEs occurring 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 CSU, 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 and Table 5 by a qualified licensed physician, physician's assistant, or a nurse practitioner. The medical history will be reviewed and recorded, including:

- Date of birth
- Sex
- Race and ethnicity

- Recent ingestion of medication (30 days prior to entering the screening period)
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases
- Smoking habits

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 and Table 5 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)

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 by the investigator.

7.2.2.3 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed. (Refer to Appendix 4 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, Table 6, Table 7, Table 8, and Table 9 of this protocol. 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 for all subjects (and documented). 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 deflation rate 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 assumed 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 caffeine, 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. If, after a single measurement is taken, there is a difference between arms in either systolic or diastolic blood pressure >10 mmHg, the site will perform triplicate BP measurements in each arm to determine the arm with the higher BP. The arm with the higher BP (based on the average of the 3 BP measurements for each arm) should be used for inclusion at screening, and the last of the 3 measurements recorded in the eCRF as the screening BP. The same (right or left) arm with the higher blood pressure will be used throughout the study.

One reading (supine systolic blood pressure/diastolic blood pressure-heart rate) should be taken.

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 Palatability Questionnaire

A palatability questionnaire (Refer to Appendix 2) will be completed following each dose administration (within 5 minutes) on Day 1, Day 4, Day 7 in Part 1 and on Day 1, Day 4, Day 7 and Day 10 in Part 2.

7.2.2.6 Clinical Laboratory Tests

All clinical laboratory tests will be performed according to the laboratory's standard procedures. 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 (8.5 mL) for serum biochemistry will be collected into a gel separator tube at the time points described in Table 1 and Table 5. The following parameters will be assessed:

Sodium	Phosphorus	β-HCG (beta Human chorionic gonadotropin)[a, b]
Potassium	Protein	
Glucose	Carbon dioxide	
Urea nitrogen	Albumin	
Creatinine	Aspartate transaminase	
Calcium	Alanine transaminase	
Chloride	Gamma glutamyl transferase	
Thyroid stimulating hormone (TSH)[a]	Alkaline phosphatase	
Thyroxine (T4 total)[a]	Total bilirubin	
FSH[a, b]	Uric acid	

[a] See Table 1 and Table 5.
[b] Females only.

Hematology

Blood samples (4 mL) for hematology will be collected into an ethylenediaminetetraacetic acid (EDTA) tube at the time points described in Table 1 and Table 5. 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 and Table 5. 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 serum beta-HCG or urine pregnancy test is performed on all females of child-bearing potential 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 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 of approximately 8 mL 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.

7.2.2.10 Electrocardiogram

Twelve-lead ECGs will be performed at the times specified in Table 1 and Table 5. All ECGs will be performed using the equipment supplied by the CRU.

The following parameters will be recorded on the appropriate CRF page: heart rate, PR, RR, QRS, and QT intervals. The QTcF will be derived. 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 caffeine, 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.

One complete recording, including a 10 second rhythm strip, should be taken at each time point. It should be immediately assessed as a valid recording and if not valid, it should be repeated. Invalid recordings will not be entered in the CRF.

When a single ECG recording is performed at each time point, the ECG collected pre-dose on Day 1 will serve as the subject's baseline ECG.

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

If the QTcF interval (calculated on line 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 2-4 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.

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.

7.2.3 Pharmacokinetic Procedures

The name and address of the bioanalytical laboratory 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 pharmacokinetic (PK) blood sample collection times versus time of dosing will be monitored. 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 2, Table 3, Table 4, Table 6, Table 7, Table 8, and Table 9 to measure plasma concentrations of maribavir. Potential metabolites may also be determined as appropriate.

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

7.2.3.2 Shipment of Plasma Pharmacokinetic Samples

Plasma sample shipment handling instructions and contact information are provided in the Laboratory Manual.

7.2.3.3 Plasma Drug Assay Methodology

Plasma concentrations 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 in Part 1

Table 12: Volume of Blood to be Drawn from Each Subject in Part 1

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic samples[a]		3	45	135
HBsAg, HIV, HCV		8	1	8
Safety	Biochemistry and β-HCG[b]	8.5	5	42.5
	Hematology	4	5	20
Total mL				205.5

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 3 mL 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 205.5 mL of blood will be drawn from all subjects, regardless of sex, in Part 1.

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; however, the total volume drawn over the course of the study should be approximately 205.5 mL. When more than one blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

7.2.5 Volume of Blood to be Drawn from Each Subject in Part 2

Table 13: Volume of Blood to be Drawn from Each Subject in Part 2

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic samples[a]		3	60	180
HBsAg, HIV, HCV		8	1	8
Safety	Biochemistry and β-HCG[b]	8.5	6	51
	Hematology	4	6	24
Total mL				263

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 1 mL is to be discarded; then take 2 mL into appropriate tube for pharmacokinetic sample. A total of 3 mL 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 263 mL of blood will be drawn from all subjects, regardless of sex, in Part 2.

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; however, the total volume drawn over the course of the study should be approximately 263 mL. When more than one 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. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

8.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the sponsor'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 pharmacokinetic, pharmacodynamic, and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

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

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

8.5 Planned Analysis

After the completion of Part 1, a selected set of analyses planned for Part 1 to evaluate the PK and palatability data from the formulations investigated will be conducted. Based on the results of the analyses of Part 1 data, one pediatric formulation may be chosen to be assessed in Part 2. All analyses will be conducted after the completion of Part 2.

8.6 Sample Size Calculation and Power Considerations

Sample size calculations were based on the following data:

- The intra-subject coefficient of variation is assumed at 0.166 and 0.218 respectively for $AUC_{0\text{-inf}}$ and C_{max}, which are estimated from the 90% confidence intervals (CIs) of the geometric mean ratio of $AUC_{0\text{-inf}}$, and C_{max} in Study 1263-104.
- Sample size estimation is performed using nQuery's two one sided test (TOST) of equivalence in ratio of mean for crossover design study.
- True mean ratio: 1.00, 1.05
- Power: 80%, 90%
- One-sided α-level: 0.05 (corresponding to 90% CI)
- Bioequivalence range: 0.8-1.25

Table 14: Number of Subjects Required

		Intra-subject coefficient of variation	
True Ratio	**Power**	0.166	0.218
1.0	80%	12	18
	90%	14	22
1.05	80%	14	22
	90%	18	28

Note: sample size estimation is performed using nQuery's TOST of equivalence in ratio of mean for crossover design study.

Assuming a true mean ratio of 1.0 with intra-subject coefficient of variation of 0.218, a total of 18 completers is required to have 80% power to show that the 90% confidence intervals of the ratios of the geometric means of the two formulations/treatment lie within the range of 0.80 to 1.25.

Therefore, for Part 1, three subjects in each sequence with a total of 18 subjects is required to randomize subjects to 1 of 6 sequences in a 1:1:1:1:1:1 treatment allocation. For Part 2, five subjects in each sequence with a total of 20 subjects is required to randomize subjects to 1 of 4 sequences in 1:1:1:1 treatment allocation.

8.7 Study Population

The **screened set** will consist of all subjects who have signed informed consent.

Enrolled set will consist of all subjects who have signed informed consent and also fulfilled the inclusion/exclusion criteria.

The following subject populations are defined to analyze the data in Part 1 and Part 2:

Part 1:

- The pharmacokinetic set 1 will consist of subjects who received at least 1 dose of maribavir, did not vomit within 4 hours of dosing, and have at least 1 evaluable post-dose maribavir concentration value in Part 1.
- The safety set 1 will consist of subjects who have received at least 1 dose of maribavir in Part 1.

Part 2:

- The pharmacokinetic set 2 will consist of subjects who received at least 1 dose of maribavir, did not vomit within 4 hours of dosing, and have at least 1 evaluable post-dose maribavir concentration value in Part 2.
- The safety set 2 will consist of subjects who have received at least 1 dose of maribavir in Part 2.

Part 1 and 2 (combined):

- The total safety set will include subjects who have received at least 1 dose of maribavir in either Part 1 or Part 2.

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

8.7.1 Pharmacokinetic Analysis

All the pharmacokinetic analyses will be based on the PK analysis dataset.

Pharmacokinetic parameters will be calculated from maribavir concentration-time data using non-compartmental analysis (NCA) and all calculations will be based on actual sampling times. Pharmacokinetic parameters will include, but not be limited to, the following:

Part 1 (Day 1, Day 4, and Day 7)

- C_{max} Maximum concentration occurring at t_{max}
- t_{max} Time of maximum observed concentration sampled during a dosing interval
- $AUC_{0\text{-last}}$ 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-$AUC_{0\text{-}last}$/$AUC_{0\text{-}inf}$)*100
- $t_{1/2}$ — Terminal half-life
- CL/F — Apparent total body clearance following extravascular administration calculated as dose divided by $AUC_{0\text{-}inf}$
- T_{lag} — Delay between the time of dosing and time of appearance of plasma concentration in the employed sampling scheme

Part 2 (Day 1, Day 4, Day 7, and Day 10)

- C_{max} — Maximum concentration occurring at t_{max}
- t_{max} — Time of maximum observed concentration sampled during a dosing interval
- $AUC_{0\text{-}last}$ — 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-$AUC_{0\text{-}last}$/$AUC_{0\text{-}inf}$)*100
- $t_{1/2}$ — Terminal half-life
- CL/F — Apparent total body clearance following extravascular administration divided by the fraction of dose absorbed calculated as dose divided by $AUC_{0\text{-}inf}$
- T_{lag} — Delay between the time of dosing and time of appearance of concentration in the sampling

In addition, dose-normalized Cmax, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ will be calculated for Treatments D, E, and F.

8.7.2 Statistical Analysis of Pharmacokinetic Parameters

8.7.2.1 Part 1

Individual concentrations and PK parameters of maribavir will be listed and summarized by treatment with descriptive statistics (number, arithmetic mean, standard deviation [SD], coefficient of variation [CV%], median, minimum, maximum, geometric mean, and %CV of geometric mean). Figures of individual and mean (+/-SD) concentration-time profiles of plasma maribavir by treatment will be generated on both linear and semi-log scales.

Following the $\log_e$-transformation, the PK parameters including $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, and C_{max} will be analyzed using a mixed effect model to include sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Analysis of variance will be performed using SAS mixed linear models procedure. Point estimates and their associated 90% CIs will be

constructed for the differences in the log-transformed parameters. The point estimates and their associated 90% CIs will be then back-transformed to provide point estimates for the ratio of geometric least squares means and associated 90% CIs on the original scale. Analysis of t_{max} and T_{lag} will be performed by nonparametric t-test.

8.7.2.2 Part 2

Dose proportionality analysis:

The dose proportionality will be first assessed using the Power Model for 50-200 mg (fasted) dose range. The Power Model: $\log(Y_{ijk})=S_i + P_j + \beta x \log(D_k) + \varepsilon_{ijk}$ where D is the total number of doses, N are the total number of subjects and P the total number of periods and i=1,…..,N, j=1,…..,P and k=1,……,D. Y_{ijk} is the log-transformed response variable, $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, or C_{max} on the kth dose, in the jth period, for the ith subject. S_i is the random subject effect for the ith subject, P_j is the fixed period effect for the jth period, β was the slope and ε_{ijk} is the error. If the 90% confidence interval for the model estimated mean slope falls within 0.8 and 1.25 limits, then dose proportionality will be concluded. The estimate and 90% confidence interval for the slope and fold increase in PK exposure when doubling the dose will be presented. The corresponding graphical display from the power model (back transformed to raw linear scale) with the 90% CI overlaid on the observed data will be provided.

Additionally, a mixed effect analysis of variance (ANOVA) model will be performed with the log-transformed dose normalized response variable, $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, or C_{max}. The geometric mean ratios and 90% CI for each dose compared to the reference dose (50 mg dose) will be provided.

Analysis of Effect of Food:

A mixed effect ANOVA model will be performed with log transformed $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ or C_{max}. Point estimates and 90% CI for geometric mean ratios will be computed for treatments (maribavir 200 mg fed vs. 200 mg fasted) . If the 90% CI for the geometric mean ratios of treatments (maribavir 200 mg fed vs. 200 mg fasted) falls within 0.8 and 1.25 limits, then equivalence will be concluded. Analysis of t_{max} and T_{lag} will be performed by nonparametric t-test.

8.8 Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number and percentage of subjects experiencing TEAEs and the number of events will be calculated and summarized by SOC, by preferred term and by study treatment for Part 1 and Part 2 separately, using the respective safety population. Treatment-emergent adverse events will be further summarized by severity and relationship to study treatment. Adverse events related to study treatment, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Additionally, TEAEs will be summarized for Part 1 and 2 combined for all subjects enrolled on study who take at least one dose of maribavir by dose level regardless of formulation.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by study treatment and visit for Part 1 and Part 2 separately, using the respective safety population.

Potentially clinically important findings will be summarized by study treatment for Part 1 and Part 2 separately.

Additionally, potentially clinically important (PCI) findings will be summarized for Part 1 and Part 2 combined for all subjects enrolled on study who take at least one dose of maribavir by dose level regardless of formulation.

8.9 Other Analyses

8.9.1 Palatability

The palatability will be evaluated to identify and characterize basic tastes, texture and mouth feel and to assess the overall acceptability. Palatability data will be summarized for Part 1 and Part 2 separately using the respective safety population.

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10. APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	**28 Aug 2019**	USA

APPENDIX 2 PALATABILITY QUESTIONNAIRE

Palatability Questionnaire

(Complete immediately following <u>each dose administration</u> in PART 1: Days 1, 4 and 7; and PART 2: Days 1, 4, 7 and 10)

Subject Initials: _____
Subject Number: _____
Date: _____
Study Part (1 or 2): _____
Treatment Period: _____
Dose administration time: _____
Time questionnaire administered: _____

1. Circle the answer below that best describes how this drug tasted to you.

bitter **salty** **sour** **sweet** **savory** **no taste**

2. If you identified a taste above, **how strong was the taste?** ☐ n/a-no taste

(mark an "X" in appropriate circle)

strong medium weak

3. Did the drug have a **rough or gritty texture** (Yes/ No)?

☐ Yes
☐ No

4. Was the drug **easy to swallow** (Yes/ No)?

☐ Yes
☐ No

5. The **overall taste and texture** of the drug was acceptable.
(mark an "X" in appropriate circle)

agree neither agree nor disagree disagree

APPENDIX 3 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

APPENDIX 3.1 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 3.2 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 investigational product 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 3.3 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. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

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

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 investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

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

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.

The CRA/study monitor will verify the contents of the completed CRF pages against the source data. 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 US FDA, EMA, UK Medicines and Healthcare Products Regulatory Agency) or an auditor.

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

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 investigational product; 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 3.4 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 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; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

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 4 ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

APPENDIX 4.1 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 investigational product 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 treatment-emergent adverse event (TEAE) is defined as any event emerging or manifesting at or after the initiation of treatment with an investigational product or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the investigational product or medicinal product.

Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, 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 Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the 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 RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated form 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

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 investigational product, 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 investigational product, 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 4.2 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 investigational product 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 4.3 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 investigational product, must be recorded as new AEs.

For example, if a subject reports mild intermittent dyspepsia prior to initiation of dosing with the investigational product, 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 investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source.

The following additional guidance may be helpful:

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

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 4.4 SAFETY REPORTING

Reference Safety Information

The reference for safety information for this study is the investigator's brochure, 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 and the CRO/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 (see Appendix 4.9) unless they result in an SAE.

The investigator must complete, sign, and date the Shire "Clinical Study Serious Adverse Event for Serious Adverse Events (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 Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the CRO/Shire Medical Monitor using the details specified in the emergency contact information section of the protocol.

APPENDIX 4.5 SERIOUS ADVERSE EVENT COLLECTION TIME FRAME

All SAEs (regardless of relationship to investigational product) 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/Shire Medical Monitor within 24 hours of the first awareness of the event.

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

APPENDIX 4.6 SERIOUS ADVERSE EVENT ONSET AND RESOLUTION DATES

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

In addition, any signs or symptoms 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 4.7 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 investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product or it is a single dose study). The investigational product action of withdrawn should not be selected solely as a result of the subject's death.

APPENDIX 4.8 PREGNANCY

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

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.

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.

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.

APPENDIX 4.9 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 4.1.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication error s unless these result in an SAE.

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

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a 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 investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)

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

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

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

APPENDIX 4.10 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 EC(s) and relevant

competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

APPENDIX 4.11 REGULATORY AGENCY, INSTITUTIONAL REVIEW BOARD, ETHICS COMMITTEE, AND SITE REPORTING

The sponsor is responsible for notifying the relevant regulatory authorities, institutional review boards (IRBs) and ethics committees (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 TAK620 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.

PROTOCOL: TAK-620-1019

TITLE: A Phase 1, Open-label, Randomized, Crossover, Bioavailability, Dose Proportionality, and Food Effect Study Comparing the Pharmacokinetics and Palatability of Two Candidate Pediatric Powder-for-Oral-Suspension Formulations of Maribavir to the Current Maribavir Tablet Formulation Administered in Healthy Adult Subjects

DRUG: TAK620 (SHP620), Maribavir

IND: 051001

EUDRACT NO.: 2015-004725-13

SPONSOR: Shire Human Genetic Therapies, Inc. (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], MD
[redacted]
USA
Telephone: [redacted] / [redacted]
Fax: [redacted]
E-mail: [redacted]

PROTOCOL HISTORY: Amendment 1: 05-Nov-2019
Original Protocol: 28-Aug-2019

Protocol Signature Page

Sponsor's (Shire) Approval

Signature: [redacted]	Date: [redacted]
[redacted], MD, PhD, MPH	

Investigator's Acknowledgement

I have read this protocol for Study TAK-620-1019.

Title: A Phase 1, Open-label, Randomized, Crossover, Bioavailability, Dose Proportionality, and Food Effect Study Comparing the Pharmacokinetics and Palatability of Two Candidate Pediatric Powder-for-Oral-Suspension Formulations of Maribavir to the Current Maribavir Tablet Formulation Administered in Healthy Adult 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 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], MD [redacted] [redacted] [redacted]

Signature: **Date:**

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **05 Nov 2019**	**Global/Country/Site Specific** **Country**
Description of Change		**Section(s) Affected by Change**
Wording was added to allow for the doses to be evaluated in Part 2 of the study to be adjusted from the planned doses of 50mg, 100mg and 200mg. Dose adjustment will be based on relative bioavailability of the selected pediatric formulation (powder for oral suspension) to the Phase 3 tablet formulation observed in Part 1. All statistical analyses will then be conducted based on the adjusted treatment groups.		Study Synopsis Section 3.1 Table 11 Figure 2 Section 8.4 Section 8.7.2.2
Clarification was added to describe the exclusion requirements for over-the counter and prescription medications. Current use of any prescription medication with the exception of hormonal replacement therapy. Current use is defined as use within 30 days of the first dose of investigational product. Current use of any over the counter medication (including herbal, or homeopathic preparations) within 14 days of the first dose of investigational product.		Study Synopsis Section 4.2
Added as a separate line item exclusion criteria “Current use of antacids and H2 antagonists		Study Synopsis Section 4.2
Clarified definition of ‘participation’ as it relates to exclusion criteria. The exclusion criteria was revised to read, “Prior screen failure, randomization, enrollment, participation in this study or participation in Part 1 of this study.”		Study Synopsis Section 4.2
Clarification was added for consistency and to confirm that a serum beta-HCG or urine pregnancy test is to be performed on all females as outlined in Table 1 and Table 5		Section 7.2.2.7
Clarified that FT_4 **not** Thyroxine (T4 Total), is required with biochemistry at screening		Section 7.2.2.6
Changed “phosphorus” to “phosphate” in the list of biochemistry laboratory tests required		Section 7.2.2.6
Added ECG to schedule of assessments at the 3 hour timepoint on Days 1, 4 and 7 in Part 1 and on Days 1, 4, 7 and 10 in Part 2.		Table 2 Table 3 Table 4 Table 6 Table 7 Table 8 Table 9
Removed biochemistry, hematology, and urinalysis from Day 1 Pre-dose in the detailed schedules of assessments.		Table 2 Table 6

Changed pre-dose window for all treatment periods in Part 2 to reflect that the assessments should be performed within 60 minutes prior to dose administration.	Table 6 Table 7 Table 8 Table 9
Added clarification that the pre-dose PK sample for subjects on Treatment G in Part 2 should be collected after the high-fat breakfast and before dose administration.	Table 6 Table 7 Table 8 Table 9
Removed section referencing respiratory rate instructions as respiratory rate is not part of the required study assessments.	Section 7.2.2.4
Changed "interim" to "planned" for consistency and to clarify the Part 1 to Part 2 analysis.	Study Synopsis Section 3.1
Added the definition of Randomized Set for Part 1 and Part 2 of the study	Section 8.7

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of an SAE, the investigator must fax or e-mail the "Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by 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)/Shire Medical Monitor using the details below.

For protocol- or safety-related questions or concerns <u>during normal business hours 8:00 am-5:00pm (local time per region),</u> the investigator must contact the Shire Medical Monitor:

[redacted], MD, PhD, MPH

Clinical Pharmacology Medical Leader/ Shire Study Medical Monitor

Telephone: [redacted] (business hours)

[redacted] (24-hour coverage)

E-mail: [redacted]

For protocol or safety-related questions or concerns <u>outside of normal business hours</u>, 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 according to procedures.

This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination); or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products); or a product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but did not result in an AE, which include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, eg, reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (eg, potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

For instructions on reporting AEs related to product complaints, see Appendix 4.4.

Please use the information below as applicable to report the Product Quality Complaint or Non-Medical Complaint:

Origin of Product Quality Complaint	E-mail Address
North and South America	[redacted]
European Union and Rest of World	[redacted]

Telephone number (provided for reference if needed):

Shire, Lexington, MA (USA)

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
AUC	area under the curve
$AUC_{0\text{-last}}$	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
β-HCG	beta-human chorionic gonadotropin
BCS	Biopharmaceutics Classification System
BMI	body mass index
CI	confidence interval
C_{max}	maximum concentration occurring at t_{max}
CL/F	oral clearance
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSU	clinical study unit
CV%	coefficient of variation
EC	ethics committee
ECG	electrocardiogram
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antibody
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HSA	serum albumin
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
PK	pharmacokinetics
PCI	potentially clinically important
QTc	corrected QT interval
SAE	serious adverse event

SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
TID	3 times daily
T_{lag}	delay between the time of dosing and time of appearance of concentration in the sampling
t_{max}	time of maximum observed concentration sampled during a dosing interval
TSH	thyroid-stimulating hormone
$t_{1/2}$	terminal half-life
US	United States

STUDY SYNOPSIS

Protocol number: TAK-620-1019	**Drug:** Maribavir
Title of the study: A Phase 1, Open-label, Randomized, Crossover, Bioavailability, Dose Proportionality, and Food Effect Study Comparing the Pharmacokinetics and Palatability of Two Candidate Pediatric Powder-for-Oral-Suspension Formulations of Maribavir to the Current Maribavir Tablet Formulation Administered in Healthy Adult Subjects	
Number of subjects (total and for each treatment arm): 38 subjects (18 in Part 1 and 20 in Part 2)	
Investigator: [redacted], MD	
Site(s) and Region(s): [redacted]	
Study period (planned): 2019-2020	**Clinical phase:** 1

Objectives:

Part 1:

- To assess the relative bioavailability of 2 candidate pediatric formulations of maribavir given as a single oral dose at 200 mg as compared to the Phase 3 adult maribavir 200 mg tablet formulation in healthy adult subjects (Primary)
- To assess the palatability of the candidate pediatric formulations measured by a questionnaire (Primary)
- To assess the safety and tolerability of 2 candidate pediatric formulations and the adult tablet formulation of maribavir given as a single oral dose at 200 mg in healthy adult subjects (Secondary)

Part 2:

- To assess the dose proportionality of 50 mg, 100 mg, and 200 mg of the selected pediatric formulation (Primary)
- To assess the impact of food on the rate and extent of absorption of the selected maribavir pediatric formulation given as 200 mg under fasted and fed conditions (Primary)
- To assess the palatability of maribavir formulations at various doses and with food (Primary)
- To assess the safety and tolerability of 2 candidate pediatric formulations and the adult tablet formulation of maribavir given as a single oral dose up to 200 mg in healthy adult subjects (Secondary)

Rationale:

In order to provide a palatable formulation for pediatric use, a taste-masking strategy that minimizes the availability of maribavir in the oral cavity is being explored. As the coating polymer has the potential to hinder drug release and absorption, 2 prototype formulations, each containing the same coating polymer but at different levels, are being evaluated in this study for their impact on palatability and rate and extent of absorption of maribavir. There were no significant effects of food on the rate and extent of absorption of maribavir from the adult tablet formulation, however, since maribavir is a Biopharmaceutics Classification System (BCS) II drug (ie, low solubility-high permeability drug) and the coating polymer may affect the rate and extent of absorption of maribavir, it is necessary to evaluate dose proportionality of the pediatric formulation and effects of food.

Investigational product, dose, and mode of administration:
Treatment A: maribavir 200 mg tablet- current Phase 3 formulation
Treatment B: maribavir 200 mg powder for oral suspension, 32.5% drug loading
Treatment C: maribavir 200 mg powder for oral suspension, 36.1% drug loading
Treatment D: maribavir powder for oral suspension (50 mg fasted)
Treatment E: maribavir powder for oral suspension (100 mg fasted)

Treatment F: maribavir powder for oral suspension (200 mg fasted)
Treatment G: maribavir powder for oral suspension (200 mg fed with a high-fat meal)

Doses for Treatment D/E/F/G may be adjusted based on relative bioavailability of the selected pediatric formulation (powder for oral suspension) to the Phase 3 tablet formulation.

Methodology:

This is a single-center (United States), open-label, randomized study. The study will be conducted sequentially in 2 parts. A total of 18 subjects will be enrolled in Part 1 of the study and a total of 20 subjects will be enrolled in Part 2. The study duration will comprise of a 28-day screening period for Part 1 and a 28-day screening period for Part 2. Part 1 will have 3 treatment periods with a 3-day washout period between each of the 3 periods and a follow-up phone call. Part 2 will have 4 treatment periods with a 3-day washout period between each of the 4 treatment periods and a follow-up phone call.

Subjects will be admitted to the clinical study unit (CSU) on Day -1.

In Part 1, 2 pediatric candidate powder formulations will be compared with maribavir 200 mg tablet under fasted conditions in regards to their bioavailability and palatability to select 1 pediatric powder formulation for further evaluation in Part 2. In Part 2 dose proportionality of 50, 100 and 200 mg dose of the selected pediatric powder formulation of maribavir will be assessed, as well as the impact of food (a high-fat meal) on the rate and extent of absorption of the selected pediatric formulation. The pediatric formulation of maribavir which will be evaluated in Part 2 will be chosen based on the results of planned analysis of Part 1 pharmacokinetic (PK) and palatability data from 2 candidate pediatric formulations and the doses to be evaluated in Part 2 may be adjusted based on relative bioavailability of the selected pediatric formulation (powder for oral suspension) to the Phase 3 tablet formulation observed in Part 1.

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/and assent as applicable to participate in the study.
3. Age 18-50 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.
4. 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. Additional details will be outlined in the protocol.
5. 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 electrocardiogram (ECG), hematology, blood chemistry (includes TSH and free T_4 [FT_4] at screening only), and urinalysis.
6. Hemoglobin for males ≥135.0 g/L and females ≥120.0 g/L at screening and on Day -1.
7. Body mass index (BMI) between 18.0 and 30.0 kg/m^2 inclusive with a body weight >50 kg (110 lbs). This inclusion criterion will only be assessed at the first screening visit.
8. Ability to swallow a dose of investigational product.

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 investigational product, 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 investigational product or procedures.
3. Known or suspected intolerance or hypersensitivity to the investigational product(s), 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 investigational product.
5. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the first dose of investigational product.
6. Within 30 days prior to the first dose of investigational product:
   a. Have used an IP (if elimination half-life is <6 days, otherwise 5 half-lives).
   b. Have been enrolled in a clinical study (including vaccine studies) that, in the investigator's opinion, may impact this Shire-sponsored study.
   c. Have had any substantial changes in eating habits, as assessed by the investigator.
7. Confirmed systolic blood pressure >139 mmHg or <89 mmHg, and diastolic blood pressure >89 mmHg or <49 mmHg.
8. 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.
9. Known history of alcohol or other substance abuse within the last year.
10. 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).
11. A positive screen for alcohol or drugs of abuse at screening or on Day -1 of Treatment Period 1.
12. A positive human immunodeficiency virus (HIV), hepatitis B surface antibody (HBsAg), or hepatitis C virus (HCV) antibody screen.

13. 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 investigational product (maribavir).
14. 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 tea, three 1 oz [85 g] chocolate bars. (Decaffeinated coffee, tea, or cola are not considered to contain caffeine).
15. Prior screen failure, randomization, enrollment, participation in this study or participation in Part 1 of this study.
16. Current use of any prescription medication with the exception of hormonal replacement therapy. Current use is defined as use within 30 days of the first dose of investigational product. Current use of any over the counter medication (including herbal, or homeopathic preparations) within 14 days of the first dose of investigational product.
17. Current use of antacids and H2 antagonists.
18. Ingestion of known CYP3A modulators within 7 days of Day 1, Period 1 (includes grapefruit or grapefruit juice, oranges, Seville oranges, apples or apple juice, vegetables from the mustard green family [eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard], charbroiled meats, and products containing these ingredients).
19. Inability or unwillingness to consume 100 percent of high-fat meal in Part 2 (including subjects with lactose or gluten intolerance).
20. History of 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.

Maximum duration of subject involvement in the study:

The maximum total duration of study participation for a subject in Part 1 is 46 days. The maximum total duration of study participation for a subject in Part 2 is 49 days.

- Planned duration of screening period Part 1: 28 days
- Planned duration of screening period Part 2: 28 days
- Planned duration of treatment period Part 1: 7 days
- Planned duration of treatment period Part 2: 10 days
- Planned duration of follow-up Part 1: 7±2 days after the last dose of investigational product.
- Planned duration of follow-up Part 2: 7±2 days after the last dose of investigational product.

Endpoints and statistical analysis:

Two analysis populations are defined for this study in Part 1 and in Part 2: pharmacokinetic and safety.

For Part 1:

- The pharmacokinetic population consists of subjects who received at least 1 dose of maribavir, did not vomit within 4 hours of dosing, and have at least 1 evaluable post-dose maribavir concentration value in Part 1.
- The safety population includes subjects who have received at least 1 dose of maribavir in Part 1.

For Part 2:

- The pharmacokinetic population consists of subjects who received at least 1 dose of maribavir, did not vomit within 4 hours of dosing, and have at least 1 evaluable post-dose maribavir concentration value in Part 2.
- The safety population includes subjects who have received at least 1 dose of maribavir in Part 2.

Pharmacokinetic endpoint:

The PK analysis will be based on the PK analysis dataset. Pharmacokinetic parameters will be calculated from maribavir concentration-time data using non-compartmental analysis (NCA) and all calculations will be based on actual sampling times. Pharmacokinetic parameters will include, but not be limited to, the following:

Part 1 (Day 1, Day 4, and Day 7)

- C_{max}: Maximum concentration occurring at t_{max}
- t_{max}: Time of maximum observed concentration sampled during a dosing interval
- $AUC_{0\text{-}last}$: 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
- $t_{1/2}$ Terminal half-life
- CL/F Apparent total body clearance following extravascular administration calculated as dose divided by $AUC_{0\text{-}inf}$
- T_{lag} Delay between the time of dosing and time of appearance of plasma concentration in the employed sampling scheme

Part 2 (Day 1, Day 4, Day 7, and Day 10)

- C_{max} Maximum concentration occurring at t_{max}
- t_{max} Time of maximum observed concentration sampled during a dosing interval
- $AUC_{0\text{-}last}$ 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
- $t_{1/2}$ Terminal half-life
- CL/F Apparent total body clearance following extravascular administration divided by the fraction of dose absorbed calculated as dose divided by $AUC_{0\text{-}inf}$
- T_{lag} Delay between the time of dosing and time of appearance of concentration in the sampling

In addition, dose-normalized C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ will be calculated for Treatments D, E, and F.

Safety endpoint:

Safety will be assessed for the following evaluations for both Part 1 and Part 2:

- Number, severity, seriousness, and causality of treatment-emergent adverse events (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.

Palatability endpoint:

The palatability will be evaluated to identify, characterize and quantify the sensory attributes of products, eg, basic tastes, texture and mouth feel and to assess the overall acceptability.

Sample Size Justification:

A sample size of 18 subjects in Part 1 and 20 subjects in Part 2 is calculated assuming a true mean ratio of 1.0 with intra-subject coefficient of variation of 0.218, a total of 18 completers is required to have 80% power to show that the 90% confidence intervals of the ratios of the geometric means of the two formulations/treatment lie within the range of 0.80 to 1.25.

The table below indicates the number of subjects required based on the following data:

- The intra-subject coefficient of variation is assumed at 0.166 and 0.218 respectively for $AUC_{0\text{-}inf}$ and C_{max},

which are estimated from the 90% confidence intervals (CIs) of the geometric mean ratio of $AUC_{0\text{-inf}}$, and C_{max} in Study 1263-104.

- Sample size estimation is performed using nQuery's two one-sided test (TOST) of equivalence in ratio of mean for crossover design study.
- True mean ratio: 1.00, 1.05
- Power: 80%, 90%
- One-sided α-level: 0.05 (corresponding to 90% CI)
- Bioequivalence range: 0.8-1.25

	Number of Subjects Required		
		Intra-subject coefficient of variation	
True Ratio	**Power**	0.166	0.218
1.0	80%	12	18
	90%	14	22
1.05	80%	14	22
	90%	18	28

Note sample size estimation is performed using nQuery's TOST of equivalence in ratio of mean for crossover design study.

Statistical Methodology for Pharmacokinetic Endpoint(s):

Part 1

Individual concentrations and PK parameters of maribavir will be listed and summarized by treatment with descriptive statistics (number, arithmetic mean, standard deviation [SD], coefficient of variation [CV%], median, minimum, maximum, geometric mean, and %CV of geometric mean). Figures of individual and mean (+/-SD) concentration-time profiles of plasma maribavir by treatment will be generated on both linear and semi-log scales.

Following the $\log_e$-transformation, the PK parameters including AUC_{last}, $AUC_{0\text{-inf}}$, and C_{max} will be analyzed using a mixed effect model to include sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Analysis of variance will be performed using SAS mixed linear models procedure. Point estimates and their associated 90% CIs will be constructed for the differences in the log-transformed parameters. The point estimates and their associated 90% CIs will be then back-transformed to provide point estimates for the ratio of geometric least squares means and associated 90% CIs on the original scale. Analysis of t_{max} and tlag will be performed by nonparametric t-test.

Part 2

Dose proportionality analysis

The dose proportionality will be first assessed using the Power Model for (fasted) dose range tested in Part 2. The Power Model: $\log(Y_{ijk})=S_i + P_j + \beta x\log(D_k) + \varepsilon_{ijk}$ where D is the total number of doses, N are the total number of subjects and P the total number of periods and i=1,…..,N, j=1,…..,P and k=1,…..,D. Y_{ijk} is the log-transformed response variable, $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, or C_{max} on the kth dose, in the jth period, for the ith subject. S_i is the random subject effect for the ith subject, P_j is the fixed period effect for the jth period, β was the slope and ε_{ijk} is the error. If the 90% confidence interval for the model estimated mean slope falls within 0.8 and 1.25 limits, then dose proportionality will be concluded. The estimate and 90% confidence interval for the slope and fold increase in PK exposure when doubling the dose will be presented. The corresponding

graphical display from the powermodel (back transformed to raw linear scale) with the 90% CI overlaid on the observed data will be provided.

Additionally, a mixed effect analysis of variance (ANOVA) model will be performed with the log-transformed dose normalized response variable, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, or C_{max}. The geometric mean ratios and 90% CI for each dose compared to the reference dose (50 mg dose) will be provided.

Analysis of Effect of Food

A mixed effect ANOVA model will be performed with log transformed $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, or C_{max}. Point estimates and 90% CI for geometric mean ratios will be computed for treatments (selected dose of maribavir fed vs. fasted). If the 90% CI for the geometric mean ratios of treatments (selected dose of maribavir fed vs. fasted) falls within 0.8 and 1.25 limits, then equivalence will be concluded. Analysis of t_{max} and tlag will be performed by nonparametric t-test.

Statistical Methodology for Palatability Endpoint:

Data collected from the palatability questionnaire will be summarized descriptively.

STUDY SCHEDULE(S)

Table 1: Schedule of Assessments Part 1

Visit[a]	Screening	Treatment Period 1				Treatment Period 2			Treatment Period 3		Follow-up[l]
Study Day	**-28 to -2**	**-1**	**1[j]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demography	X										
Medical/medication history	X	X									
Physical examination[b]	X	X	X			X			X	X	
Randomization			X[k]								
Vital signs (blood pressure, pulse)[b,c]	X	X	X	X	X	X	X	X	X	X	
Oral temperature	X	X	X			X			X	X	
Height and weight[d]	X	X	X			X			X	X	
Electrocardiogram (12-lead)[b,e]	X	X	X	X		X	X		X	X	
Biochemistry, hematology, and urinalysis[b, f, m]	X	X		X			X			X	
HIV, HBsAg, and HCV antibodies	X										
Beta HCG Pregnancy test (females only)[b, g]	X	X								X	
FSH[h] test in perimenopausal women	X										
Urine drug and alcohol screening[i]	X	X									
Investigational Drug Administration			X			X			X		
Pharmacokinetic blood sampling[j, n]			X	X		X	X		X	X	
Palatability Assessment			X			X			X		
Admit to the CSU (Day -1)		X									
Discharge from the CSU (Day 8 after last assessment)										X	
Washout between treatment periods			X	X	X	X	X	X			
Adverse events/serious adverse events[b]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X

β-hCG=beta-human chorionic gonadotropin; CSU-clinical study unit; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PK=pharmacokinetic; SAE=serious adverse event; TSH=thyroid-stimulating hormone

[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. Treatment Period 1 includes washout (Days 1 through 3), Treatment Period 2 includes washout (Days 4 through 6), and Treatment Period 3 is from Days 7 through 8.

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

Table 1: Schedule of Assessments Part 1

Visit[a]	Screening	Treatment Period 1				Treatment Period 2			Treatment Period 3		Follow-up[l]
Study Day	-28 to -2	-1	1[j]	2	3	4	5	6	7	8	

[c] Vital signs will be obtained while subject is in the supine position on study days noted. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

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

[e] Twelve-lead ECGs will be measured in the supine position. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

[f] Clinical laboratory assessments include serum biochemistry, TSH and FT_4, at (screening only), hematology, and urinalysis.

[g] Serum β-HCG test at Screening is required for all females. Urine pregnancy test is required for all females at subsequent scheduled time points.

[h] Females only, to confirm menopausal status.

[i] Drugs of abuse and alcohol at screening and Day-1

[j] See Table 2, Table 3, and Table 4 for detailed collection time points.

[k] Randomization is for Treatment Period 1, Day 1 only.

[l] There will be a follow-up telephone call approximately 7±2 days following the last dose of investigational product in Treatment Period 3 (Day 7). AEs/SAEs occurring up to the time of the follow-up telephone call will be captured. The follow-up telephone call should be completed for all subjects including those who withdraw or are removed from the study prior to Day 8 of Treatment Period 3.

[m] If screening occurs on Day -2, biochemistry, hematology and urinalysis is not required on Day -1

[n] 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.

Table 2: Detailed Schedule of Assessments for Treatment Period 1 (Day 1), Part 1

Study Day	Day 1																Day 2
Hour (relative to dosing time)	**Predose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																
Randomization[b]	X																
Vital signs (blood pressure, pulse) [a, c]	X[e]								X								X
Oral Temperature[a]	X[e]																
Weight	X[e]																
Electrocardiogram (12-lead)[a,d]	X[e]								X								X
Biochemistry, hematology, and urinalysis[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[g]	X[e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[f]														

ECG=electrocardiogram; 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] Randomization will occur in Treatment Period 1, Day 1 only.

[c] Vital signs will be obtained while subject is in the supine position on study days noted. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

[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] These assessments should be performed within 30 minutes prior to dose administration.

[f] Palatability questionnaire should be given within 5 minutes of receiving dose

[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. 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.

Table 3: Detailed Schedule of Assessments for Treatment Period 2 (Day 4), Part 1

Study Day	**Day 4**																**Day 5**
Hour (relative to dosing time)	**Pre-dose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Oral Temperature[a]	X[d]																
Weight	X[d]																
Electrocardiogram (12-lead)[a,c]	X[d]								X								X
Biochemistry, hematology, and urinalysis[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[f]	X[d]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

ECG=electrocarodiogram; 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. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.
[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] These assessments should be performed within 30 minutes prior to dose administration.
[e] Palatability questionnaire should be given within 5 minutes of receiving dose
[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. 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.

Table 4: Detailed Schedule of Assessments for Treatment Period 3 (Day 7), Part 1

Study Day	Day 7																Day 8
Hour (relative to dosing time)	**Pre-dose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																X
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Electrocardiogram (12-lead)[a,c]	X[d]								X								X
Oral Temperature[a]	X[d]																X
Weight	X[d]																X
Biochemistry, hematology, and urinalysis[a]																	X
Pregnancy (females only)[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[f]	X[d]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

ECG=electrocardiogram; 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. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.
[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] These assessments should be performed within 30 minutes prior to dose administration.
[e] Palatability questionnaire should be given within 5 minutes of receiving dose
[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. 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.

Table 5: Schedule of Assessments Part 2

Visit[a]	Screening	Treatment Period 1				Treatment Period 2			Treatment Period 3			Treatment Period 4		Follow-up[l]
Study Day	**-28 to -2**	**-1**	**1[j]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Informed consent	X													
Inclusion/ exclusion criteria	X	X												
Demography	X													
Medical/medication history	X	X												
Physical examination[b]	X	X	X			X			X			X	X	
Randomization			X[k]											
High-fat meal prior to dose administration			X[n]			X[n]			X[n]			X[n]		
Vital signs (blood pressure, pulse)[b,c]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Oral temperature	X	X	X			X			X			X	X	
Height and weight[d]	X	X	X			X			X			X	X	
Electrocardiogram (12-lead)[b,e]	X	X	X	X		X	X		X	X		X	X	
Biochemistry, hematology, and urinalysis[b, f, m]	X	X		X			X			X			X	
HIV, HBsAg, and HCV antibodies	X													
Pregnancy (females only)[b, g]	X	X											X	
FSH[h] test in perimenopausal women	X													
Urine drug and alcohol screening[i]	X	X												
Investigational Drug Administration			X			X			X			X		
Pharmacokinetic blood sampling[j, o]			X	X		X	X		X	X		X	X	
Palatability Assessment			X			X			X			X		
Admit to the CSU (Day -1)		X												
Discharge from the CSU (Day 11 after last assessment)													X	
Washout between treatment periods			X	X	X	X	X	X	X	X	X			
Adverse events/serious adverse events[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5: Schedule of Assessments Part 2

Visit[a]	Screening	Treatment Period 1				Treatment Period 2			Treatment Period 3			Treatment Period 4		Follow-up[l]
Study Day	**-28 to -2**	**-1**	**1[j]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

β-hCG=beta-human chorionic gonadotropin; CSU=clinical study unit; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PK=pharmacokinetic; SAE=serious adverse event; TSH=thyroid-stimulating hormone

[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 3-day washout period between administration of the last dose of investigational product in Treatment Period 2 and Treatment Period 3 and between administration of the last dose in Treatment 4. Treatment Period 1 includes washout (Days 1 through 3), Treatment Period 2 includes washout (Days 4 through 6), and Treatment Period 3 is from Days 7 through 9.

[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. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

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

[e] Twelve-lead ECGs will be measured in the supine position. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

[f] Clinical laboratory assessments include serum biochemistry, (TSH and FT_4 at screening only), hematology, and urinalysis.

[g] Serum β-HCG test at Screening is required for all females. Urine pregnancy test is required for all females at subsequent scheduled time points

[h] Females only, to confirm menopausal status

[i] Drugs of abuse and alcohol at screening, and drugs of abuse and alcohol Day -1.

[j] See Table 6, Table 7, Table 8, and Table 9 for detailed collection time points

[k] Randomization is for Treatment Period 1, Day 1 only.

[l] There will be a follow-up telephone call approximately 7±2 days following the last dose of investigational product in Treatment Period 43 (Day 10). Adverse events/SAEs occurring up to the time of the follow-up telephone call will be captured. The follow-up telephone call should be completed for all subjects including those who withdraw or are removed from the study prior to Day 11 of Treatment Period 4.

[m] If screening occurs on Day -2, biochemistry, hematology and urinalysis is not required on Day -1.

[n] Subjects in Part 2 will receive maribavir depending on his/her randomized assignment to treatment sequence following an overnight fast of at least 10 hours. The study subjects should start the high-fat meal 30 minutes before administration of the drug product. Trial subjects should eat this meal in 30 minutes or less and consume 100 percent of the meal.

[o] 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.

Table 6: Detailed Schedule of Assessments for Treatment Period 1 (Day 1), Part 2

Study Day	Day 1																Day 2
Hour (relative to dosing time)	**Predose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																
Randomization[b]	X																
Vital signs (blood pressure, pulse)[a, c]	X[e]								X								X
Oral Temperature[a]	X																
Weight	X[e]																
Electrocardiogram (12-lead)[a,d]	X[e]								X								X
Biochemistry, hematology, and urinalysis[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[g,]	X[e, h]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[f]														

ECG=electrocarodiogram; 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] Randomization will occur in Treatment Period 1, Day 1 only.
[c] Vital signs will be obtained while subject is in the supine position on study days noted. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.
[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] These assessments should be performed within 60 minutes prior to dose administration.
[f] Palatability questionnaire should be given within 5 minutes of receiving dose
[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. 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.
[h] The pre-dose PK sample for subjects on Treatment G should be collected after the high-fat breakfast and before dose administration.

Table 7: Detailed Schedule of Assessments for Treatment Period 2 (Day 4), Part 2

Study Day	Day 4																Day 5
Hour (relative to dosing time)	**Pre-dose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Oral Temperature[a]	X[d]																
Weight	X[d]																
Electrocardiogram (12-lead)[a,c]	X[d]								X								X
Biochemistry, hematology, and urinalysis[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[f]	X [d, g]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

ECG=electrocarodiogram; 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. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

[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] These assessments should be performed within 60 minutes prior to dose administration.

[e] Palatability questionnaire should be given within 5 minutes of receiving dose

[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. 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.

[g] The pre-dose PK sample for subjects on Treatment G should be collected after the high-fat breakfast and before dose administration.

Table 8: Detailed Schedule of Assessments for Treatment Period 3 (Day 7), Part 2

Study Day	Day 7																Day 8
Hour (relative to dosing time)	**Pre-dose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination [a]	X																
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Electrocardiogram (12-lead)[a,c]	X[d]								X								X
Oral Temperature[a]	X[d]																
Weight	X[d]																
Biochemistry, hematology, and urinalysis[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[f]	X[d, g]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

[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. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.
[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] These assessments should be performed within 60 minutes prior to dose administration.
[e] Palatability questionnaire should be given within 5 minutes of receiving dose.
[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. 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.
[g] The pre-dose PK sample for subjects on Treatment G should be collected after the high-fat breakfast and before dose administration.

Table 9: Detailed Schedule of Assessments for Treatment Period 4 (Day 10), Part 2

Study Day	Day 10																Day 11
Hour (relative to dosing time)	**Pre-dose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																X
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Electrocardiogram (12-lead)[a,c]	X[d]								X								X
Oral Temperature[a]	X[d]																X
Weight	X[d]																X
Biochemistry, hematology, and urinalysis[a]																	X
Pregnancy (females only)[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[f]	X[d, g]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

ECG=electrocardiogram; 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. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.
[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] These assessments should be performed within 60 minutes prior to dose administration.
[e] Palatability questionnaire should be given within 5 minutes of receiving dose
[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. 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.
[g] The pre-dose PK sample for subjects on Treatment G should be collected after the high-fat breakfast and before dose administration.

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

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

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 virus's ability to modulate the immune system, either directly or secondary to the host antiviral response through regulation of cytokine, chemokine, and/or growth factor production.

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

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

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

with 3 months of oral ganciclovir. Ganciclovir-resistant disease accounted for 20% of CMV disease, occurred late (a median of 10 months after transplantation), was associated with higher intensity of immunosuppression, and was considered a clinically serious concern (Avery, 2007).

There are no approved therapies for the treatment of CMV infection or CMV disease in transplant recipients, and no approved treatment for CMV infection or disease that is resistant or refractory to currently available therapies in any population. Maribavir is currently 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 Investigator's Brochure.

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- 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, metabolism and drug-drug interactions

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). Pharmacokinetic data obtained in Phase 2 studies was similar to the data observed in healthy volunteers.

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

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

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-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 pharmacokinetics 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 50-2400 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. A definitive QT study demonstrated no clinically significant repolarization effect of maribavir administered orally at single doses of 100 mg and 1200 mg in healthy subjects. In addition, no other significant electrocardiographic effects of maribavir were found.

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

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

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 investigator's brochure for the most detailed and most current information regarding the drug metabolism, pharmacokinetics, 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 SCT 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 investigator's brochure (IB) for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, pharmacokinetics, 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 3.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

In the previous study SHP620-118, taste assessment study of maribavir, maribavir taste was characterized as a strong and lingering bitter taste at clinically-relevant doses, posing a taste-masking challenge.

In order to provide a palatable formulation for pediatric use, a taste-masking strategy that minimizes the availability of maribavir in the oral cavity is being explored. The taste-masking relies on the use of a coating polymer that is insoluble at neutral pH (ie, of saliva) but soluble at acidic pH (ie, of gastric fluid). By encapsulating maribavir inside the coating polymer, maribavir would be unavailable for taste perception in the mouth but, released in the stomach for absorption. As the coating polymer has the potential to hinder drug release and absorption, 2 prototype formulations, each containing the same coating polymer, but with different amounts, are being evaluated in this study for their impact on palatability and rate and extent of absorption of maribavir.

There were no significant effects of food on the rate and extent of absorption of maribavir from the adult tablet formulation; however, since maribavir is a Biopharmaceutics Classification System (BCS) II drug and the coating polymer may affect the rate and extent of absorption of maribavir, it is necessary to evaluate the dose proportionality of the pediatric formulation and the effects of food. This study will be conducted in 2 parts and a planned analysis will be conducted after Part 1 to decide if 1 of the 2 candidate pediatric formulations can be selected based on palatability and relative bioavailability and will be further evaluated for dose proportionality and effects of food in Part 2. The results from this study may be used for further optimization of the pediatric formulation and will provide guidance on dose selection of the pediatric formulation in clinical development for pediatric patients.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objectives of Part 1 of this study are to assess the relative bioavailability of 2 candidate pediatric formulations of maribavir given as a single oral dose at 200 mg as compared to the Phase 3 adult maribavir 200 mg tablet formulation in healthy adult subjects. In addition, the palatability of the candidate pediatric formulations will be assessed by a questionnaire.

The primary objectives of Part 2 of this study are to assess the dose proportionality of 50 mg, 100 mg, and 200 mg of the selected pediatric formulation, to assess the impact of food on the rate and extent of absorption of the selected pediatric formulation given as 200 mg under fasted and fed conditions and to assess the palatability at various doses and with food.

2.2.2 Secondary Objectives

The secondary objective of Part 1 and Part 2 of this study is to assess the safety and tolerability of 2 candidate pediatric formulations and the adult tablet formulation of maribavir given as a single oral dose up to 200 mg in healthy adult subjects.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

The study will be conducted sequentially in 2 parts. In Part 1, two pediatric candidate powder formulations will be compared with maribavir 200 mg tablet under fasted conditions in regards to their bioavailability and palatability. In Part 2 dose proportionality of 50, 100, and 200 mg dose of the selected pediatric powder formulation will be assessed, as well as the impact of food (a high-fat meal) on the rate and extent of absorption of the selected pediatric formulation. The pediatric formulation which will be evaluated in Part 2 will be chosen based on the results of planned analysis of Part 1 PK and palatability data from two candidate pediatric formulations and the doses to be evaluated in Part 2 may be adjusted based on relative bioavailability of the selected pediatric formulation (powder for oral suspension) to the Phase 3 tablet formulation observed in Part 1.

Part 1: Relative Bioavailability and Palatability

A total of 18 healthy male and female subjects, 18-50 years of age, inclusive, will be enrolled and expected to complete Part 1 of this study. Subjects who withdraw early will be replaced; the replacement subjects will receive the same treatment sequence assigned to subject who withdraw early. The study will be comprised of the following periods: a screening lasting up to 28 days, 3 treatment periods in which subjects will receive a single dose of the study drug on the first day of each period after a 10-hour overnight fasting, a drug washout of a minimum of 72 hours and maximum of 73 hours between dosing in periods 1 and 2 and periods 2 and 3, and a follow-up phone call (7±2 days) after the last dose of investigational drug (maribavir) is administered (Figure 1). The maximal total duration of study participation for a subject in Part 1 is 46 days, if the maximum screening, washout and follow-up durations are used.

Screening will occur within 28 days prior to randomization to assess eligibility of subjects to participate in the study. Subjects will be admitted to the clinical study unit (CSU) on Day -1. On the morning of Day 1, subjects will be randomized to 1 of 6 sequences in a 1:1:1:1:1:1 treatment allocation. Subjects will receive assigned treatment under fasted conditions in each treatment period. The treatment sequences to be used in the study is shown in Table 10:

Table 10: Treatment Sequence Part 1: N=18

Sequence number (number of subjects per sequence)	Treatment Sequence
1 (n=3)	ABC
2 (n=3)	BCA
3 (n=3)	CAB
4 (n=3)	CBA

Table 10: Treatment Sequence Part 1: N=18

Sequence number (number of subjects per sequence)	Treatment Sequence
5 (n=3)	ACB
6 (n=3)	BAC

Treatment A: maribavir 200 mg tablet- current Phase 3 formulation

Treatment B: maribavir 200 mg powder for oral suspension, 32.5% drug loading

Treatment C: maribavir 200 mg powder for oral suspension, 36.1% drug loading

Treatment Period 1

- On Day 1, subjects in each cohort will receive 200 mg maribavir depending on his/her randomized assignment to the treatment sequence as presented in Table 10.

Washout Period

- There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4).

Treatment Period 2

- On Day 4, subjects in each cohort will receive 200 mg maribavir depending on his/her randomized assignment to treatment sequence (Table 10).

Washout Period

- There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7).

Treatment Period 3

- On Day 7, subjects in each cohort will receive 200 mg maribavir depending on his/her randomized assignment to treatment sequence (Table 10).

Assessments

Pharmacokinetic (PK) Assessment
Serial blood samples for PK analysis of maribavir concentrations will be collected over 24 hours on Day 1, Day 4, and Day 7. These blood samples will be collected according to the Detailed Schedule of Assessments (Table 2, Table 3, and Table 4).

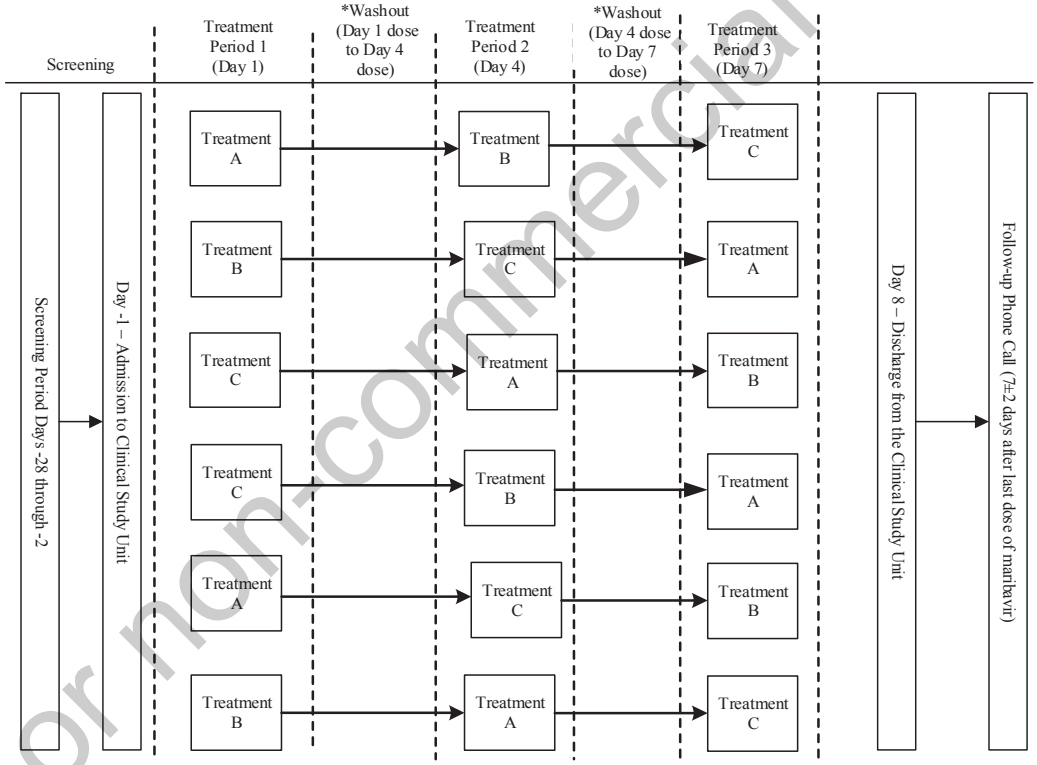
- **Safety and Tolerability Assessment**
  Safety and tolerability will be assessed based on treatment-emergent adverse events (TEAEs), vital signs, laboratory values, electrocardiogram (ECG) findings, and evaluation of clinical signs.

- **Palatability Assessment**
  Palatability will be assessed based on subjects' responses to a questionnaire that will be completed following each dose administration on Day 1, Day 4 and Day 7.

Follow-up

- Subjects will remain in the CSU until completion of the last post dose assessment on Day 8. A post-treatment follow-up telephone call will be performed 7 (±2) days after the last dose of investigational product.

Figure 1: Study Design Flow Chart Part 1



Treatment A: Maribavir 200mg tablet
Treatment B: Maribavir powder for oral suspension, 32.5% drug loading
Treatment C: Maribavir powder for oral suspension, 36.1% drug loading
*NOTE: Treatment will be dependent on randomization sequence.
*NOTE: There will be a drug washout of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4) and between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7)

Part 2: Dose Proportionality and Food Effect

A total of 20 healthy male and female subjects, 18-50 years of age, inclusive, will be enrolled and expected to complete Part 2 of this study. Subjects who withdraw early will be replaced and the replacement subjects will receive the same treatment sequence assigned to subject who withdraw early. The study will be comprised of the following periods: a screening lasting up to 28 days, 4 treatment periods in which subjects will receive a single dose of the study drug on the first day of each period after a 10-hour overnight fasting, one treatment period in which subjects will receive a single dose of the study drug on the first day of the period after consuming a high-fat meal, a drug washout of a minimum of 72 hours and maximum of 73 hours between dosing in periods 1 and 2, periods 2 and 3, and periods 3 and 4, and a follow-up phone call (7±2 days) after the last dose of investigational drug (maribavir) is administered (Figure 2). The maximal total duration of study participation for a subject in Part 2 is 49 days, if the maximum screening, washout and follow-up durations are used.

A planned analysis is planned after the completion of Part I to evaluate the PK and palatability data from the formulations investigated. Based on the results of the planned analysis of Part 1 data, 1 pediatric formulation may be chosen to be assessed in Part 2.

Screening will occur within 28 days prior to randomization to assess eligibility of subjects to participate in the study. Subjects will be admitted to the CSU on Day -1. On the morning of Day 1, subjects will be randomized to 1 of 4 sequences in a 1:1:1:1 treatment allocation. The treatment sequences to be used in the study is shown in Table 11:

Table 11: Treatment Sequence Part 2: N=20

Sequence number (number of subjects per sequence)	Treatment Sequence
1 (n=5)	DEGF
2 (n=5)	EFDG
3 (n=5)	FGED
4 (n=5)	GDFE

Treatment D: maribavir powder for oral suspension (50 mg fasted)

Treatment E: maribavir powder for oral suspension (100 mg fasted)

Treatment F: maribavir powder for oral suspension (200 mg fasted)

Treatment G: maribavir powder for oral suspension (200 mg fed with a high-fat meal)

The doses for Treatment D/E/F/G may be adjusted based on relative bioavailability of the selected pediatric formulation (powder for oral suspension) to the Phase 3 tablet formulation observed in Part 1.

Treatment Period 1

- On Day 1, subjects in each cohort will receive maribavir depending on his/her randomized assignment to the treatment sequence as presented in Table 11.

Washout Period

- There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4).

Treatment Period 2

- On Day 4, subjects in each cohort will receive maribavir depending on his/her randomized assignment to treatment sequence (Table 11).

Washout Period

- There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7).

Treatment Period 3

- On Day 7, subjects in each cohort will receive maribavir depending on his/her randomized assignment to treatment sequence (Table 11).

Washout Period

- There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 3 (Day 7) and the administration of maribavir in Period 4 (Day 10).

Treatment Period 4

- On Day 10, subjects in each cohort will receive maribavir depending on his/her randomized assignment to treatment sequence (Table 11).

Assessments

Pharmacokinetic (PK) Assessment
Serial blood samples for PK analysis of maribavir concentrations will be collected over 24 hours on Day 1, Day 4, Day 7 and Day 10. These blood samples will be collected according to the Detailed Schedule of Assessments (Table 6, Table 7, Table 8, and Table 9).

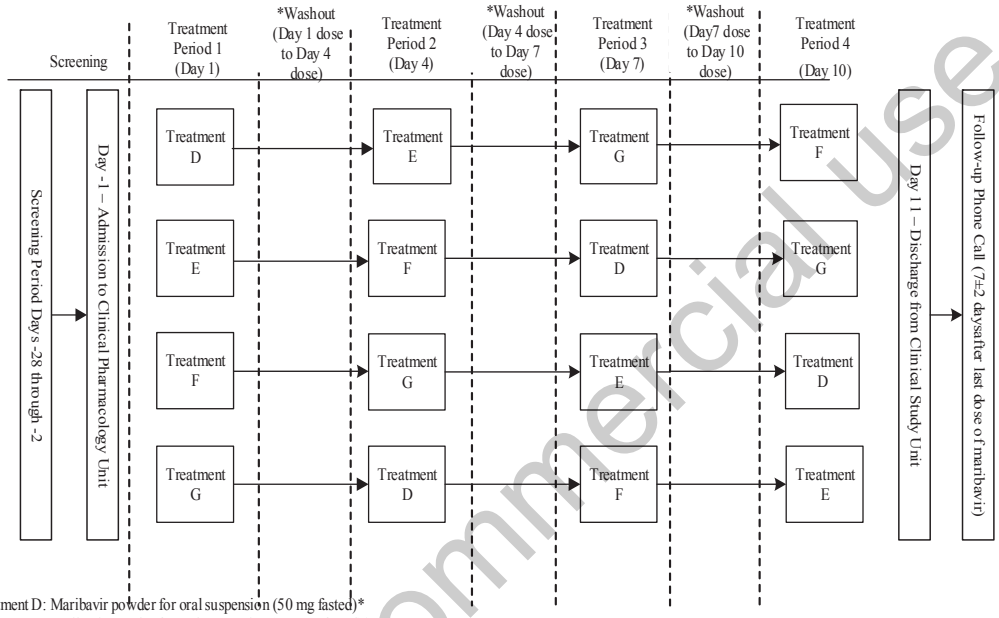
- **Safety and Tolerability Assessment**
  Safety and tolerability will be assessed based on treatment-emergent adverse events (TEAEs), vital signs, laboratory values, electrocardiogram (ECG) findings, and evaluation of clinical signs.

- **Palatability Assessment**
  Palatability will be assessed based on subjects' responses to a questionnaire that will be completed following each dose administration on Day 1, Day 4, Day 7, and Day 10.

Follow-up

- Subjects will remain in the CSU until completion of the last post dose assessment on Day 11. A post-treatment follow-up telephone call will be performed 7 (±2) days after the last dose of investigational product.

Figure 2: Study Design Flow Chart Part 2



Treatment D: Maribavir powder for oral suspension (50 mg fasted)*
Treatment E: Maribavir powder for oral suspension (100 mg fasted)*
Treatment F: Maribavir powder for oral suspension (200 mg fasted)*
Treatment G: Maribavir powder for oral suspension (200 mg fed with a high-fat meal)*
*NOTE: Treatment will be dependent on randomization sequence. The doses to be evaluated in Part 2 may be adjusted based on relative bioavailability of the selected pediatric formulation (powder for oral suspension) to the Phase 3 tablet formulation observed in Part 1.
*NOTE: There will be a drug washout of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4) between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7), and between the administration of maribavir in Period 3 (Day 7) and the administration of maribavir in Period 4 (Day 10)

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 46 days for Part 1 and 49 days for Part 2. The study will be completed in approximately 12 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 phone call, 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 1 clinical site in the 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 subject will not be considered eligible for the study without meeting all of the inclusion and exclusion criteria.

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/and assent as applicable to participate in the study.
3. Age 18-50 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.
4. 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. Additional details will be outlined in the protocol.
5. 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 TSH and free T_4 (FT_4) at screening only), and urinalysis.
6. Hemoglobin for males ≥135.0 g/L and females ≥120.0 g/L at screening and on Day -1.
7. Body mass index (BMI) between 18.0 and 30.0 kg/m^2 inclusive with a body weight >50 kg (110 lbs). This inclusion criterion will only be assessed at the first screening visit.
8. Ability to swallow a dose of investigational product.

4.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met at the screening visit or Day -1 (if reassessed):

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 investigational product, 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 investigational product or procedures.
3. Known or suspected intolerance or hypersensitivity to the investigational product(s), 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 investigational product.
5. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the first dose of investigational product.
6. Within 30 days prior to the first dose of investigational product:
   - Have used an investigational product (if elimination half-life is <6 days, otherwise 5 half-lives).
   - Have been enrolled in a clinical study (including vaccine studies) that, in the investigator's opinion, may impact this Shire-sponsored study.
   - Have had any substantial changes in eating habits, as assessed by the investigator.
7. Confirmed systolic blood pressure >139 mmHg or <89 mmHg, and diastolic blood pressure >89 mmHg or <49 mmHg.
8. 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.
9. Known history of alcohol or other substance abuse within the last year.
10. 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).
11. A positive screen for alcohol or drugs of abuse at screening or on Day -1 of Treatment Period 1.
12. A positive HIV, hepatitis B surface antibody (HBsAg), or hepatitis C virus (HCV) antibody screen.
13. 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 investigational product (maribavir).
14. 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 tea, three 1 oz [85 g] chocolate bars. (Decaffeinated coffee, tea, or cola are not considered to contain caffeine).
15. Prior screen failure, randomization, enrollment, participation in this study or participation in Part 1 of this study.

16. Current use of any prescription medication with the exception of hormonal replacement therapy. Current use is defined as use within 30 days of the first dose of investigational product. Current use of any over the counter medication (including herbal, or homeopathic preparations) within 14 days of the first dose of investigational product.
17. Current use of antacids and H2 antagonists.
18. Ingestion of known CYP3A modulators within 7 days of Day 1, Period 1 (includes grapefruit or grapefruit juice, oranges, Seville oranges, apples or apple juice, vegetables from the mustard green family [eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard], charbroiled meats, and products containing these ingredients).
19. Inability or unwillingness to consume 100 percent of high-fat meal in Part 2 (including subjects with lactose or gluten intolerance).
20. History of 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.

4.3 Restrictions

1. Subjects should refrain from strenuous physical exercise 48 hours prior to admission to the CRU and during the in-house stays at the CRU.
2. Subjects should refrain from consuming grapefruit, Seville oranges, 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. Subjects should refrain from consuming pine nuts 7 days prior to Day 1 of the first treatment period through the completion of the last treatment period.
4. Subjects should refrain from alcohol 48 hours prior to admission to the CRU and during the in-house stay at the CRU.
5. Subjects should refrain from 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. Subjects should refrain from taking or regularly using any prescription medication with the exception of those listed in Section 5.2 from 30 days prior to receiving the first dose of the investigational product 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 investigational product through the completion of the discharge assessments and procedures. Subjects should not use antacids or zinc supplementation.
7. Subjects should refrain from foods or beverages containing caffeine/xanthine 48 hours prior to admission to the CRU and during the in-house stay at the CRU.
8. Subjects will be required to follow standardized meal schedules and eat the meals provided by the site while housed in the CRU. No outside food or beverages (including gum, mints,

etc) will be permitted. Menus will be identical for all subjects at the CRU. Copies of the menus will be provided to the sponsor for approval prior to the start of the study. While confined, the total daily nutritional composition should be approximately 50% carbohydrate, 35% fat, and 15% protein. The daily caloric intake per subject should not exceed approximately 3200 kcal. For Treatment G in Part 2, a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is to taken within 30 minutes prior to maribavir doses. This high-fat meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.
(An example of a High Fat Breakfast: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, 8 ounces of whole milk.
*50 percent of calories are derived from fat. Substitutions can be made to this meal, if the content, volume, and viscosity are maintained.)

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 should be using an acceptable form of contraception. Females of child-bearing potential must be advised to use acceptable contraceptives throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. 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 investigational product.

Female subjects should be either:

- Post-menopausal (12 consecutive months of spontaneous amenorrhea and ≥ age 50 years)
- 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
- Females of child-bearing potential with a negative urine and/or 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 investigational product, 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.

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 investigational product. 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 investigational product. 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 investigational product. Male subjects must not donate sperm until 3 months after the last dose of investigational product.

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 investigational product is discontinued, regardless of the reason, the early withdrawal evaluations listed in Table 3 and Table 7 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 investigational product, and the total amount of investigational product administered must be recorded in the source documents and the case report form (CRF).

Subjects who discontinue from the study may be replaced at the sponsor's discretion to ensure that 18 subjects complete Part 1 of the study and 20 subjects complete Part 2 of the study.

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:

- Adverse event
- 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 investigational product.

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 pharmacokinetic equivalent of 5 half-lives, whichever is longer) of the date of first dose of investigational product. 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 investigational product 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 investigational products) 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 (see Section 4.4.1)
- Hormone replacement therapy

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 test product is maribavir, which will be provided in tablet and powder form.

Maribavir tablet is a blue, film-coated tablet containing 200 mg of maribavir. The tablets are packaged in a 60 cc, white, HDPE bottle containing 40 tablets.

Maribavir powder for oral suspension is a white to off-white granular powder. The 32.5% w/w powder contains 325 mg of maribavir for every 1 g of powder; the 36.1% w/w powder contains 361 mg of maribavir for every 1 g of powder. The powders are packaged in a 150 cc, white, HDPE bottle containing 40 g of powder. The powders are to be compounded to form unit dose oral suspensions. Additional information and detailed instructions are provided in the maribavir investigator's brochure, and in a Pharmacy Manual that will be provided.

The sponsor will provide the test product, maribavir.

6.1.1 Blinding 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.

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.

Once a randomization number/unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a randomization number/unique identifier is allocated incorrectly, the clinical research associate (CRA)/study monitor must be notified as soon as the error is discovered.

6.2.2 Dosing

6.2.2.1 Part 1, Treatment Period 1

On Day 1, subjects will receive either a single 200 mg dose of maribavir, either in tablet form or as an oral suspension, depending on his/her randomized assignment to the treatment sequence. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 1. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration

6.2.2.2 Washout Period

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4).

6.2.2.3 Part 1, Treatment Period 2

On Day 4, subjects in each cohort will receive 200 mg maribavir depending on his/her randomized assignment to treatment sequence. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 4. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration

6.2.2.4 Washout Period

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7).

6.2.2.5 Part 1, Treatment Period 3

On Day 7, subjects in each cohort will receive 200 mg maribavir depending on his/her randomized assignment to treatment sequence. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 7. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration.

6.2.2.6 Part 2, Treatment Period 1

On Day 1, subjects in each cohort will receive maribavir depending on his/her randomized assignment to the treatment sequence. For treatments D, E, and F, subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 1. For treatment G, subjects will go through an overnight fast of at least 10 hours, receive the high-fat meal 30 minutes before administration of the drug product, and fast for 4 hours after dosing on Day 1. Trial subjects should eat this meal in 30 minutes or less and consume 100 percent of the meal. Refer to Section 4.3, Number 9 for specific information about the high-fat meal. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration. Subjects will fast for 4 hours after dosing on Day 1.

6.2.2.7 Washout Period

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4).

6.2.2.8 Part 2, Treatment Period 2

On Day 4, subjects in each cohort will receive maribavir depending on his/her randomized assignment to treatment sequence. For treatments D, E, and F, subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 4. For treatment G, subjects will go through an overnight fast of at least 10 hours, receive the high-fat meal 30 minutes before administration of the drug product, and fast for 4 hours after dosing on Day 4. Refer to Section 4.3, Number 9 for specific information about the high-fat meal. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration. Subjects will fast for 4 hours after dosing on Day 4.

6.2.2.9 Washout Period

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7).

6.2.2.10 Part 2, Treatment Period 3

On Day 7, subjects in each cohort will receive maribavir depending on his/her randomized assignment to treatment sequence. For treatments D, E, and F, subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 7. For treatment G, subjects will go through an overnight fast of at least 10 hours, receive the high-fat meal 30 minutes before administration of the drug product, and fast for 4 hours after dosing on Day 7. Refer to Section 4.3, Number 9 for specific information about the high-fat meal. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration. Subjects will fast for 4 hours after dosing on Day 7.

6.2.2.11 Washout Period

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 3 (Day 7) and the administration of maribavir in Period 4 (Day 10).

6.2.2.12 Part 2, Treatment Period 4

On Day 10, subjects in each cohort will receive maribavir depending on his/her randomized assignment to treatment sequence. For treatments D, E, and F, subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 10. For treatment G, subjects will go through an overnight fast of at least 10 hours, receive the high-fat meal 30 minutes before administration of the drug product, and fast for 4 hours after dosing on Day 10. Refer to Section 4.3, Number 9 for specific information about the high-fat meal. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration. Subjects will fast for 4 hours after dosing on Day 10.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container.

All investigational product (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 investigational product 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 containers:

- Maribavir tablet: 60 cc, white, square, HDPE bottle
- Maribavir powder for oral suspension: 150 cc, white, round, 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 investigational product 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 investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that

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

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

6.4 Drug Accountability

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

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

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All dispensed medication will be documented in the subject's source and/or other investigational product record.

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

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

With the written agreement of the sponsor, at the end of the study all unused stock and empty/used investigational product 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 investigational products must be in accordance with local, state, and national laws.

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

6.5 Subject Compliance

Compliance must be assessed by observation of dosing by the investigator or designee. In addition, the CRU personnel should perform a hand and mouth check (mouth check is only required for oral dosing) of the subject to assure the investigational product 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 Testing Samples

In compliance with 21 CFR 320.38 (1999), and as recommended in the Center for Drug Evaluation and Research Guidance for Industry dated May 2004 regarding retention of relevant reserve (BA and BE test samples), CROs, site management organizations, or clinical investigators must retain samples when relevant BA/BE testing has been performed under contract by the sponsor. Retained samples must meet 21 CFR 320.38 (1999) and 320.63 (1999) requirements for reserve samples of test article and reference standards according to the following:

- Reserve samples must be representative of the test batches provided and therefore must be randomly selected from identical test article and/or reference standards provided to the site
- The quantity should be sufficient optimally to permit the Food and Drug Administration (FDA) to perform all release testing identified in the application 5 times
- Are adequately identified so that the reserve sample can be positively identified as having come from the same batches as used in the BA/BE studies
- Be stored under conditions that maintain the samples identity, integrity, strength, quality, and purity
- Be retained for at least 5 years following the date of New Drug Application or supplemental New Drug Application approval or, if the Investigational New Drug is discontinued, at least 5 years following the date of completion of the BA/BE study
- Samples must be annually inspected and documented to confirm integrity.

7. STUDY PROCEDURES

Details regarding scheduled assessments and procedures to be conducted in this study are provided below and in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9.

7.1 Study Schedule

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
- Pharmacokinetic blood sampling
- Palatability Questionnaire
- Clinical laboratory tests
- Physical examination.

NOTE: Blood sampling for pharmacokinetic 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

Screening procedures must be completed within 28 days of Day 1 as appropriate prior to receiving the first dose of investigational product. 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 enrolled or administered investigational product(s).

7.1.1.2 Rescreening of Subjects

Subjects who fail to meet all inclusion/exclusion criteria will not be permitted to be rescreened for the study at any point.

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 Treatment Period Part 1

7.1.2.1 Admission to the Clinical Study Unit (CSU) (Day -1)

Following the screening visit, eligible subjects will return to the CSU on Day -1 of the study. See Table 1 for a list of procedures to be completed upon admission to the CSU.

Subjects who successfully complete the pre-admission assessments and procedures will be admitted to the CSU on Day -1 and assigned a subject number on Day 1 as described in Section 6.2. Eligible subjects will be confined to the CSU from the morning of Day -1 until Day 8.

7.1.2.2 Day 1 to Day 3 (Part 1, Period 1)

Study Assessments for Day 1 to Day 3 are outlined in Table 1 and Table 2. Administration of maribavir will occur on Day 1. Subjects will be given a palatability questionnaire immediately following medication administration. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 1.

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4).

7.1.2.3 Day 4 to Day 6 (Part 1, Period 2)

Study Assessments for Day 4 to Day 6 are outlined in Table 1 and Table 3. Administration of maribavir will occur on Day 4. Subjects will be given a palatability questionnaire immediately following medication administration. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 4.

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7).

7.1.2.4 Day 7 to Day 8 (Part 1, Period 3)

Study Assessments for Day 7 to Day 8 are outlined in Table 1 and Table 4. Administration of maribavir will occur on Day 7. Subjects will be given a palatability questionnaire immediately following medication administration. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 7.

7.1.2.5 Final Visit

Subjects will remain in-house for the entire study. Final evaluation will be on Day 8. For any subject who discontinues prematurely, the final visit will be the day they discontinue.

7.1.3 Treatment Period Part 2

7.1.3.1 Admission to the Clinical Pharmacology Unit (Day -1)

Following the screening visit, eligible subjects will return to the CSU on Day -1 of the study. See Table 5 for a list of procedures to be completed upon admission to the CSU.

Subjects who successfully complete the pre-admission assessments and procedures will be admitted to the CSU on Day -1 and assigned a subject number on Day 1 as described in Section 6.2. Eligible subjects will be confined to the CSU from the morning of Day -1 until Day 11.

7.1.3.2 Day 1 to Day 3 (Part 2, Period 1)

Study Assessments for Day 1 to Day 3 are outlined in Table 5 and Table 6. Administration of maribavir will occur on Day 1. Subjects will be given a palatability questionnaire immediately following medication administration. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 1.

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4).

7.1.3.3 Day 4 to Day 6 (Part 2, Period 2)

Study Assessments for Day 4 to Day 6 are outlined in Table 5 and Table 7. Administration of maribavir will occur on Day 4. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 4.

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7).

7.1.3.4 Day 7 to Day 9 (Part 2, Period 3)

Study Assessments for Day 7 to Day 9 are outlined in Table 5 and Table 8. Administration of maribavir will occur on Day 7. Subjects will be given a palatability questionnaire immediately following medication administration. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 7.

There will be a drug washout period of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 3 (Day 7) and the administration of maribavir in Period 4 (Day 10).

7.1.3.5 Day 10 to Day 11 (Part 2, Period 4)

Study Assessments for Day 10 to Day 11 are outlined in Table 5 and Table 9. Administration of maribavir will occur on Day 10. Subjects will be given a palatability questionnaire immediately following medication administration. Subjects will fast for at least 10 hours prior to dosing and 4 hours after dosing on Day 10.

7.1.3.6 Final Visit

Subjects will remain in-house for the entire study. Final evaluation will be on Day 11. For any subject who discontinues prematurely, the final visit will be the day they discontinue.

7.1.4 Follow-up Period

The follow-up period for this protocol is 7±2 days for Part 1 and Part 2.

At the end of this period there will be a telephone call initiated by staff to query for serious adverse events (SAEs), AEs, and concomitant treatments. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Appendix 4.2)

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

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 precise 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 investigational product), TEAEs (all AEs occurring 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 CSU, 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 and Table 5 by a qualified licensed physician, physician's assistant, or a nurse practitioner. The medical history will be reviewed and recorded, including:

- Date of birth
- Sex
- Race and ethnicity

- Recent ingestion of medication (30 days prior to entering the screening period)
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases
- Smoking habits

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 and Table 5 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)

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 by the investigator.

7.2.2.3 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed. (Refer to Appendix 4 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, Table 6, Table 7, Table 8, and Table 9 of this protocol. 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 for all subjects (and documented). 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 deflation rate 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 assumed 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 caffeine, 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. If, after a single measurement is taken, there is a difference between arms in either systolic or diastolic blood pressure >10 mmHg, the site will perform triplicate BP measurements in each arm to determine the arm with the higher BP. The arm with the higher BP (based on the average of the 3 BP measurements for each arm) should be used for inclusion at screening, and the last of the 3 measurements recorded in the eCRF as the screening BP. The same (right or left) arm with the higher blood pressure will be used throughout the study.

One reading (supine systolic blood pressure/diastolic blood pressure-heart rate) should be taken.

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.

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 Palatability Questionnaire

A palatability questionnaire (Refer to Appendix 2) will be completed following each dose administration (within 5 minutes) on Day 1, Day 4, Day 7 in Part 1 and on Day 1, Day 4, Day 7 and Day 10 in Part 2.

7.2.2.6 Clinical Laboratory Tests

All clinical laboratory tests will be performed according to the laboratory's standard procedures. 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 (8.5 mL) for serum biochemistry will be collected into a gel separator tube at the time points described in Table 1 and Table 5. The following parameters will be assessed:

Sodium	Phosphate	β-HCG (beta Human chorionic gonadotropin)[a, b]
Potassium	Protein	
Glucose	Carbon dioxide	
Urea nitrogen	Albumin	
Creatinine	Aspartate transaminase	
Calcium	Alanine transaminase	
Chloride	Gamma glutamyl transferase	
Thyroid stimulating hormone (TSH)[a]	Alkaline phosphatase	
FT_4[a]	Total bilirubin	
FSH[a, b]	Uric acid	

[a] See Table 1 and Table 5.
[b] Females only.

Hematology

Blood samples (4 mL) for hematology will be collected into an ethylenediaminetetraacetic acid (EDTA) tube at the time points described in Table 1 and Table 5. 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 and Table 5. 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 serum beta-HCG or urine 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 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 of approximately 8 mL 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.

7.2.2.10 Electrocardiogram

Twelve-lead ECGs will be performed at the times specified in Table 1 and Table 5. All ECGs will be performed using the equipment supplied by the CRU.

The following parameters will be recorded on the appropriate CRF page: heart rate, PR, RR, QRS, and QT intervals. The QTcF will be derived. 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 caffeine, 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.

One complete recording, including a 10 second rhythm strip, should be taken at each time point. It should be immediately assessed as a valid recording and if not valid, it should be repeated. Invalid recordings will not be entered in the CRF.

When a single ECG recording is performed at each time point, the ECG collected pre-dose on Day 1 will serve as the subject's baseline ECG.

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

If the QTcF interval (calculated on line 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 2-4 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.

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.

7.2.3 Pharmacokinetic Procedures

The name and address of the bioanalytical laboratory 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 pharmacokinetic (PK) blood sample collection times versus time of dosing will be monitored. 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 2, Table 3, Table 4, Table 6, Table 7, Table 8, and Table 9 to measure plasma concentrations of maribavir. Potential metabolites may also be determined as appropriate.

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

7.2.3.2 Shipment of Plasma Pharmacokinetic Samples

Plasma sample shipment handling instructions and contact information are provided in the Laboratory Manual.

7.2.3.3 Plasma Drug Assay Methodology

Plasma concentrations 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 in Part 1

Table 12: Volume of Blood to be Drawn from Each Subject in Part 1

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic samples[a]		3	45	135
HBsAg, HIV, HCV		8	1	8
Safety	Biochemistry and β-HCG[b]	8.5	5	42.5
	Hematology	4	5	20
Total mL				205.5

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 3 mL 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 205.5 mL of blood will be drawn from all subjects, regardless of sex, in Part 1.

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; however, the total volume drawn over the course of the study should be approximately 205.5 mL. When more than one blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

7.2.5 Volume of Blood to be Drawn from Each Subject in Part 2

Table 13: Volume of Blood to be Drawn from Each Subject in Part 2

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic samples[a]		3	60	180
HBsAg, HIV, HCV		8	1	8
Safety	Biochemistry and β-HCG[b]	8.5	6	51
	Hematology	4	6	24
Total mL				263

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 1 mL is to be discarded; then take 2 mL into appropriate tube for pharmacokinetic sample. A total of 3 mL 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 263 mL of blood will be drawn from all subjects, regardless of sex, in Part 2.

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; however, the total volume drawn over the course of the study should be approximately 263 mL. When more than one 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. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

8.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the sponsor'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 pharmacokinetic, pharmacodynamic, and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

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

The doses for Treatment D/E/F/G in Part 2 may be adjusted based on relative bioavailability of the selected pediatric formulation (powder for oral suspension) to the Phase 3 tablet formulation observed in Part 1. All statistical analyses will then be conducted based on the adjusted treatment groups.

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

8.5 Planned Analysis

After the completion of Part 1, a selected set of analyses planned for Part 1 to evaluate the PK and palatability data from the formulations investigated will be conducted. Based on the results of the analyses of Part 1 data, one pediatric formulation may be chosen to be assessed in Part 2. All analyses will be conducted after the completion of Part 2.

8.6 Sample Size Calculation and Power Considerations

Sample size calculations were based on the following data:

- The intra-subject coefficient of variation is assumed at 0.166 and 0.218 respectively for $AUC_{0\text{-inf}}$ and C_{max}, which are estimated from the 90% confidence intervals (CIs) of the geometric mean ratio of $AUC_{0\text{-inf}}$, and C_{max} in Study 1263-104.
- Sample size estimation is performed using nQuery's two one sided test (TOST) of equivalence in ratio of mean for crossover design study.
- True mean ratio: 1.00, 1.05
- Power: 80%, 90%
- One-sided α-level: 0.05 (corresponding to 90% CI)
- Bioequivalence range: 0.8-1.25

Table 14: Number of Subjects Required

True Ratio	Power	Intra-subject coefficient of variation	
		0.166	0.218
1.0	80%	12	18
	90%	14	22
1.05	80%	14	22
	90%	18	28

Note: sample size estimation is performed using nQuery's TOST of equivalence in ratio of mean for crossover design study.

Assuming a true mean ratio of 1.0 with intra-subject coefficient of variation of 0.218, a total of 18 completers is required to have 80% power to show that the 90% confidence intervals of the ratios of the geometric means of the two formulations/treatment lie within the range of 0.80 to 1.25.

Therefore, for Part 1, three subjects in each sequence with a total of 18 subjects is required to randomize subjects to 1 of 6 sequences in a 1:1:1:1:1:1 treatment allocation. For Part 2, five subjects in each sequence with a total of 20 subjects is required to randomize subjects to 1 of 4 sequences in 1:1:1:1 treatment allocation.

8.7 Study Population

The **Screened Set** will consist of all subjects who have signed informed consent.

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

The following subject populations are defined to analyze the data in Part 1 and Part 2:

Part 1:

- The **Randomized Set 1** will consist of all subjects who were randomized to a treatment sequence in Part 1.
- The **Safety Set 1** will consist of subjects who have received at least 1 dose of maribavir in Part 1.
- The **Pharmacokinetic Set 1** will consist of subjects who received at least 1 dose of maribavir, did not vomit within 4 hours of dosing, and have at least 1 evaluable post-dose maribavir concentration value in Part 1.

Part 2:

- The **Randomized Set 2** will consist of all subjects who were randomized to a treatment sequence in Part 2.
- The **Safety Set 2** will consist of subjects who have received at least 1 dose of maribavir in Part 2.
- The **Pharmacokinetic Set 2** will consist of subjects who received at least 1 dose of maribavir, did not vomit within 4 hours of dosing, and have at least 1 evaluable post-dose maribavir concentration value in Part 1 and 2 (combined):
- The **Total Safety Set** will include subjects who have received at least 1 dose of maribavir in either Part 1 or Part 2.

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

8.7.1 Pharmacokinetic Analysis

All the pharmacokinetic analyses will be based on the PK analysis dataset.

Pharmacokinetic parameters will be calculated from maribavir concentration-time data using non-compartmental analysis (NCA) and all calculations will be based on actual sampling times. Pharmacokinetic parameters will include, but not be limited to, the following:

Part 1 (Day 1, Day 4, and Day 7)

- C_{max} Maximum concentration occurring at t_{max}
- t_{max} Time of maximum observed concentration sampled during a dosing interval

- $AUC_{0\text{-}last}$ 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-$AUC_{0\text{-}last}$/$AUC_{0\text{-}inf}$)*100
- $t_{1/2}$ Terminal half-life
- CL/F Apparent total body clearance following extravascular administration calculated as dose divided by $AUC_{0\text{-}inf}$
- T_{lag} Delay between the time of dosing and time of appearance of plasma concentration in the employed sampling scheme

Part 2 (Day 1, Day 4, Day 7, and Day 10)

- C_{max} Maximum concentration occurring at t_{max}
- t_{max} Time of maximum observed concentration sampled during a dosing interval
- $AUC_{0\text{-}last}$ 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-$AUC_{0\text{-}last}$/$AUC_{0\text{-}inf}$)*100
- $t_{1/2}$ Terminal half-life
- CL/F Apparent total body clearance following extravascular administration divided by the fraction of dose absorbed calculated as dose divided by $AUC_{0\text{-}inf}$
- T_{lag} Delay between the time of dosing and time of appearance of concentration in the sampling

In addition, dose-normalized Cmax, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ will be calculated for Treatments D, E, and F.

8.7.2 Statistical Analysis of Pharmacokinetic Parameters

8.7.2.1 Part 1

Individual concentrations and PK parameters of maribavir will be listed and summarized by treatment with descriptive statistics (number, arithmetic mean, standard deviation [SD], coefficient of variation [CV%], median, minimum, maximum, geometric mean, and %CV of geometric mean). Figures of individual and mean (+/-SD) concentration-time profiles of plasma maribavir by treatment will be generated on both linear and semi-log scales.

Following the log_e-transformation, the PK parameters including $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, and C_{max} will be analyzed using a mixed effect model to include sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Analysis of variance will be performed

using SAS mixed linear models procedure. Point estimates and their associated 90% CIs will be constructed for the differences in the log-transformed parameters. The point estimates and their associated 90% CIs will be then back-transformed to provide point estimates for the ratio of geometric least squares means and associated 90% CIs on the original scale. Analysis of t_{max} and T_{lag} will be performed by nonparametric t-test.

8.7.2.2 Part 2

Dose proportionality analysis:

The dose proportionality will be first assessed using the Power Model for (fasted) dose range tested in Part 2. The Power Model: $\log(Y_{ijk})=S_i + P_j + \beta x \log(D_k) + \varepsilon_{ijk}$ where D is the total number of doses, N are the total number of subjects and P the total number of periods and i=1,…..,N, j=1,…..,P and k=1,……,D. Y_{ijk} is the log-transformed response variable, $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, or C_{max} on the kth dose, in the jth period, for the ith subject. S_i is the random subject effect for the ith subject, P_j is the fixed period effect for the jth period, β was the slope and ε_{ijk} is the error. If the 90% confidence interval for the model estimated mean slope falls within 0.8 and 1.25 limits, then dose proportionality will be concluded. The estimate and 90% confidence interval for the slope and fold increase in PK exposure when doubling the dose will be presented. The corresponding graphical display from the power model (back transformed to raw linear scale) with the 90% CI overlaid on the observed data will be provided.

Additionally, a mixed effect analysis of variance (ANOVA) model will be performed with the log-transformed dose normalized response variable, $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, or C_{max}. The geometric mean ratios and 90% CI for each dose compared to the reference dose (50 mg dose) will be provided.

Analysis of Effect of Food:

A mixed effect ANOVA model will be performed with log transformed $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ or C_{max}. Point estimates and 90% CI for geometric mean ratios will be computed for treatments (selected dose of maribavir fed vs. fasted) . If the 90% CI for the geometric mean ratios of treatments (selected dose of maribavir fed vs. fasted) falls within 0.8 and 1.25 limits, then equivalence will be concluded. Analysis of t_{max} and T_{lag} will be performed by nonparametric t-test.

8.8 Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number and percentage of subjects experiencing TEAEs and the number of events will be calculated and summarized by SOC, by preferred term and by study treatment for Part 1 and Part 2 separately, using the respective safety population. Treatment-emergent adverse events will be further summarized by severity and relationship to study treatment. Adverse events related to study treatment, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Additionally, TEAEs will be summarized for Part 1 and 2 combined for all subjects enrolled on study who take at least one dose of maribavir by dose level regardless of formulation.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by study treatment and visit for Part 1 and Part 2 separately, using the respective safety population.

Potentially clinically important findings will be summarized by study treatment for Part 1 and Part 2 separately.

Additionally, potentially clinically important (PCI) findings will be summarized for Part 1 and Part 2 combined for all subjects enrolled on study who take at least one dose of maribavir by dose level regardless of formulation.

8.9 Other Analyses

8.9.1 Palatability

The palatability will be evaluated to identify and characterize basic tastes, texture and mouth feel and to assess the overall acceptability. Palatability data will be summarized for Part 1 and Part 2 separately using the respective safety population.

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10. APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	**28 Aug 2019**	USA
Amendment 1.0	**05 Nov 2019**	USA

APPENDIX 2 PALATABILITY QUESTIONNAIRE

Palatability Questionnaire

(Complete immediately following <u>each dose administration</u> in PART 1: Days 1, 4 and 7; and PART 2: Days 1, 4, 7 and 10)

Subject Initials: _____
Subject Number: _____
Date: _____
Study Part (1 or 2): _____
Treatment Period: _____
Dose administration time: _____
Time questionnaire administered: _____

1. Circle the answer below that best describes how this drug tasted to you.

bitter **salty** **sour** **sweet** **savory** **no taste**

2. If you identified a taste above, **how strong was the taste?** ☐ n/a-no taste

(mark an "X" in appropriate circle)

strong medium weak

3. Did the drug have a **rough or gritty texture** (Yes/ No)?

☐ Yes
☐ No

4. Was the drug **easy to swallow** (Yes/ No)?

☐ Yes
☐ No

5. The **overall taste and texture** of the drug was acceptable.
(mark an "X" in appropriate circle)

agree neither agree nor disagree disagree

APPENDIX 3 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

APPENDIX 3.1 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 3.2 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 investigational product 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 3.3 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. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

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

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 investigational product, containers, and other study materials to

the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

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

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.

The CRA/study monitor will verify the contents of the completed CRF pages against the source data. 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 US FDA, EMA, UK Medicines and Healthcare Products Regulatory Agency) or an auditor.

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

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 investigational product; 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 3.4 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 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; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

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 4 ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

APPENDIX 4.1 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 investigational product 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 treatment-emergent adverse event (TEAE) is defined as any event emerging or manifesting at or after the initiation of treatment with an investigational product or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the investigational product or medicinal product.

Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, 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 Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the 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 RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated form 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

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 investigational product, 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 investigational product, 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 4.2 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 investigational product 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 4.3 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 investigational product, must be recorded as new AEs.

For example, if a subject reports mild intermittent dyspepsia prior to initiation of dosing with the investigational product, 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 investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source.

The following additional guidance may be helpful:

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

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 4.4 SAFETY REPORTING

Reference Safety Information

The reference for safety information for this study is the investigator's brochure, 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 and the CRO/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 (see Appendix 4.9) unless they result in an SAE.

The investigator must complete, sign, and date the Shire "Clinical Study Serious Adverse Event for Serious Adverse Events (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 Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the CRO/Shire Medical Monitor using the details specified in the emergency contact information section of the protocol.

APPENDIX 4.5 SERIOUS ADVERSE EVENT COLLECTION TIME FRAME

All SAEs (regardless of relationship to investigational product) 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/Shire Medical Monitor within 24 hours of the first awareness of the event.

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

APPENDIX 4.6 SERIOUS ADVERSE EVENT ONSET AND RESOLUTION DATES

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

In addition, any signs or symptoms 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 4.7 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 investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not

changed" or "not applicable" (if the subject never received investigational product or it is a single dose study). The investigational product action of withdrawn should not be selected solely as a result of the subject's death.

APPENDIX 4.8 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/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.

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.

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.

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.

APPENDIX 4.9 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 4.1.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication error s unless these result in an SAE.

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

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a 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 investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)

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

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

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

APPENDIX 4.10 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 EC(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

APPENDIX 4.11 REGULATORY AGENCY, INSTITUTIONAL REVIEW BOARD, ETHICS COMMITTEE, AND SITE REPORTING

The sponsor is responsible for notifying the relevant regulatory authorities, institutional review boards (IRBs) and ethics committees (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 TAK620 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.