STATISTICAL ANALYSIS PLAN

TAK-620-1020
PHASE 1

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

PROTOCOL IDENTIFIER: TAK-620-1020

Study Sponsor(s): Shire ViroPharma LLC (Shire, [and affiliates]);
Shire is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 300 Shire Way, Lexington, MA 02421 USA

Author: [redacted], PhD [redacted]

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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	06 Aug 2020	Final Version

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ABBREVIATIONS

AE	adverse event
AUC	area under the curve
$AUC_{0\text{-}inf}$	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-$AUC_{last}/AUC_{0\text{-}inf}$)*100
AUC_{last}	area under the curve from the time of dosing to the last measurable concentration
β-HCG	beta-human chorionic gonadotropin
BLQ	below limit of quantification
BMI	body mass index
CI	confidence interval
C_{max}	maximum concentration
CL/F	oral clearance
CRF	case report form
CV	coefficient of variation
CV%	percent coefficient of variation
ECG	electrocardiogram
IP	investigational product, maribavir
λz	first order rate constant associated with the terminal (log linear) portion of the curve
PK	pharmacokinetics
PT	preferred term
QTc	corrected QT interval
QTcF	corrected QT interval by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event

TOST	two one-sided test
T_{lag}	delay between the time of dosing and time of appearance of drug concentration in plasma in the employed sampling scheme
t_{max}	time of maximum observed concentration sampled during a dosing interval
TSH	thyroid-stimulating hormone
Vz/F	apparent volume of distribution

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of pharmacokinetic (PK), safety, and tolerability data as described in the TAK-620-1020 protocol amendment 1 dated 08 July 2020. Specifications for tables, figures, and listings will be contained in a separate document. Methods used in the final analysis of pharmacokinetic (PK) parameters and the reporting of the results from these analyses will be described in Clinical Pharmacology Analysis Plan (CPAP).

Within this document, the term investigational product is used to refer to maribavir.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

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

2.1.3 Exploratory Objective

- [redacted]

2.2 Endpoints

2.2.1 Pharmacokinetic Endpoints

Primary Pharmacokinetic Endpoints

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

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

- C_{max} Maximum observed plasma concentration
- t_{max} Time of maximum observed concentration sampled during a dosing interval
- AUC_{last} Area under the curve from the time of dosing to the last measurable concentration
- $AUC_{0\text{-}inf}$ Area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration
- $AUC_{0\text{-}inf}$%extrap The percent of $AUC_{0\text{-}inf}$ extrapolated, calculated by (1-$AUC_{last}/AUC_{0\text{-}inf}$) *100
- λz elimination rate in the terminal phase
- $t_{1/2}$ Terminal half-life

- CL/F — Apparent total body clearance following extravascular administration calculated as dose divided by $AUC_{0\text{-}inf}$
- Vz/F — Apparent volume of distribution following extravascular administration calculated as CL/F divided by λz
- T_{lag} — Delay between the time of dosing and time of appearance of plasma concentration in the employed sampling scheme

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

2.2.2 Exploratory Pharmacokinetic Endpoints

[redacted]

2.2.3 Safety Endpoints

The safety analysis will be performed using the Safety Analysis Set. Safety endpoints include AEs, vital signs, ECG variables, and clinical laboratory variables. The following safety evaluations will be performed:

- 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.

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

3. STUDY DESIGN

3.1 General Description

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

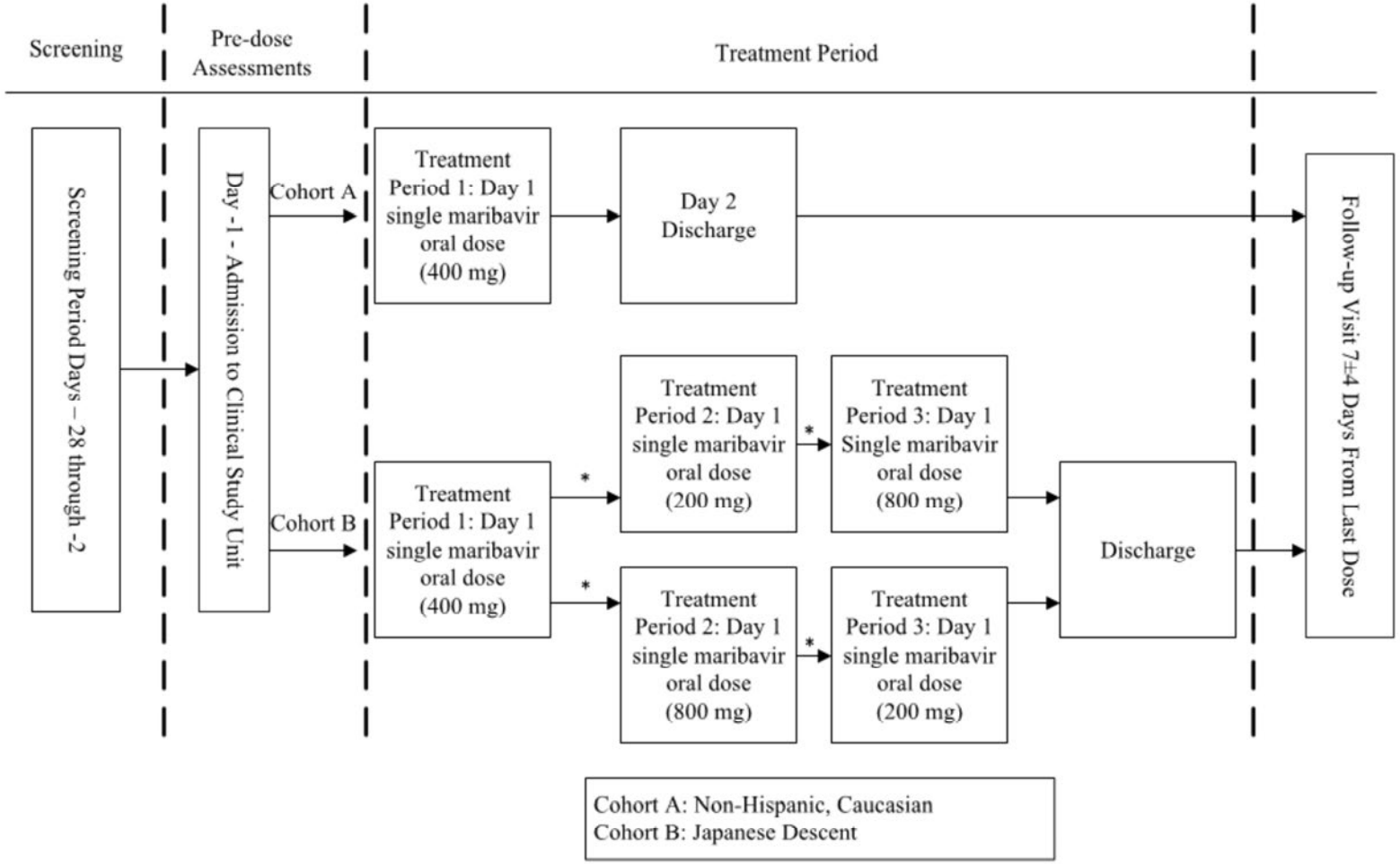
Treatment Period:

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

- In Treatment Period 1, all study subjects (both Japanese and Caucasian) will receive maribavir as a single 400 mg oral dose.
- Depending upon the randomization assignment on Day 1 of treatment period 2, all subjects of Japanese descent will be dosed in a crossover fashion in Treatment Periods 2 and 3. They will receive a single oral dose of either 200 mg followed by 800 mg maribavir or a single oral dose of 800 mg followed by 200 mg maribavir.

The study design flow chart is presented in Figure 1.

Figure 1 Study Design Flow Chart



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

3.2 Randomization

Subjects of Japanese descent who meet all the inclusion criteria and none of the exclusion criteria will be randomized (1:1 ratio) to either maribavir 200 mg or 800 mg on Day 1 in treatment period 2. Subjects will then be dosed in a crossover fashion with a single dose of maribavir based on their randomization assignment on Day 1 in Treatment Periods 2, and 3. There is no stratification for this study.

3.3 Blinding

This is an open-label study. Blinding is not applicable.

3.4 Sample Size and Power Considerations

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

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

4. STATISTICAL ANALYSIS SETS

4.1 Enrolled Set

The Enrolled Set consists of all subjects who have signed informed consent and also met inclusion/exclusion criteria.

4.2 Safety Set

The Safety Set consists of subjects who are administered at least 1 dose of investigational product (maribavir) and have at least 1 post-dose safety assessment. Analysis will be performed according to the treatment regimen actually received regardless of the randomized treatment regimen.

4.3 Pharmacokinetic Set

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

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

5. STUDY SUBJECTS

5.1 Disposition of Subjects

The number of subjects who were included in each defined statistical analysis set (Enrolled, Safety, and PK) will be summarized by cohort and overall.

Summaries and listing of subject disposition will be based on the Enrolled Set.

The reasons for exclusion from the PK set will be presented in the listings with details of any AEs.

The number and percentage of subjects who completed and prematurely discontinued the study, as well as subjects who completed dosing and prematurely discontinued the study drug, as recorded on the termination page of the electronic case report form (eCRF), will be presented for each cohort and overall for the Safety Set. Reasons for premature discontinuation from the study, as well as discontinuation from study drug, as recorded on the termination page of the eCRF will be summarized (number and percentage) by cohort and overall, for the Safety Set. All subjects who prematurely discontinued the study and/or discontinued the study drug will be listed by discontinuation reason.

5.2 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by cohort and overall, for the Safety Set as well as the PK Set. Demographics and other baseline characteristics data will be listed for the Safety Set.

The following demographic characteristics will be summarized in the following order in the tables: age (years), sex, race, and ethnicity. The following baseline characteristics will be summarized in the following order in the baseline table: weight (kg), height (cm), and body mass index (BMI, kg/m^2).

Age, sex, race, and ethnicity will be summarized based on data obtained at the Screening Visit. Height and weight will be summarized from the last available measurement prior to the first single dose of IP, and BMI will be calculated.

Age will be calculated as the integer part of: (date of informed consent is signed – date of birth + 1)/365.25. Body mass index will be calculated using the following formula: weight (kg) / (height $[m])^2$.

5.3 Medical History

Medical history will be collected at the Screening Visit and will be coded using agreed upon MedDRA Version 23.0 or newer. Listings will be provided using the Safety Set.

Medical history will be summarized by system organ class (SOC) and preferred term (PT) for each cohort, based on the Safety Set. The summary of medical history will include the number

and percentage of subjects who experienced the event and number of events experienced. System organ class will be sorted alphabetically, and within each SOC, PT will be sorted in the table Total column by descending order of frequency.

5.4 Prior Medications (Therapies), and Procedures

All prior medications, therapies, and procedures will be listed based on the Safety Set.
Prior medications will be coded using the World Health Organization Drug Dictionary Global B3 dated March 2020.

Prior medications (therapies) and procedures are defined as the medications (therapies) and procedures with a start date prior to the date of the first single dose of IP.

Prior medication usage presented by therapeutic class according to Anatomical Therapeutic Chemical (ATC) classification and PT will be summarized based on the number and proportion of subjects in each cohort and in overall subjects based on the Safety Set. Multiple medication usage by a subject in the same category will be counted only once.

5.5 Concomitant Medications (Therapies) and Procedures

Concomitant medications will be coded using the World Health Organization Drug Dictionary Global B3 dated September 2019.

Medications (therapies) and procedures taken during the study will be considered concomitant to the treatment(s) a subject has taken during the duration of the medications. Medications with start and stop dates and times during the wash-out period or the 7 days follow-up period after last single dose of IP will be considered concomitant to the prior treatment(s) subject received. Any medication/ therapy and procedure with a start date and time after 7 days following the date and time of the last single dose of IP will be considered post-treatment medication /therapy and procedure and not be considered a concomitant medication/therapy and procedure.

Concomitant medication usage presented by therapeutic class (according to Anatomical Therapeutic Chemical classification) and PT will be summarized based on the number and proportion of subjects by cohort, treatment group and overall, based on the Safety Set. Multiple medication usage by a subject in the same category will be counted only once.

All concomitant therapies, procedures and medication will be listed for the Safety Set.

5.6 Exposure to Investigational Product

Exposure to the IP (maribavir) will be summarized in terms of total planned dose in mg. Descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) will be presented to describe the exposure to IP by cohort and treatment group based on the Safety Set.

Listings will be created by subject number and visit presenting the date and time of dose administration separately based on the Safety Set.

5.7 Measurements of Treatment Compliance

Treatment compliance will be summarized in terms of number of subjects who completed the drug administration, who fasted 10 hours before the investigational drug administration, and who fasted 4 hours after the investigational drug administration, by cohort and treatment group based on the Safety Set.

5.8 Protocol Deviations

Protocol deviations will be recorded by the site separately from the clinical database using a Protocol Deviation tracker. Protocol deviations will be classified as major or minor per the agreed protocol deviation management plan and will be documented in the Protocol Deviation tracker. The Sponsor study team will review the protocol deviations and their classification throughout the study and before database lock.

Major/minor protocol deviations will be summarized by category for each cohort, each treatment group, and overall based on the Safety Set. Major/minor protocol deviations will be listed based on the Safety Set.

6. EFFICACY ANALYSES

Not applicable.

7. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Set. Safety variables include AEs, vital signs, ECG, and clinical laboratory variables. For each safety variable, the last value collected before the first dose of investigational product will be used as baseline for all analyses of that safety variable. Last Value on Treatment (LVOT) will be defined as the last valid assessment obtained after Baseline and until 7 days after last dose of investigational product.

All safety analyses will be conducted according to the treatment the subject actually received.

7.1 Adverse Events

Adverse events will be coded using MedDRA Version 23.0 or newer.

An AE (classified by preferred term) that occurs during the study will be considered a TEAE if it has a start date on or after the first dose of investigational product or if it has a start date before the date of the first dose of investigational product, but increases in severity on or after the date of the first dose of investigational product. If more than 1 AE with the same preferred term is reported before the date of the first dose of investigational product, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the study under the preferred term. Adverse events during the study will be assigned to the treatment(s) a subject has taken at the onset of the event. An AE with start date and time during the wash-out period or the 7 days follow-up period after last single dose of IP will be assigned to the prior treatment subject received. An AE that occurs more than 7 days after the date of the last dose of investigational product will not be counted as a TEAE.

An overall summary of the number of subjects with TEAEs as well as the number of events will be presented, including the number and percentage of subjects with any TEAEs, serious TEAEs, TEAEs related to investigational product and TEAEs leading to discontinuation of investigational product.

The number and percentage of subjects reporting TEAEs, as well as the number of events, in each cohort, each treatment group, and overall will be tabulated by system organ class (SOC) and preferred term (PT); by SOC, preferred term (PT), and maximum severity. TEAEs considered related to investigational product will also be summarized by SOC and preferred term. If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending incidence.

TEAEs and related TEAEs will be summarized by preferred term by descending frequency. Serious TEAEs, TEAEs leading to discontinuation of investigational product and serious TEAEs leading to death, will be summarized by SOC, preferred term, cohort, and treatment group.

7.1.1 Selected Adverse Events

The following TEAEs and related TEAEs will be summarized by SOC, preferred term, cohort, and treatment group:

- Dysgeusia
- Nausea
- Vomiting
- Diarrhea
- Neutropenia

These TEAEs and related TEAEs will also be summarized by PT by descending order of frequency.

7.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline at each assessment time point as well as shift tables from baseline to each visit for quantitative variables will be presented by cohort and treatment group for the following clinical laboratory variables (copy from the protocol).

Hematology Hemoglobin, hematocrit, red blood cells (RBC), platelet count, white blood cell count – total and differential (WBC), i.e. total neutrophils (absolute), eosinophils (absolute), monocytes (absolute), basophils(absolute), and lymphocytes (absolute).

Biochemistry Sodium, potassium, glucose(fasting), urea nitrogen, creatinine, calcium, chloride, thyroid stimulating hormone (TSH) [a], thyroxine (free T4)triiodothyronine (T3), phosphate, protein, carbon dioxide, albumin, aspartate transaminase, alanine transaminase, gamma glutamyl transferase, alkaline phosphatase, total bilirubin, uric acid, and β-HCG [a].

[a] Females only.

Urinalysis pH, glucose, protein, blood, ketones, bilirubin, nitrites, leukocyte esterase, and specific gravity.

Clinical laboratory test values are potentially clinically significant (PCS) if they meet either the low or high PCS criteria listed in Table 1. The number and percentage of subjects with post-baseline PCS values will be tabulated by cohort and treatment group. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 post-baseline

PCS value. A supportive listing of subjects with post-baseline PCS values will be provided including the subject number, baseline, and post-baseline values.

Table 1 Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	Classification	Criteria: SI Units (Conventional Units)
Hematology		
Hemoglobin	High	>200 g/L (20g/dL)
	Low and Decrease	<100 g/L (10g/dL) AND Decrease of ≥ 20 g/L (2.0 g/dL) from baseline value
Hematocrit	High	>1.3 × ULN
	Low and Decrease	≤0.6 × LLN AND Decrease of ≥6.0% from baseline value
RBC	High	$>7.5 \times 10^{12}$/L
	Low	$<3.0 \times 10^{12}$/L
Platelets (thrombocytes)	High	>1.5 × ULN OR $>500 \times 10^{9}$/L (500×10^{3}/μL)
	Low	<0.6 × LLN OR $<100 \times 10^{9}$/L (100×10^{3}/μL)
WBC	High	>2 × ULN OR $>16.0 \times 10^{9}$/L (16×10^{3}/μL)
	Low	<0.5 × LLN OR $<3.0 \times 10^{9}$/L (3×10^{3}/μL)
Neutrophils	High	$>6.2 \times 10^{9}$/L (6.2×10^{3}/μL) OR > 70 %
	Low	$<1.5 \times 10^{9}$/L (1.5×10^{3}/μL) OR < 40%
Lymphocytes	High	$> 4.0 \times 10^{9}$/L (4.0×10^{3}/μL) OR > 44 %
	Low	$<0.8 \times 10^{9}$/L (0.8×10^{3}/μL) OR < 22 %
Monocytes	High	$>1.1 \times 10^{9}$/L (1.1×10^{3}/μL) OR >11 %
	Low	< 4 %
Eosinophils	High	$>0.5 \times 10^{9}$/L (0.5×10^{3}/μL) OR > 10.0%
	Low	NA
Basophils	High	>0.2 × 109/L (0.2 × 103/μL) OR > 2%
	Low	NA
Biochemistry		
Sodium	High	>5 mmol/L (5 mEq/L) above ULN
	Low	>5 mmol/L (5 mEq/L) below LLN
Potassium	High and Increase	Above ULN AND Increase of > 0.5 mmol/L (0.5 mEq/L) from baseline value
	Low and Decrease	Below LLN AND Decrease of >0.5 mmol/L (0.5 mEq/L) from baseline value
Glucose (fasting)	High	≥6.7 mmol/L
	Low	≤4.2 mmol/L
BUN	High	>1.5 × ULN

Table 1 Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	Classification	Criteria: SI Units (Conventional Units)
Creatinine	High and Increase	>150 µmol/L AND Increase > 30% from baseline value
	Low and Decrease	NA
Calcium	High and Increase	Above ULN AND Increase of ≥ 0.25 mmol/L (1.0 mg/dL) from baseline value
	Low and Decrease	Below LLN AND Decrease of ≥0.25 mmol/L (1.0 mg/dL) from baseline value
Carbon dioxide (Total)	High	>32 mmol/l (mEq/l)
	Low	< 20 mmol/l (mEq/l))
Phosphate	High	>0.162 mmol/L (0.5 mg/dL) above ULN
	Low	>0.162 mmol/L (0.5 mg/dL) belowLLN
Chloride	High	>110 mmol/L (>110 mEq/L)
	Low	<98 mmol /L (<98 mEq/L)
Protein (Total)	High and Increase	Above ULN AND Increase of ≥20 g/L (2.0 g/dL) from baseline value
	Low and Decrease	Below LLN AND Decrease of ≥20 g/L (2.0 g/dL) from baseline value
Albumin	High and Increase	Above ULN AND Increase of ≥10 g/L (1.0 g/dL) from baseline value
	Low and Decrease	Below LLN AND Decrease of ≥10 g/L (1.0 g/dL) from baseline value
Aspartate transaminase	High	>2 × ULN
Alanine transaminase (ALT)	High	>2 × ULN
Gamma glutamyl transferase (GGT)	High	>1.5 × ULN
Alkaline phosphatase (ALP)	High	>1.5 × ULN
Total bilirubin	High and Increase	>1.5 × ULN
Uric acid (with normal diet)	High and Increase	Above ULN AND Increase of >0.119 mmol/L (2.0 mg/dL) from baseline value
	Low and Decrease	Below LLN AND Decrease of >0.119 mmol/L (2.0 mg/dL) from baseline value
Thyroid stimulating hormone (TSH)	High	>5.0 µU/L (>5.0 µU/mL)
	Low	<0.5 µU/L (<0.5 µU/mL)

Table 1 Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	Classification	Criteria: SI Units (Conventional Units)
Thyroxine (free T4)	High	> 24.54 pmol/L (>1.9 ng/dL)
	Low	< 9.01 pmol/ L (<0.7 ng/dL)
Triiodothyronine (T3) Total	High	>2.78 nmol/L (<181 ng/dL)
	Low	<0.92 nmol/L (<60ng/dL)
Urinalysis		
Glucose	High	≥1+
Protein	High	≥2+
Blood	High	≥2+
Ketones	High	≥2+
Bilirubin	Abnormal	Positive
Nitrites	Abnormal	Positive
Leukocyte esterase	Abnormal	Positive

BUN-Blood Urea Nitrogen, LLN=lower limit of normal value provided by the laboratory, RBC=Red Blood Cells, ULN=upper limit of normal value provided by the laboratory, WBC=White Blood Cells.

All laboratory data will be listed for the Safety Set.

7.3 Vital Signs

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, pulse rate, body temperature, respiratory rate, and body weight) and their changes from baseline at each post-baseline visit and at the end of study will be presented by cohort and treatment group.

Vital sign values will be considered PCS if they meet both the observed value criteria and the change from baseline criteria listed in Table 2. The number and percentage of subjects with PCS post-baseline values will be tabulated by cohort and treatment group. The percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCS post-baseline vital sign value. A supportive listing of subjects with post-baseline PCS values will be provided including the subject number, baseline, and post-baseline PCS values.

Table 2 Criteria for Potentially Clinically Significant Vital Signs and Body Weight

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	Change from Baseline Value
Systolic blood pressure (mmHg)	High	≥140	Increase of ≥20
	Low	≤90	Decrease of ≥20
Diastolic blood pressure (mmHg)	High	≥90	Increase of ≥15
	Low	≤50	Decrease of ≥15
Heart rate	High	≥100	Increase of ≥15

Table 2 Criteria for Potentially Clinically Significant Vital Signs and Body Weight

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	Change from Baseline Value
(beats per minute)	Low	≤45	Decrease of ≥15
Weight (kg)	High	-	Increase of ≥5%
	Low	-	Decrease of ≥5%
Body temperature	High	> 38.3°C or > 100.9°F	
	Low	< 35°C or < 95°F	
Respiratory rate (breaths/min)	High	> 25	
	Low	< 10	

[a] A post-baseline value is considered as a PCI value if its meets both criteria for observed value and change from baseline.

All vital signs data will be listed for the Safety Set.

7.4 Electrocardiogram (ECG)

Descriptive statistics for ECG variables (eg, heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval) and their changes from baseline at each assessment time point will be presented by cohort and treatment group. QTc interval will be calculated using both Bazett ($QTcB=QT/(RR)^{1/2}$) and Fridericia ($QTcF=QT/(RR)^{1/3}$) corrections; and if RR is not available, it will be replaced with 60/hr in the correction formula. ECG interpretation will be summarized by visit. A shift table from baseline to each visit for qualitative ECG results will be presented. If the QTcF interval is increased by >45 msec from the baseline, or an absolute QTcF value is >500 msec for any scheduled ECG, then ECG should be repeated 2 more times and the average of the 3 QTc values will be recorded in the CRF and used to generate descriptive summary.

Electrocardiogram variable values will be considered PCS if they meet or exceed the normal limit values listed in Table 3. The number and percentage of subjects with post-baseline PCS values will be tabulated by cohort and treatment group. The percentages will be calculated relative to the number of subjects with available non-PCS baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCS post-baseline ECG value. A listing of all subjects with post-baseline PCS value will be provided including the subject number, baseline, and post-baseline PCS values.

Table 3 Criteria for Potentially Clinically Significant ECG Values

Parameter	Classification	Criteria
Overall evaluation	ABNORMAL	Overall evaluation is ABNORMAL
Heart rate (bpm)	LOW and DECREASE	≤45 and decrease of >15 from baseline value
	HIGH and INCREASE	≥100 and increase of >15 from baseline value
PR interval (msec)	HIGH and INCREASE	≥200 and increase of ≥20 from baseline value
QRS interval (msec)	HIGH	≥120
QTc interval (men) (msec)*	HIGH	>430 and increase from baseline value >30
QTc interval (women) (msec)*	HIGH	>450 and increase from baseline value >30

Abbreviations: bpm=beats per minute; QTc=QT interval corrected.
*Values noted refer to both Bazett's (QTcB) and Fridericia's (QTcF) formula

All ECG results will be presented in data listings.

8. PHARMACOKINETIC ANALYSIS

All summaries and analyses of the PK data will be based on the Pharmacokinetic Set defined in Section 4.3.

Each subject's data (eg, dosing records, sample collection records, protocol deviations, etc.) will be reviewed for data exclusion from the descriptive statistics and statistical analysis on a case-by-case basis at the discretion of the pharmacokineticists. Rationale of data exclusion will be provided in a data listing.

Derivations of the PK parameters will be found in the Clinical Pharmacology Analysis Plan.

8.1 Drug Concentration

A PK evaluation of maribavir concentrations and [redacted] concentrations will be performed based on the PK Set. During this study, blood samples will be drawn from each subject for the determination of plasma concentration of maribavir and [redacted]. Serial blood samples will be collected at the following time points.

Collection of Blood Samples for Pharmacokinetic Analysis

Cohort	Analyte	Matrix	Dosing Day	Scheduled Time (hours)
A: Non-Hispanic Caucasian subjects	Maribavir and [redacted]	Plasma	Day1 of treatment period 1	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, and 24 hours post dose
B: Subjects of Japanese descent	Maribavir and [redacted]	Plasma	Day 1of all 3 treatment periods	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, and 24 hours post dose

Plasma concentrations of maribavir and [redacted] will be measured using a validated analytical method.

The concentration of plasma maribavir and [redacted] will be summarized by cohort, treatment group, and scheduled sampling time using descriptive statistics (n, arithmetic mean, SD, geometric mean median, minimum, and maximum). Individual plasma concentration data will be presented in data listings by cohort and treatment group.

Individual concentrations of plasma maribavir and [redacted] will be plotted by actual time on linear and semilogarithmic scales for each subject, displaying all treatments. Plots of mean plasma maribavir and [redacted] concentrations versus nominal time for all treatments will also be provided on linear and semilogarithmic scales.

8.1.1 Handling Data with Below Limit of Quantitation (BLQ) Values

The following procedures will be used for plasma maribavir concentrations below the lower limit of quantification (LLOQ):

- Concentrations that are below limit of quantification (BLQ) are reported as <LLOQ on the

data listings, where LLOQ is replaced by the actual LLOQ value for respective PK assay.

- Concentrations that are BLQ are treated as zero in the calculation of summary statistics (eg, mean, SD, etc.) for the plasma concentrations at individual time points. Geometric mean will be set to missing where zero values exist.
- Mean concentrations are reported as zero if all values are BLQ or zero, and no other descriptive statistics are reported. If the calculated mean (± SD) concentration is less than the LLOQ, the value will be reported as calculated. The mean values derived using these conventions will be used to create the mean plasma concentration versus time plots.
- For calculation of PK parameters, BLQ values prior to the first measurable concentration will be set to zero All BLQ values following the first measurable concentration will be set to "missing".
- Missing values will not be imputed.

8.2 Pharmacokinetic Parameters

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

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

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

- C_{max} Maximum observed plasma concentration
- t_{max} Time of maximum observed concentration sampled during a dosing interval
- AUC_{last} Area under the curve from the time of dosing to the time of 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-$AUC_{last}/AUC_{0\text{-}inf}$)*100
- λz Elimination rate in the terminal phase
- $t_{1/2}$ Terminal half-life
- CL/F Apparent total body clearance following extravascular administration calculated as dose divided by $AUC_{0\text{-}inf}$
- Vz/F Apparent volume of distribution following extravascular administration calculated as CL/F divided by λz

- T_{lag} Delay between the time of dosing and time of appearance of drug concentration in plasma in the employed sampling scheme

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

Individual plasma PK parameters for maribavir and [redacted] will be summarized by cohort and treatment group using descriptive statistics (n, arithmetic mean, SD, median, minimum, maximum, and %CV). In addition, geometric mean, 95% CI of geometric mean and geometric CV% will be computed for original and dose-normalized C_{max}, AUC_{last} and $AUC_{0\text{-}inf}$. Individual plasma PK parameters will be presented in a data listing for each cohort and treatment group.

Scatter plots of individual plasma C_{max} and AUCs for maribavir and [redacted] versus dose will be provided. Box-Whisker plots for selected dose-normalized PK parameters will be generated with Japanese cohort and Non-Hispanic Caucasian side by side at 400 mg.

8.3 Statistical Analysis of Pharmacokinetic Data

In order to compare the PKs of maribavir between subjects of Japanese descent and matched non-Hispanic, Caucasian subjects, the differences of log-transformed PK parameters (C_{max} , AUC_{last}, and $AUC_{0\text{-}inf}$) from the maribavir 400 mg oral dose will be examined between cohorts using an analysis of variance (ANOVA) model. The geometric mean ratio and its 90% CI of PK parameters for Japanese descent vs Caucasian will be provided from the model.

In addition, the difference of log-transformed dose-normalized C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ will be examined between the following dose groups using an ANOVA model.

- the Japanese cohort estimated at the 200 mg dose and the Non-Hispanic Caucasian cohort estimated at the 400 mg dose
- the Japanese cohort estimated at the 800 mg dose and the Non-Hispanic Caucasian cohort estimated at 400 mg dose

The geometric mean ratio and its 90% CI will be provided from the model. Forest plots of geometric mean ratios for selected PK parameters between Japanese cohort vs the Non-Hispanic Caucasian cohort at 400 mg will be generated.

[redacted]

Dose proportionality

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

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

where α is the intercept, β is the slope, and Random error is a random residual error. Dose proportionality will be assessed by estimating mean slope with the corresponding two-sided 90% CI from the power model. Dose proportionality is concluded when the 90% CIs of the slope β lie entirely within (1 + ln(0.8)/ln(r), 1 + ln(1.25)/ln(r)), where r is a ratio that describes the dose range and is defined as (highest dose/lowest dose). The fold increase in PK parameters and associated 90% CI when doubling the dose will be presented.

[redacted]

9. PHARMACODYNAMIC ANALYSIS

Not applicable.

10. OTHER ANALYSES

No other analyses are planned for this study.

11. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

Not applicable.

12. DATA HANDLING CONVENTIONS

12.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, SD, minimum, and maximum. Categorical and count variables will be summarized by the number and the percent of subjects (n, %) in each category.

The following rules will be applied for decimal places and rounding:

1. For measures of median and mean, 1 decimal place beyond those used for the measurement will be reported.

2. For measures of SD and standard error of the mean, 2 decimal places, beyond those used for the measurement, will be reported.

3. For measures of minimum and maximum values, the same number of decimal places will be used as those used for the measurement.

4. >=5 will be rounded up away from zero, whereas <5 will be rounded down toward zero to account for rounding of negative numbers.

5. For p-values, 3 decimal places will be used.

6. P-values that would round to 0.000 will be displayed as <0.001.

7. BMI should be rounded to 1 decimal place for reporting.

8. Averaged lab results (e.g. diastolic/systolic blood pressure and pulse [when taken in triplicate]) should be rounded to 1 decimal place for reporting.

9. For PK Related shells, display should be to the defined level of significant digits.

12.2 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of investigational product, then the results from the final assessment made prior to the start of investigational product will be used as baseline. If end of study assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating descriptive statistics. If there are repeated assessments at other post-baseline timepoints, the assessment from scheduled visit will be considered for summarizing data. However, all post-baseline assessments will be used for PCS value determination and all assessments will be presented in the data listings.

12.3 Handling of Missing, Unused, and Spurious Data

12.3.1 Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

For prior or concomitant medications (and/or therapies/procedures), incomplete (ie, partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

12.3.1.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

12.3.1.2 Missing Day and Month

- If the year of the incomplete start date is;
  - The same as the year of the date of the first dose of IP, then the day and month of the date of the first dose of IP will be assigned to the missing fields.
  - Before the year of the date of the first dose of IP, then December 31 will be assigned to the missing fields.
  - After the year of the date of the first dose of IP, then 01 January will be assigned to the missing fields.

12.3.1.2.1 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

12.3.1.2.2 Missing Day Only

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

12.3.1.3 Incomplete Stop Date

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

12.3.1.3.1 Missing Day and Month

- If the year of the incomplete stop date is;
  - The same as the year as of the date of the last dose of IP, then the day and month of the date of the last dose of IP will be assigned to the missing fields.
  - Before the year of the date of the last dose of IP, then 31 December will be assigned to the missing fields.
  - After the year of the date of the last dose of IP, then 01 January will be assigned to the missing fields.

12.3.1.3.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

12.3.1.3.3 Missing Day Only

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

12.3.2 Missing Date Information for Adverse Events

For AEs with partial start dates, non-missing date parts will be used to determine if the AE is a TEAE or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, eg AE start year and month are the same as the year and month of the first dose of IP, then the AE will be classified as a TEAE.

To facilitate categorization of AEs as TEAEs, imputation of dates can be used. For AEs, the default is to only impute incomplete (ie, partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

12.3.2.1 Incomplete Start Date

Follow the same rules as in Section 12.3.1.1.

12.3.2.2 Incomplete Stop Date

Follow the same rules as in Section 12.3.1.3.

12.3.3 Missing Severity Assessment for Adverse Events

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

12.3.4 Missing Relationship to Investigational Product for Adverse Events

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

12.3.5 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, a character string being reported for a numerical variable, then the appropriately determined coded value will be used in the statistical analysis. However, the actual values as reported in the database will be presented in data listings.

13. ANALYSIS SOFTWARE

Phoenix WinNonlin version 8.0 or higher will be used to perform the PK analysis. Statistical analyses will be performed using Version 9.4 (or newer) of SAS® (version to be delineated in the CSR) on a suitably qualified environment.

14. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

The following change is made to this statistical analysis:

- More clarification is added for the Safety Analysis Set.

15. REFERENCES

Not applicable

16. APPENDICES

16.1 Schedule of Assessments

Table 4 Schedule of Assessments for Subjects of Japanese Descent

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

Table 4 Schedule of Assessments for Subjects of Japanese Descent

Visit	Screening	Pre-dose Assessments	Treatment Period 1		Washout Period[i]	Treatment Period 2		Washout Period[i]	Treatment Period 3		Early Termination	Follow-up[j]
Study Day	**-28 to -02**	**-1**	**1**	**2**	**3-5**	**1**	**2**	**3-5**	**1**	**2**		**7 (±4)**
PK blood sampling[h]			X	X		X	X		X	X		
Check-in to the CRC		X										
Discharge from the CRC										X		
Adverse events/serious adverse events[i]	X	X	X	X		X	X		X	X	X	X
Concomitant medications	X	X	X	X		X	X		X	X	X	X

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

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

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

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

d Height will be recorded at the screening visit only.

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

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

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

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

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

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

Table 5 Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 1

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

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

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

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

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

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

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

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

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

Table 6 Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 2

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

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

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

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

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

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

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

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

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

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

Table 7 Detailed Schedule of Assessments for Subjects of Japanese Descent for Days 1 and 2 of Treatment Period 3

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

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

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

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

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

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

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

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

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

CLINICAL PHARMACOLOGY ANALYSIS PLAN (CPAP)

STUDY NUMBER: TAK-620-1020

STUDY TITLE: A PHASE 1, OPEN-LABEL, RANDOMIZED, CROSS-OVER STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF A SINGLE ORAL DOSE OF MARIBAVIR ADMINISTERED IN HEALTHY JAPANESE SUBJECTS COMPARED WITH MATCHED, HEALTHY, NON-HISPANIC, CAUCASIAN SUBJECTS AND TO ASSESS DOSE-PROPORTIONALITY OF 3 DOSES OF MARIBAVIR IN THE JAPANESE SUBJECTS

TAKEDA CLINICAL PHARMACOLOGY

Date: 24 July 2020

1.0 APPROVAL SIGNATURES

Title	Printed Name	Signature	Date
Clinical Pharmacology Lead (CPL)	[redacted], PhD qPharmetra	[redacted]	[redacted]
PK/PD Analysis Vendor Representative	[redacted], PhD PPD	[redacted]	[redacted]
Clinical Pharmacology Manager/Designee	[redacted], PhD Quantitative Clinical Pharmacology Takeda	[redacted]	[redacted]

2.0 TABLE OF CONTENTS

3.0 INTRODUCTION

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). 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.

Study TAK-620-1020 is being conducted to compare the PK, safety, and tolerability of maribavir administered as a single oral dose in healthy adult subjects of Japanese descent and matched, healthy, adult, non-Hispanic, Caucasian subjects. In accordance with the ICH-E5, this study is designed to evaluate whether there is any ethnic difference in PK and safety of maribavir between Japanese and non-Japanese subjects. The results from this study will be utilized to guide dose selection for a future Phase 3 study in Japanese transplant patients with CMV infection.

This document describes the methods used in the final analysis of pharmacokinetic and/or pharmacodynamic (PK/PD) parameters and the reporting of the results from these analyses.

4.0 PK/PD METHODS OF ANALYSIS AND DATA PRESENTATION

4.1 PK/PD PARAMETER CALCULATIONS

Details of the PK/PD methods to be used and the analytes for which PK/PD parameters are to be calculated are defined in Table 1 and Table 2.

Table 1 Final Pharmacokinetic (PK) Parameter Calculations

Table 1. Final Pharmacokinetic (PK) Parameter Calculations

☐ No PK calculations will be performed.

or

☒ PK calculations will be performed as follows (select one):

☒ PK parameters will be determined using noncompartmental PK methods.
☐ PK parameters will be determined using compartmental methods.

☒ List the analytes for which PK parameters will be calculated: Maribavir and [redacted]

☒ Actual sampling times will be used for PK parameter calculations.

or

☐ Other (describe):

☐ An interim analysis (a protocol specified analysis which requires release of the interim analysis database) will be conducted (specify timing and extent of analysis):

☐ Additional information:

Table 2 Final Pharmacodynamic (PD) Parameter Calculations

☒ No PD parameter calculations are under the purview of Clinical Pharmacology for this study.

or

☐ List the analytes for which PD parameters will be calculated:

☐ Actual sampling times will be used for PD parameter calculations.

or

☐ Nominal sampling times will be used for PD parameter calculations.

or

☐ Nominal sampling times will be used for PD parameter calculations unless the actual sampling time deviates by more than ____ minutes or more than _____ percent from the nominal time.

☐ Additional information:

4.2 EVALUABILITY OF PK/PD PARAMETER ESTIMATES

Details regarding the evaluability of the PK/PD parameter estimates are defined in Table 3. Parameter estimates that are considered unreliable (e.g., less than 3 data points were used to determine the terminal elimination slope by regression analysis, the regression line fitted to the terminal elimination phase data is of poor fit, etc.) will not be included in the clinical database, except for rare circumstances (e.g., a subject vomits after drug administration, in which case this subject's PK parameters may be included in the clinical database, but are considered unreliable).

Table 3 Evaluability of PK/PD Parameter Estimates

Assay data:

- ☐ A value of zero will be substituted for any assay result below the lower limit of quantification (BLQ) for that assay.
- ☒ Individual assay concentrations deemed anomalous will be excluded from concentration summary statistics, concentration plots and PK/PD parameter calculations.[a]
- ☒ Additional/other information: Assay results of BLQ will be handled as follows for the non-compartmental analysis:

1. BLQ values that occur prior to the first quantifiable concentration of a profile will be set to 0
2. A single BLQ value that occurs between 2 quantifiable concentrations in a profile will be set to missing.
3. If 2 or more consecutive BLQ values occur after a quantifiable concentration, the concentration-time profile is considered to end at the time of the last prior quantifiable concentration and subsequent BLQ values will be set to missing.

A subject's PK parameter data is considered unreliable and will not be reported if the following criteria is met:

- ☐ Insufficient data to determine a reliable $t_{1/2}$ value (Therefore unable to determine AUC_{∞}, CL, V_z and other terminal elimination rate constant dependent parameters).
- ☒ Other (list): Concentration results cannot be associated with a unique subject number.

A subject's PK/PD parameter data will be included in the listings but excluded from the descriptive statistics and statistical evaluation if the following criteria is met:

- ☒ A predose (0 hr) concentration is greater than 5% of that subject's C_{max} value in that period (e.g. single dose BE studies).
- ☐ A subject drops out of the study prior to completing all arms of the study.
- ☒ A subject did not meet inclusion/exclusion criteria that may have an effect on the PK.[a]
- ☒ A subject deviates substantially from the protocol defined study procedures including but not limited to dosing, dose timing, sample collection, meal timing, etc.[a]
- ☒ Additional information: Terminal elimination rate constant dependent parameters ($AUC_{0\text{-}inf}$, CL/F, Vz/F) will not be reported if there are insufficient data to determine a reliable $t_{1/2}$ value and/or if the $AUC_{0\text{-}inf}$%Extrap exceeds 20%. Parameters such as C_{max}, t_{max}, and AUC_{last} may be reported on a case-by-case basis after discussion with the CPL.

[a] As determined by the CPL after consultation with the CPL's manager (or designee).

4.3 PK/PD Parameter Specifications

The PK/PD parameter specifications are defined in Tables 4-5. Any selected parameters that are calculated using formulae other than the defined Phoenix WinNonlin calculation and interpolation formulae are considered "User Defined", and the formulae used for the User Defined parameters must be included in Table 4 and/or Table 5.

Table 4 PK/PD Parameter Specifications for Presentation of Data in In-text Tables

Analyte(s): Maribavir, [redacted]		**In-Text Table(s)**			**Software**	**User Defined Formula for Parameter Calculation[b]**
Matrix	**Parameter[a]**	**Units**	# of Significant Figures	**Summary Statistics**	**Used for Parameter Calculation**	
Plasma	t_{max}	h	e	c	Phoenix WinNonlin 8.0	□ Yes x No
Plasma	C_{max}	µg/mL	3	d	Phoenix WinNonlin 8.0	□ Yes x No
Plasma	AUC_{last}	h·µg/mL	3	d	Phoenix WinNonlin 8.0	□ Yes x No
Plasma	$AUC_{0\text{-}inf}$	h·µg/mL	3	d	Phoenix WinNonlin 8.0	□ Yes x No
Plasma	Dose-normalized C_{max}	µg/mL/400mg	3	d	Phoenix WinNonlin 8.0	x Yes □ No
Plasma	Dose-normalized AUC_{last}	h·µg/mL/400mg	3	d	Phoenix WinNonlin 8.0	x Yes □ No
Plasma	Dose-normalized $AUC_{0\text{-}inf}$	h·µg/mL/400mg	3	d	Phoenix WinNonlin 8.0	x Yes □ No
Plasma	$t_{1/2}$	h	3	f	Phoenix WinNonlin 8.0	□ Yes x No
Plasma	CL/F[g]	L/h	3	f	Phoenix WinNonlin 8.0	□ Yes x No

a AUC values are calculated using the linear-up and log-down trapezoidal method unless otherwise noted below.
b If yes, list below the parameter along with the equation that will be used for calculation of that parameter.
c Number of observations, median, range
d Number of observations, geometric mean, minimum, maximum, geometric mean coefficient of variation
e t_{max} will be reported up to 2 decimal places
f Mean, SD, and CV%
g Maribavir only

User defined equations (list parameter and equation):

Dose-normalized parameters will be calculated for Japanese subjects and normalized to 400 mg dose of maribavir as:
Dose-normalized C_{max} = C_{max} / maribavir dose [mg] *400
Dose-normalized AUC_{last} = AUC_{last} / maribavir dose [mg] * 400
Dose-normalized $AUC_{0\text{-}inf}$ = $AUC_{0\text{-}inf}$ /maribavir dose [mg] *400

Table 5 PK/PD Parameter Specifications for Presentation of Data in Listings

Analytes: Maribavir, [redacted]		**Listings (end of text tables)**			**Software**	**User Defined Formula for Parameter**
Matrix	**Parameter[a]**	**Units**	# of Significant Figures	**Summary Statistics**	**Used for Parameter Calculation**	**Calculation[b]**
Plasma	Concentration	µg /mL	3	d	na	na
Plasma	t_{max}	h	f	c	Phoenix WinNonlin 8.0	□ Yes x No
Plasma	C_{max}	µg/mL	3	e	Phoenix WinNonlin 8.0	□ Yes x No
Plasma	AUC_{last}	h·µg/mL	3	e	Phoenix WinNonlin 8.0	□ Yes x No
Plasma	$AUC_{0\text{-}inf}$	h·µg/mL	3	e	Phoenix WinNonlin 8.0	□ Yes x No
Plasma	$AUC_{0\text{-}inf}$%Extrap.	%	3	e	Phoenix WinNonlin 8.0	□ Yes x No
Plasma	Vz/F[g]	L	3	e	Phoenix WinNonlin 8.0	□ Yes x No
Plasma	Dose-normalized C_{max}	µg/mL/400mg	3	e	Phoenix WinNonlin 8.0	x Yes □ No
Plasma	Dose-normalized AUC_{last}	h·µg/mL/400mg	3	e	Phoenix WinNonlin 8.0	x Yes □ No
Plasma	Dose-normalized $AUC_{0\text{-}inf}$	h·µg/mL/400mg	3	e	Phoenix WinNonlin 8.0	x Yes □ No
Plasma	CL/F[g]	L/h	3	e	Phoenix WinNonlin 8.0	□ Yes x No
Plasma	$t_{1/2z}$	hr	3	e	Phoenix WinNonlin 8.0	□ Yes x No
Plasma	λ_z	1/h	3	e	Phoenix WinNonlin 8.0	□ Yes x No
Plasma	T_{lag}	h	f	e	Phoenix WinNonlin 8.0	□ Yes x No

na not applicable
a AUC values are calculated using the linear-up and log-down trapezoidal method.
b If yes, list below the parameter along with the equation that will be used for calculation of that parameter.
c Number of observations, median, range
d Number of observations, mean, geometric mean, standard deviation, CV%, minimum, median, maximum
e Number of observations, mean, standard deviation, CV%, minimum, median, maximum. In addition, geometric mean, geometric meancoefficient of variation, and 95% CI of the geometric mean are only reported for original and dose-normalized C_{max}, AUC_{last}, $AUC_{0\text{-}inf}$.
f t_{max} and T_{lag} will be reported up to 2 decimal places
g Maribavir only

User defined equations (list parameter and equation):

Dose-normalized parameters will be calculated for Japanese subjects and normalized to 400 mg dose of maribavir as:
Dose-normalized C_{max} = C_{max} / maribavir dose [mg] *400
Dose-normalized AUC_{last} = AUC_{last} / maribavir dose [mg] * 400
Dose-normalized $AUC_{0\text{-}inf}$ = $AUC_{0\text{-}inf}$ /maribavir dose [mg] *400

4.4 DATA TRANSFER FILES

Details concerning the electronic data transfer files that are to be prepared are defined in

Table 6 and Table 7:

Table 6 Electronic Data Files from Clinical Database for PK/PD Parameter Analysis

Files to be used for PK/PD parameter analysis which contain information from the clinical database:

☐ No files containing information from the database will be transferred.

☒ Database output file (DBO) containing final assay concentrations and actual sampling times (which may contain additional database information as described below) will be transferred as follows:

☒ DBO data transferred from database will be at full precision as received from the BA vendor.

or

☐ DBO data transferred from database will be up to _____decimal places.

or

☐ DBO data transferred from database will be _____significant figures.

DBO file type: ☐ EXCEL ☐ CSV ☒SAS ☐ Pipe Delimited ☐Other (list): _____

Additional subject information requested from the database (may be included in the DBO or may be in a separate file[s]):

☒ Age (years)
☐ Height (inches) ☐ Height (cm)
☐ Baseline Weight (lb.) ☒ Baseline Weight (kg) ☐ Body Mass Index (BMI)
☒ Gender
☒ Race
☒ Nominal Sampling Time Post Dose ☒ Actual Sampling Time Post Dose
☐ Dosing Time Deviations ☐ Sample Time Deviations
☒ Dose Group ☒ Dosing Period ☒ Dosing Sequence
☐ Baseline Creatinine Clearance
☐ Concomitant Medications
☐ Other(s) (list):

Additional information (eg, descriptors needed to clarify any of the above selections):

☒ Other file(s) to be transferred (list): Files from the bioanalytical vendor may be transferred in Excel or .csv format.

Table 7. Electronic Data Files from PK/PD Parameter Analysis transferred to the Clinical Database

PK/PD parameter data files to be transferred to the clinical database:

☐ No files will be transferred to the clinical database.

☒ PK parameter (PKP) file(s) will be transferred as follows.
- ☐ PKP data transferred will be at full precision.
  or
- ☐ PKP data transferred will be up to _____ decimal places.
  or
- ☒ PKP data transferred will be 3 significant figures.

PKP file type: ☐ EXCEL ☐ CSV ☒ SAS export ☐Other (list):_____

☐ PD parameter (PDP) file(s) will be transferred as follows.
- ☐ PDP data transferred will be at full precision.
  or
- ☐ PDP data transferred will be up to _____ decimal places.
  or
- ☐ PDP data transferred will be _____ significant figures.

PDP file type: ☐ EXCEL ☐ CSV ☐ SAS export ☐Other (list): _____

☒ File containing analyte concentrations and actual sampling times.
- ☒ File transferred will be at full precision as received from the BA vendor.
  or
- ☐ File transferred will be up to _____ decimal places.
  or
- ☐ File transferred will be _____ significant figures.

File type: ☐ EXCEL ☐ CSV ☐ SAS export ☐ Other (list): _____

☐ Other File(s) (list): _____

4.5 DATA DISPLAYS

Details concerning tables and figures related to PK/PD concentrations and/or parameters (those under the purview of Clinical Pharmacology) that are to be included in the clinical report are defined in Table 8.

Table 8. Clinical Study Report (CSR) Data Displays

Tables

The following PK/PD tables are to be included in the final CSR:

☒ Analyte concentration tables:

☐ Mean concentration data (☐ with or ☐ without) descriptive statistics for (list matrix, analyte, and summary statistics to be included):

☒ Individual concentration data (☒ with or ☐ without) descriptive statistics for plasma maribavir and [redacted]; number of observations, geometric mean, arithmetic mean, standard deviation, minimum, median, maximum

☒ PK/PD parameter tables:

☐ Mean PK/PD parameters (☐ with or ☐ without descriptive statistics) for (list matrix and summary statistics to be included; parameters to be included also should be in Table 4 or 5):

☒ Individual PK/PD parameters (☒ with or ☐ without) descriptive statistics for plasma maribavir and [redacted]; number of observations, geometric mean, percent coefficient of variation for the geometric mean, 95% CI of the geometric mean, arithmetic mean, standard deviation, minimum, median, maximum

☐ Other table(s) (describe table and the matrix and analyte/parameter(s) to be included in the table):

Figures

The following PK/PD figures are to be included in the final CSR:

☒ Mean (☒ linear ☒ log-linear) concentration-time curves for: Plasma maribavir and [redacted]

☒ Individual (☒ linear ☒ log-linear) concentration-time curves for: Plasma maribavir and [redacted]

☐ Mean (☐ C_{max} ☐ AUC) vs. dose for (list matrix and analyte for each):

☐ Individual (☐ C_{max} ☐ AUC) vs. dose for (list matrix and analyte for each):

☐ Box plots (☐ C_{max} ☐ AUC) vs. cohort (list matrix and analyte for each):

☐ Scatter plots (☐ C_{max} ☐ AUC) vs. regimen for (list matrix and analyte for each):

☒ Other figure(s): Forest plots of geometric mean ratios for maribavir $C_{max,}$ AUC_{last}, and $AUC_{0\text{-}inf}$ between Japanese cohort vs the Non-Hispanic Caucasian cohort at 400 mg maribavir will be generated. Box-Whisker plots for dose-normalized maribavir $C_{max,}$ dose-normalized AUC_{last}, and dose-normalized $AUC_{0\text{-}inf}$ across doses will be generated with Japanese cohort and Non-Hispanic Caucasian side by side. [redacted]

5.0 MODIFICATION OF A CPAP

Modification/changes to an approved CPAP will be managed by amendment using FORM-0002707 (Clinical Pharmacology Analysis Plan (CPAP) Amendment).

6.0 REFERENCE

TOOL-0001296 Standard Pharmacokinetic Terminology

Chulay, J., Biron, K., Wang, L., Underwood, M., Chamberlain, S., Frick, L., Good, S., Davis, M., Harvey, R., Townsend, L., Drach, J. & Koszalka, G. 1999. Development of novel benzimidazole riboside compounds for treatment of cytomegalovirus disease. *Adv Exp Med Biol,* 458, 129-34.

Williams, S. L., Hartline, C. B., Kushner, N. L., Harden, E. A., Bidanset, D. J., Drach, J. C., Townsend, L. B., Underwood, M. R., Biron, K. K. & Kern, E. R. 2003. In vitro activities of benzimidazole D- and L-ribonucleosides against herpesviruses. *Antimicrob Agents Chemother,* 47, 2186-92.