Statistical Analysis Plan

NCT Number: NCT05918822

Title: A Phase 1, Open-Label, Randomized, Two-Part Study in Healthy Adult Participants to Evaluate the Relative Bioavailability of Maribavir Pediatric Formulation Compared to the Commercial Formulation, as well as, Food Effect, and Rabeprazole Gastric Acid-Reducing Effect on the Pharmacokinetics of Single Dose Maribavir Pediatric Formulation

Study Number: TAK-620-1024

Document Version and Date: Final, 06 June 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

Study Number: TAK-620-1024

A Phase 1, Open-Label, Randomized, Two-Part Study in Healthy Adult Participants to Evaluate the Relative Bioavailability of Maribavir Pediatric Formulation Compared to the Commercial Formulation, as well as, Food Effect, and Rabeprazole Gastric Acid-Reducing Effect on the Pharmacokinetics of Single Dose Maribavir Pediatric Formulation

Phase: 1

Version: Final

Date: 06-June-2023

Prepared by:

[redacted], MS
[redacted]
Data Management and Biometrics
Celerion

[redacted], MSc
[redacted], Clinical Pharmacology & Pharmacometrics
Data Management and Biometrics
Celerion

Based on:

Protocol Version: Original

Protocol Date: 11 April 2023
Protocol Clarification Letter Date: 19 May 2023

REVISION HISTORY

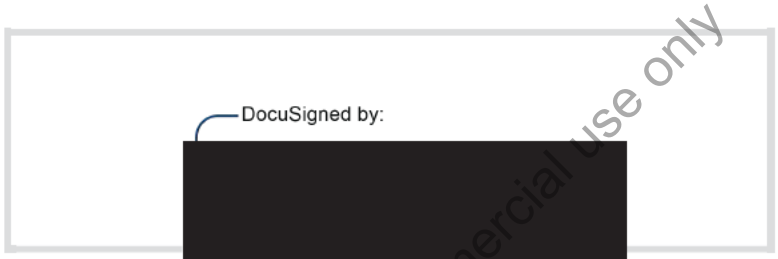
Version	Approval Date	Primary Rationale for Revision
Original version	06-June-2023	Not Applicable

APPROVAL SIGNATURES

Electronic signature can be found on the last page of this document.

Study Title: A Phase 1, Open-Label, Randomized, Two-Part Study in Healthy Adult Participants to Evaluate the Relative Bioavailability of Maribavir Pediatric Formulation Compared to the Commercial Formulation, as well as, Food Effect, and Rabeprazole Gastric Acid-Reducing Effect on the Pharmacokinetics of Single Dose Maribavir Pediatric Formulation

Approvals:

Signature: 

[redacted], P
[redacted],
Statistical and Quantitative Sciences
Takeda Development Center Americas, Inc.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ANOVA	analysis of variance
AUC	area under the concentration-time curve
AUC_{12}	area under the concentration-time curve from time 0 to 12 hours postdose
AUC_{∞}	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{∞_pred}	area under the concentration-time curve from time 0 to infinity, calculated using the predicted value of the last quantifiable concentration
$AUC_{extrap}\%$	area under the concentration-time curve from the last quantifiable concentration to infinity, calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞}
$AUC_{extrap}\%\_pred$	area under the concentration-time curve from the last quantifiable concentration to infinity, calculated using the predicted value of the last quantifiable concentration, expressed as a percentage of AUC_{∞_pred}
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BID	twice-daily
BLQ	below the lower limit of quantitation
BMI	body mass index
C_{τ}	projected trough concentration at 12 hours postdose after twice-daily dosing
C_{12}	concentration at 12 hours postdose
CI	confidence interval
CL/F	apparent clearance after oral administration, calculated using the observed value of the last quantifiable concentration
$CL/F_{\_pred}$	apparent clearance after oral administration, calculated using the predicted value of the last quantifiable concentration
C_{max}	maximum observed concentration
COVID-19	coronavirus disease 2019
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRF	case report form
CRU	clinical research unit
CV%	coefficient of variation
DMP	data management plan
ECG	electrocardiogram
ET	early termination
Geom CV%	geometric percent coefficient of variation
Geom Mean	geometric mean
GMR	geometric mean ratio
ICF	informed consent form

ID	investigational drug
LLN	lower limit of normal
LSM	least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
n	number of observations
NCA	non-compartmental analysis
PCS	potentially clinically significant
PK	pharmacokinetic
PPI	proton pump inhibitor
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEM	standard error of the mean
SI	International System
SOC	system organ class
$t_{½z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{lag}	lag time to first quantifiable concentration in plasma
t_{max}	time to first occurrence of C_{max}
US	United States of America
V_z/F	apparent volume of distribution during the terminal disposition phase after oral administration, calculated using the observed value of the last quantifiable concentration
$V_z/F_{\_pred}$	apparent volume of distribution during the terminal disposition phase after oral administration, calculated using the predicted value of the last quantifiable concentration
WHO	World Health Organization
λ_z	terminal disposition phase rate constant

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objectives

Part 1:

- *To compare the relative bioavailability of a single dose of 200 mg maribavir pediatric formulation administered orally as water suspension to 200 mg maribavir commercial tablet.*
- *To assess the effect of a high-fat, high-calorie meal on the pharmacokinetic (PK) exposure of a single 200 mg dose of maribavir pediatric formulation administered orally as water suspension.*

Part 2:

- *To assess the gastric acid-reducing effect of multiple doses of the proton pump inhibitor (PPI) rabeprazole, on the PK exposure of a single dose of 200 mg maribavir pediatric formulation administered orally as water suspension.*

1.1.2 Secondary Objective

Parts 1 and 2:

To evaluate the safety and tolerability of 200 mg maribavir pediatric formulation administered orally as water suspension under fasting conditions, fed conditions, or with the PPI rabeprazole.

1.1.3 Exploratory Objectives

Part 1:

- *To assess the palatability of a single 200 mg dose of maribavir pediatric formulation administered orally as water suspension under fasting and fed conditions.*

Parts 1 and 2:

- *To evaluate additional maribavir PK parameters following a single 200 mg dose of maribavir commercial tablet administered orally under fasting conditions, and a single 200 mg dose of maribavir pediatric formulation administered orally as water suspension under fasting and fed conditions, or with the PPI rabeprazole.*

1.2 Endpoints

1.2.1 Primary Endpoints

In Parts 1 and 2, the following PK parameters in plasma will be analyzed for maribavir:

- *Maximum observed concentration (C_{max})*

- *Area under the concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC_{last})*
- *AUC from time 0 to infinity, calculated using the observed value of the last quantifiable concentration (AUC_{∞})*

1.2.2 Secondary Endpoints

In Parts 1 and 2, the safety endpoints will include the following:

- *Treatment-emergent adverse events (TEAEs) and their number, severity, seriousness, and causality*
- *Changes in vital signs, electrocardiograms (ECGs), and clinical laboratory results (hematology, chemistry, and urinalysis) from baseline to post-baseline time points, and evaluation of clinical signs.*

1.2.3 Exploratory Endpoints

In Part 1, the palatability of the maribavir pediatric formulation will be evaluated. A semi-validated questionnaire will be used to identify, characterize, and quantify the sensory attributes of maribavir pediatric formulation including basic tastes, texture, and mouth feel, and to assess the overall acceptability.

In Parts 1 and 2, exploratory PK endpoints include (if applicable, but are not limited to) additional maribavir PK parameters as follows:

- *Time to first occurrence of C_{max} (t_{max})*
- *AUC from the last quantifiable concentration to infinity, calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞} (AUC_{extrap}%)*
- *Terminal disposition phase rate constant (λ_z)*
- *Terminal disposition phase half-life ($t_{½z}$)*
- *Apparent volume of distribution during the terminal disposition phase after oral administration, calculated using the observed value of the last quantifiable concentration (V_z/F)*
- *Apparent clearance after oral administration, calculated using the observed value of the last quantifiable concentration (CL/F)*
- *Lag time to first quantifiable concentration in plasma (t_{lag})*
- *Concentration at 12 hours postdose (C_{12h})*
- *AUC from time 0 to 12 (AUC_{12h})*
- *Projected trough concentration at 12 hours postdose after twice-daily (BID) dosing (C_{τ})*

1.2.4 Additional Endpoints

In Part 1 only, additional PK endpoints include (if applicable) the following maribavir PK parameters:

- *AUC from time 0 to infinity, calculated using the predicted value of the last quantifiable concentration (AUC_{∞_pred}).*
- *AUC from the last quantifiable concentration to infinity, calculated using the predicted value of the last quantifiable concentration, expressed as a percentage of AUC_{∞_pred} ($AUC_{extrap}\%_{\_pred}$).*
- *Apparent clearance after oral administration, calculated using the predicted value of the last quantifiable concentration ($CL/F_{\_pred}$).*
- *Apparent volume of distribution during the terminal disposition phase after oral administration, calculated using the predicted value of the last quantifiable concentration ($V_z/F_{\_pred}$).*

1.3 Estimand(s)

Not applicable.

2.0 STUDY DESIGN

This single-center, open-label study in healthy adult participants will be conducted at Celerion in the US. The study will include two parts (Part 1 and Part 2). Each study part will be composed of a screening period, treatment periods (three treatment periods in Part 1 and two treatment periods in Part 2), and a follow-up period. Participants will only participate in one study part.

In Part 1, the relative bioavailability of maribavir pediatric formulation compared to maribavir commercial tablet formulation will be evaluated, as well as the effect of a high-fat, high-calorie meal on the PK exposure of a single dose of maribavir pediatric formulation.

In Part 2, the gastric acid-reducing effect of multiple doses of a PPI, rabeprazole, on the PK of a single dose of maribavir pediatric formulation will be evaluated.

Study schematics and dose regimens are shown in Table 2.a (Part 1), Table 2.b (Part 2), and Table 2.c.

Table 2.a Study Schematic for Part 1

Screening	*Treatment Period*									*Follow-up*
Within 28 days of Day 1 Treatment Period 1	Check-in	Sequence	N	Treatment Period 1 Day 1	Washout (3 days)	Treatment Period 2 Day 1	Washout (3 days)	Treatment Period 3 Day 1	Day after last dose	7 (±4) days after last dose of ID/study drug
Screening Period	Admission to CRU on Day -1	1	3	Treatment A		Treatment B		Treatment C	Discharge from the CRU	Follow-up phone call or other methods
		2	3	Treatment A		Treatment C		Treatment B		
		3	3	Treatment B		Treatment A		Treatment C		
		4	3	Treatment B		Treatment C		Treatment A		
		5	3	Treatment C		Treatment A		Treatment B		
		6	3	Treatment C		Treatment B		Treatment A		
	Confinement									

Treatment A: Maribavir single dose (200 mg) administered as commercial tablet under fasting conditions.
Treatment B: Maribavir single dose (200 mg) pediatric formulation administered as water suspension under fasting conditions.
Treatment C: Maribavir single dose (200 mg) pediatric formulation administered as water suspension under fed conditions.
CRU: Clinical Research Unit, ID: Investigational drug, N: Sample size

Table 2.b Study Schematic for Part 2

Screening	*Treatment Period*							*Follow-up*
Within 28 days of Day 1 Treatment Period 1	Check-in	Sequence	N	Treatment Period 1 Day 1	Washout (3 days)	Treatment Period 2		Day after last dose	7 (±4) days after last dose of ID/study drug
						Days 1 to 4	Day 5		
Screening period	Admission to CRU on Day -1	1	14	Treatment D		Treatment E		Discharge from the CRU	Follow-up phone call or other methods
						Rabeprazole dosing	Rabeprazole + maribavir		
	Confinement								

Treatment D: Maribavir single dose (200 mg) pediatric formulation administered as water suspension.
Treatment E: Maribavir single dose (200 mg) pediatric formulation administered as water suspension in the presence of multiple doses of rabeprazole.
CRU: Clinical Research Unit, ID: Investigational drug, N: Sample size

Table 2.c Study Treatments with Investigational Drug/Study Drug

Treatment	Investigational Drug/Study Drug	Dose	Dose Regimen	Days on Investigational Drug/Study Drug
A	Maribavir commercial tablet	200 mg (1 x 200 mg)	Single tablet dose, oral, fasted	Day 1
B and D	Maribavir pediatric powder-for-oral suspension	200 mg (1 x 200 mg)	Single water suspension dose, oral, fasted	Day 1
C	Maribavir pediatric powder-for-oral suspension	200 mg (1 x 200 mg)	Single water suspension dose, oral, fed: following a high-fat/high-calorie meal	Day 1
E	Rabeprazole tablet	20 mg (1 x 200 mg)	Once daily, oral, fasted	Days 1 through Day 5
	Maribavir pediatric powder-for-oral suspension	200 mg (1 x 200 mg)	Single water suspension dose, oral, fasted, 2 hours after rabeprazole dose	Day 5

Participants will be screened within four weeks (28 days) prior to the first administration of maribavir in Treatment Period 1 (Screening Period: Day -28 to first dosing, Day 1). Eligible

participants will be admitted to the clinical research unit (CRU) on Day -1 of Treatment Period 1, at the time indicated by the CRU, and will remain confined until after the last study procedures on Day 2 of Treatment Period 3 (Part 1), or Day 6 of Treatment Period 2 (Part 2).

Part 1:

Part 1 is a crossover design with three treatments (Treatments A, B, and C), six sequences, and three periods.

The relative bioavailability of 200 mg maribavir pediatric formulation administered orally as water suspension under fasting conditions (Treatment B) will be compared to 200 mg maribavir commercial tablet administered orally under fasting conditions (Treatment A). In addition, the effect of food on the PK of 200 mg maribavir pediatric formulation administered orally as water suspension under fasting conditions (Treatment B) and fed conditions (Treatment C) will be assessed.

A total of 18 participants will be enrolled, with three participants per sequence in each of the six sequences. In each sequence, participants will receive three treatments (Treatments A, B, and C) per schedule.

There will be a washout period of a minimum of 72 hours between each dosing.

PK sample collections will be conducted predose and up to 24 hours postdose in each treatment period.

Within five minutes after administration of maribavir as pediatric formulation (Treatment B and Treatment C), participants will be asked to answer a questionnaire regarding its palatability. The palatability questionnaire will be provided to the participants for preview during check-in.

Part 2:

Part 2 is a single fixed-sequence design with two treatments (Treatments D and E). The two treatments will be administered to evaluate the gastric acid-reducing effect of multiple doses of rabeprazole on the PK of a single dose of 200 mg maribavir pediatric formulation administered orally as water suspension.

In Treatment Period 1, on Day 1, participants will receive a single oral dose of 200 mg maribavir pediatric formulation under fasting conditions (Treatment D).

In Treatment Period 2, on Days 1 to 5, participants will receive a single oral dose of 20 mg rabeprazole under fasting conditions. On the morning of Day 5, two hours after rabeprazole dosing, participants will receive a single oral dose of 200 mg maribavir pediatric formulation under fasting conditions (Treatment E).

A total of 14 participants will be enrolled. Participants will receive two treatments (Treatments D and E) in a single fixed order.

There will be a washout period of a minimum of 72 hours between maribavir dosing in Treatment Period 1 and first dose of rabeprazole in Treatment Period 2.

PK sample collections will be conducted pre-maribavir dose and up to 24 hours post maribavir dose in each treatment period.

Parts 1 and 2:

Safety and tolerability will be assessed throughout the study by TEAEs, vital signs, ECGs, and clinical laboratory evaluations. Palatability will also be assessed in Part 1. The CRU will contact all participants (including participants who terminate the study early) 7 (± 4) days after the last dose of ID/study drug by telephone or other methods per CRU standards to determine if any AE has occurred or any medications have been taken since the last study visit. If clinically significant findings are observed upon discharge from the CRU, participants may return to the CRU for re-evaluation per Investigator's discretion.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not applicable.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

Table 4.a shows the estimated 90% confidence interval (CI) for the geometric mean ratio (GMR) for maribavir AUC_∞ and C_{max} between Test versus Reference formulations based on expected intra-participant variability and different number of participants in Part 1 and Part 2. The sample size for Part 1 and Part 2 is based on precision.

Table 4.a Estimated 90% CI for the Test / Reference GMR of AUC_∞ or C_{max} Based on Different Number of Participants for Part 1 and Part 2

N	*90% CI for the GMR*	
	AUC_∞ *Intra-participant CV% = 14.9*	*C_{max}* *Intra-participant CV% = 20.6*
Part 1 (3x6x3 design)		
12	*(0.90, 1.11)*	*(0.87, 1.15)*
18	*(0.92, 1.09)*	*(0.89, 1.12)*
24	*(0.93, 1.07)*	*(0.91, 1.10)*
Part 2 (fixed-sequence design)		
12	*(0.90, 1.11)*	*(0.86, 1.16)*
14	*(0.90, 1.10)*	*(0.87, 1.15)*
16	*(0.91, 1.10)*	*(0.88, 1.13)*

AUC_∞: AUC extrapolated to infinity; C_{max}: maximum concentration; CI: confidence interval, CV%: coefficient of variation (%); GMR: geometric mean ratio, N: sample size

The intra-participant CV% estimates for maribavir AUC_∞ and C_{max} were obtained from the upper 75% confidence limit on the weighted average intra-participant CV% observed in previous studies (Studies TAK-620-1019, TAK-620-1025, and 1263-104). Point estimate of 1 is used to allow the 90% CI to be compared with (0.80, 1.25).

As shown above, for both Part 1 and Part 2, a sample size of 12 participants provides an adequate 90% CI for the GMR within (0.80, 1.25).

In Part 1, six participants will be added for replacements to account for potential dropouts and to avoid potential sequence effect if replacement is required. Thus, a total of 18 participants will be enrolled and randomly assigned to one of six sequences with a 1:1:1:1:1:1 treatment allocation and requirement of three participants per sequence.

In Part 2, two participants will be added for replacements to account for potential dropouts. Thus, a total of 14 participants will be enrolled.

5.0 ANALYSIS SETS

5.1 PK Set

All participants who received at least one dose of maribavir, did not vomit or had diarrhea within four hours of the maribavir dosing, and have five or more postdose time points with evaluable postdose maribavir concentration values that enable noncompartmental analysis (NCA) will be included in PK set.

5.2 Safety Set

All participants who received at least one dose of maribavir will be included in the safety evaluations.

5.3 Palatability Set (Part 1 Only)

All participants who received at least one dose of maribavir pediatric formulation and have provided at least one response to the palatability questionnaire will be included in the Palatability Set.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All PK analyses will be conducted using Phoenix® WinNonlin® Version 8.3.4, or higher. All statistical analyses will be conducted using SAS® Version 9.4 or higher. All data recorded on the case report form (CRF) will be listed by participant and treatment. Laboratory data will be received separately, and results will be listed. All table, figure, and listing (TFL) shells and numbering list will be included and specified in the TFL Shells document.

The number of observations (n) will be presented as an integer (no decimal places). Formats of concentration and PK parameter data and their descriptive statistics will be detailed in the Clinical Pharmacology Analysis Plan (CPAP).

Geometric least-squares means (LSMs) will be reported with 1 more level of precision than the individual data. GMRs and 90% CIs for the GMRs will be reported to 2 decimal places. Intra-participant CVs will be reported to 2 decimal places.

Concentration values below the lower limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. BLQ values will be treated as zero for the calculation of summary statistics, the generation of concentration plots, and the calculation of PK parameters, unless they are deemed questionable (eg, BLQ value between measurable values), in which case they will be treated as missing and excluded from the concentration summary statistics and the PK analysis. Missing concentration data will not be imputed.

A participant's PK parameter data will be included in the listings but may be excluded from the descriptive summary and statistical model if one or more of the following criteria are met:

- A predose (0 hour) concentration is greater than 5% of that participant's C_{max} value in that period
- A participant did not meet inclusion/exclusion criteria that may have an effect on the PK (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)
- A participant deviates substantially from the protocol defined study procedures including but not limited to dosing, dose timing, sample collection, meal timing, etc. (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)
- A participant may be excluded from statistics due to incidence of vomiting or diarrhea within 4 hours post maribavir dosing
- A participant may be excluded from statistics if they have < 5 postdose time points with quantifiable postdose maribavir concentrations.

The details on PK parameter calculations and TFLs will be outlined in the clinical CPAP and TFL Shells document including specifics on the following:

- Insufficient data to determine a reliable $t_{½z}$ value and other λ_z-dependent parameters
- PK parameters presented by treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables
- Concentration data presented by treatment, including the units, precision, and summary statistics that will be presented in end-of-text tables
- Concentration data file used for PK analysis
- PK parameter Phoenix® WinNonlin® output file used to generate the TFLs
- PK parameter ratios for C_{max}, AUC_{last}, AUC_{∞}, and AUC_{∞_pred} presented in end-of-text tables.
- Linear mixed-effect model results presented in in-text and end-of-text tables
- Non-parametric statistical analysis results presented in in-text and end-of-text tables
- Arithmetic mean concentration-time figures presented as in-text and end-of-text figures
- Listings of concentration data for individual participants in Appendix 16.2.5.
- Individual concentration-time figures presented in Appendix 16.2.6.

Continuous demographic and safety data will be summarized descriptively. For categorical variables, the count and percentages of each reported value will be tabulated, where applicable. The denominator for the percent calculation will be the number of participants in the safety set for overall summaries, and the number of participants dosed with each treatment in by-treatment summaries. For continuous variables, n, mean, SD, minimum, median, and maximum values will be tabulated. The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer. Counts and percentages will be presented as integers. Baseline is defined as the last observation prior to dosing.

6.1.1 Handling of Treatment Misallocations

Participants with any treatment misallocations will be analyzed based on the treatment the participants actually received rather than per the treatment they were supposed to receive.

6.2 Study Information

An overall study information table will be generated including the following items for each part: date of first participant's signed informed consent form (ICF), date of first dose of investigational drug (ID), date of last dose of ID, date of last participant's discontinuation or completion, and the date of last participant's last procedure for collection of data for primary endpoint. The version of Medical Dictionary for Regulatory Activities (MedDRA®), the version of World Health Organization (WHO) Dictionary, and SAS version used for creating the datasets will also be displayed.

6.3 Disposition of Participants

Disposition of participants (number of participants dosed, completed the study, discontinued from the study and/or ID, and reason(s) for discontinuation(s)) will be summarized by randomized treatment sequence and overall for Part 1, and overall only for Part 2. Study completion status, including reason for discontinuation of ID and/or study, will be listed by part and participant.

6.4 Demographic and Other Baseline Characteristics

6.4.1 Demographics

Demographic and baseline characteristics will be summarized by randomized treatment sequence and overall for Part 1, and overall only for Part 2. Summaries will be based on the safety set. Summary statistics (n, mean, SD, minimum, median, and maximum) will be generated for continuous variables (age, weight, height, and body mass index [BMI]) and the number and percentages of participants within each category will be presented for categorical variables (sex, race, and ethnicity). Height, weight, and BMI measured at screening will be used in the summaries. Demographic data will also be listed as recorded on the CRF, including the date of informed consent and protocol version. Age will be calculated based on year of birth.

6.4.2 Medical History and Concurrent Medical Conditions

Medical history to be recorded will include determining whether the participant has any significant conditions or diseases that resolved at or before signing the ICF. All medical history reported by the participant will be recorded regardless of when it may have occurred. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Each participant's medical history and concurrent medical conditions will be listed.

Any medical condition starting or worsening after taking the first dose of ID will be classified as a TEAE. All medical history will be coded using MedDRA® version specified in the data management plan (DMP). If available, the medical history and concurrent medical condition listings will include the coded term (preferred term and system organ class [SOC]), start date (if known) and end date (if known) or whether the condition was ongoing, and a description of the condition or event. No summaries or statistical analysis will be performed for these data.

6.5 Medication History and Concomitant Medications

Medication history to be obtained includes any relevant medication stopped at or within 28 days prior to signing the ICF. Concomitant medication includes any medication other than ID taken at any time between first dosing and the end of the study (including follow-up contact). All medication history and concomitant medications recorded during the study will be coded with the WHO Drug Dictionary version specified in the DMP and listed. If available, the listings will include the medication name, coded term, dosage, route of administration, start date and time (if known), end date and time (if known), or whether it continued after study completion, and indication for use. No summaries or statistical analysis will be performed for these data.

6.6 Efficacy Analysis

Not applicable.

6.7 Safety Analysis

Safety will be evaluated by the incidence of TEAEs, severity and relationship(s) of TEAEs, and changes from baseline in the participants' clinical laboratory results, vital signs, and 12-lead ECGs using the safety set. Potentially clinically significant (PCS) laboratory, vital signs, and ECG results will be tabulated. Clinically significant laboratory values, vital signs, and ECGs will be reported as AEs, as applicable. All safety data will be listed by study part, participant, treatment, and assessment time points, including rechecks, unscheduled assessments, and early termination (ET), chronologically.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts and percentages will be reported for categorical data when appropriate. Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators. Postdose recheck, unscheduled, or early termination results will not be used in summaries.

Tables summarizing safety data by assessment time point will only include summaries for baseline and post-baseline time points.

6.7.1 Adverse Events

All AEs captured in the database will be listed in by-participant data listings including verbatim term, coded term, severity (mild, moderate, severe), relationship to ID/study drug (related or not related), frequency, and action relative to ID/study drug as recorded in the CRF. Study procedure taken due to AE will also be listed. All AEs occurring during this study will be coded using the MedDRA® version specified in the DMP. Only TEAEs will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after the first dose of ID (maribavir) administered in the study. Each TEAE will be attributed to the treatment prior to and the closest to the AE based on the AE onset date and time. Period 2 of Part 2 will be split into 2 treatments only for AE summaries. The method for assigning treatments is presented in Table 6.a.

Table 6.a AE Treatment Assignment Algorithm for Part 2 Period 2

Date and Time of AE With Respect to Date and Time of Dosing	Treatment
Period 2 Day 1 maribavir dosing time ≤ Date and Time of AE < Period 2 Day 5 maribavir dosing time	E1: Maribavir Alone
Period 2 Day 5 maribavir dosing time ≤ Date and Time of AE	E2: Maribavir + rabeprazole

If the onset time of an AE is missing and the onset date is the same as a treatment dosing date, then the AE will be counted under the treatment given on the same day. If onset time of an AE is missing and the onset date does not fall on a dosing date, then the AE will be considered treatment emergent for the most recent treatment administered. If the onset date of an AE is missing, then the AE will be considered treatment emergent and attributed to the first treatment received. If severity is missing, the AE will be counted as severe, and if relationship is missing, the AE will be counted as related.

TEAEs will be tabulated for each part by treatment (including overall), SOC, and preferred term. Summary tables will include number of participants reporting the TEAE as percent of safety set by treatment and overall. The most commonly reported non-serious TEAEs in the study (i.e., those events reported by >1 participant in any treatment, excluding serious adverse events (SAEs)) will also be summarized. The denominators for percent calculations will be the number of participants dosed for each treatment. In addition, TEAEs will be summarized as number of TEAEs and percentage of TEAEs for each treatment and overall.

Additional TEAE summary tables will be presented by severity and relationship to ID. If a participant has multiple TEAEs with different severity levels within the same preferred term, the participant will be counted in the most severe category only. For relationship to ID, if a participant has both related and unrelated TEAEs with the same PT, the participant will be counted as having related TEAEs.

An overview summary of TEAEs table, including number of participants with TEAEs, SAEs, ID-related TEAEs, treatment-related SAEs, adverse events of special interest (AESIs), TEAEs by severity, and AEs leading to discontinuation will be provided.

Should any SAEs (including all-cause mortalities) occur, they will be summarized the same way as TEAEs. All AEs will be displayed in the data listings and TEAEs will be discussed in the text of the CSR.

6.7.2 Adverse Events of Special Interest

AESIs will be summarized similarly to all TEAEs. AESI will be flagged in the data listings, and will be discussed in the CSR. AESIs for maribavir include preferred terms of dysgeusia, nausea, vomiting, and diarrhea.

6.7.3 Clinical Laboratory Evaluation

Clinical laboratory tests will be measured as described in Table 6.b:

Table 6.b Collection of Laboratory Samples

Clinical Laboratory Panels	Time Point			
	Study Part	Period	CRF/Listing Day and Hour	Table
Chemistry, Hematology, Urinalysis	Part 1	Screening		NA
		1	Day -1 PREDOSE	Baseline
		2	Day 1 PREDOSE	Period 2 Predose
		3	Day 1 PREDOSE Day 2 Hour 24	Period 3 Predose Period 3 Day 2
	Part 2	Screening		NA
		1	Day -1 PREDOSE	Baseline
		2	Day 1 PREDOSE Day 5 PREDOSE Day 6 Hour 24	Period 2 Predose Period 2 Day 5 Period 2 Day 6

Time points in the CRF/Listing column are approximated/based on the protocol and it should be noted that the data listings will reflect the data found in the final participant CRFs.
If applicable, an early termination assessment will be performed.
NA = Not Applicable

For all numeric values of laboratory test results, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented at each scheduled visit using the international system of units (SI). Part 1 will be summarized by treatment sequence and Part 2 will be summarized overall. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment including rechecks taken prior to the first dose in Period 1. The mean value calculated for each assessment time point will be compared to the reference range and flagged if outside of the reference range (* if above the reference range and ^ if below the reference range). In the event there is more than one reference range for a laboratory test, the comparison will be made against the lowest of the lower ranges and the highest of the higher ranges. Postdose unscheduled, recheck, or ET assessments will not be used in summaries. All clinical laboratory

data will be listed by participant. Urine drug screen will be performed at screening and check-in, and results will be listed by participant.

Out-of-reference range flags will be recorded as high (H) and low (L) for numerical results and did-not-match (*) for categorical results. For each laboratory test, a shift table will be developed comparing the frequency and percentage of the results at baseline (above normal (H), normal (N), or below normal (L)) with the postdose time points. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

Individual postdose chemistry or hematology results that meet Takeda's PCS criteria, including recheck, unscheduled, and ET results, will be listed and tabulated. A participant's value will be considered PCS if it meets one of the criteria described in Appendix A and if it is worse than the participant's baseline value. The number and percentages of participants in each part with at least one postdose result considered PCS will be provided. A participant mapping table will also be provided to show which participants with worsened postdose values met each category. All clinical laboratory PCS values will also be listed in by-participant data listings.

6.7.4 Vital Signs

Vital signs will be measured as described in Table 6.c:

Table 6.c Collection of Vital Signs

Parameter	Time Point			
	Study Part	Period	CRF/Listing Day and Hour	Table
Blood Pressure, Pulse Rate	Part 1	Screening		NA
		1, 2, 3	Day 1 PREDOSE Day 2 Hour 24	Baseline Hour 24
Respiration, Temperature		Screening		NA
		3	Day 2 Hour 24	NA
Blood Pressure, Pulse Rate	Part 2	Screening		NA
		1	Day 1 PREDOSE Day 2 Hour 24	Baseline Hour 24
		2	Day 5 PREDOSE Day 6 Hour 24	Baseline Hour 24
Respiration, Temperature		Screening		NA
		2	Day 6 Hour 24	NA

Time points in the CRF/Listing column are approximated/based on the protocol and it should be noted that the data listing will reflect the data found in the final participant CRFs.
If applicable, an early termination assessment will be performed.
NA = Not applicable

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for pulse rate and blood pressure results by treatment and time point. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment including rechecks taken prior to dosing of ID (maribavir) in each treatment. Postdose unscheduled or recheck assessments will not be used in analysis. Vital sign data will be listed by study part and participant.

Individual postdose vital sign results that meet Takeda's PCS criteria, including recheck, unscheduled, and ET results, will be listed and tabulated. A participant's value will be considered PCS if it meets one of the criteria described in Appendix B and if it is worse than the participant's baseline value. The number and percentages of participants in each part with at least one post-baseline result considered PCS will be provided. A participant mapping table will also be provided to show which participants with worsened post-baseline values met each category. All vital sign PCS values will also be listed in by-participant data listings.

6.7.5 12-Lead ECG

ECGs will be measured as described in Table 6.d:

Table 6.d Collection of ECG Measurements

Parameter	Time Point			
	Study Part	Period	CRF/Listing Day and Hour	Table
HR, PR, QRS, QT, QTcF, RR	Part 1	Screening		NA
		1, 2, 3	Day 1 PREDOSE Day 2 Hour 24	Baseline Hour 24
	Part 2	Screening		NA
		1	Day 1 PREDOSE Day 2 Hour 24	Baseline Hour 24
		2	Day 5 PREDOSE Day 6 Hour 24	Baseline Hour 24

Time points in the CRF/Listing column are approximated/based on the protocol and it should be noted that the data listing will reflect the data found in the final participant CRFs.
If applicable, an early termination assessment will be performed.
NA = Not applicable

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for ECG results by treatment and time point. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment including rechecks taken prior to dosing of ID in each treatment. Postdose unscheduled or recheck assessments will not be used in analysis. ECG data will be listed by participant

Individual postdose ECG results that meet Takeda's PCS criteria, including recheck, unscheduled, and ET results, will be listed and tabulated. A participant's value will be considered PCS if it meets one of the criteria described in Appendix C and if it is worse than the participant's baseline value. The number and percentages of participants in each part with at least one post-baseline result considered PCS will be provided. A participant mapping table will also be provided to show which participants with worsened post-baseline values met each category. All clinical laboratory PCS values will also be listed in by-participant data listings.

6.7.6 Palatability Assessment (Part 1 only)

Within five minutes after administration of maribavir as pediatric formulation (Treatment B and Treatment C), participants will be asked to answer a questionnaire regarding its palatability. Data collected from the palatability questionnaire will be summarized descriptively using the

Palatability Set. Percentages will be reported, based on the number of participants in the Palatability Set with any response to the corresponding question in each treatment.

6.7.7 Physical Examinations

Full physical examinations will be performed at screening, check-in and at the end of the study in each part. Additional physical examinations may be performed at other times at the discretion of the Investigator. Physical examination findings will be presented in the data listings by study part and participant.

6.7.8 Overdose

All cases of overdose will be presented in a data listing by study part and participant. Any AEs associated with overdose will be documented.

6.7.9 Extent of Exposure and Compliance

Dosing status for each participant in each period will be displayed in a table. The dates, times, and doses of maribavir will be listed by study part and participant.

6.8 Pharmacokinetic Analysis

Blood samples for assessment of plasma maribavir concentrations will be collected as outlined in Table 6.e below:

Table 6.e Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Part	Period(s)	Day	Scheduled Time (Hours)*
Maribavir	Plasma	1	1, 2, and 3	1	Predose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours postdose.
		2	1	1	Predose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours postdose.
			2	5	

*The actual dates and times of sample collection will be recorded on the source document in the CRF.

Plasma concentrations of maribavir will be listed and summarized descriptively by PK sampling time and treatment using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, and maximum. Excluded concentrations will be presented and footnoted as such in the concentration table listings, and those values will be excluded from the descriptive statistics.

Individual participant concentration-time curves will be plotted by treatment on linear and semi-log scales. The arithmetic mean profiles of the concentration-time data will be plotted by treatment on linear (with and without SD) and semi-log scales (without SD). For concentration summary statistics and arithmetic mean concentration-time plots, the nominal PK sampling time will be used. For individual participant concentration-time plots, the actual PK sampling time will be used.

The PK parameters will be calculated from plasma maribavir concentration-time profiles using NCA methods where all calculations will be based on actual sampling times after dosing. The PK parameters will be summarized by treatment for each study part using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, maximum, geom mean, and

geom CV%. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from descriptive statistics.

Part 1 – Relative Bioavailability and Food Effect Estimation

This analysis will be based on the PK set (Part 1 data).

A mixed-effects model will be applied to log-transformed C_{max}, AUC_{last}, and AUC_{∞} with treatment, period and sequence as fixed effects, and participant within sequence as a random effect. Point estimates and their associated 90% CIs will be constructed for the differences between Treatment B (test) versus Treatment A (reference), and Treatment C (test) versus Treatment B (reference). The point estimates and their associated 90% CIs will then be back transformed to provide point estimates and 90% CIs for the ratios of Treatment B (test) versus Treatment A (reference), and Treatment C (test) versus Treatment B (reference).

The same analysis will be performed for AUC_{∞_pred}.

The following SAS® code will be used to perform the analysis:

```
PROC MIXED DATA=xxx;
CLASS SEQUENCE PERIOD TREAT PARTICIPANT;
MODEL LN_PARAM = SEQUENCE PERIOD TREAT / DDFM=KR;
RANDOM PARTICIPANT(SEQUENCE);
ESTIMATE “Treatment B vs Treatment A” TREAT -1 1 0 / CL ALPHA=0.1 E;
ESTIMATE “Treatment C vs Treatment B” TREAT 0 -1 1 / CL ALPHA=0.1 E;
LSMEANS TREAT;
RUN;
```


Additionally, analysis of t_{max} and t_{lag} will be performed by nonparametric Wilcoxon Signed-Rank test. The difference of medians (treatment effect) and the corresponding 90% CI will be estimated using the Hodges-Lehmann method and Walsh Averages. The t_{max} and t_{lag} parameters will not be natural log (ln)-transformed. The comparisons of interest are the same as in the linear mixed-effects model.

Part 2 – PPI Effect Estimation

This analysis will be based on the PK set (Part 2 data).

A mixed-effects model will be applied to log-transformed C_{max}, AUC_{last}, and AUC_{∞} with treatment as a fixed effect, and participant as a random effect. Point estimates and their associated 90% CIs will be constructed for the differences between Treatment E (test) versus Treatment D (reference). The point estimates and their associated 90% CIs will then be back transformed to provide point estimates and 90% CIs for the ratios of Treatment E (test) versus Treatment D (reference).

The following SAS® code will be used to perform the analysis:

```
PROC MIXED DATA=xxx;
CLASS TREAT PARTICIPANT;
MODEL LN_PARAM = TREAT / DDFM=KR;
RANDOM PARTICIPANT;
ESTIMATE "Treatment E vs Treatment D" TREAT -1 1 / CL ALPHA=0.1 E;
LSMEANS TREAT;
RUN;
```

Additionally, analysis of t_{max} and t_{lag} will be performed by nonparametric Wilcoxon Signed-Rank test. The difference of medians (treatment effect) and the corresponding 90% CI will be estimated using the Hodges-Lehmann method and Walsh Averages. The t_{max} and t_{lag} parameters will not be ln-transformed. The comparisons of interest are the same as in the linear mixed-effects model.

6.9 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

Not applicable.

6.10 Interim Analysis

Not applicable.

6.11 Preliminary Analysis

A preliminary PK analysis will be completed as described in the CPAP and Section 6.8 of the statistical analysis plan (SAP), with the following changes: 1) QCed data will be used (not QAed); 2) nominal times (not actual sampling times) will be used to calculate PK parameters; and 3) tables and figures will be created using Phoenix® WinNonlin® Version 8.3.4 or higher.

6.12 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not applicable.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

The following PK parameters not specified in the protocol will also be calculated for plasma maribavir in Part 1 only: AUC_{∞_pred}, $AUC_{extrap}\%_{\_pred}$, $CL/F_{\_pred}$, and $V_z/F_{\_pred}$. Contrary to the protocol, PK parameters will not be calculated for subjects with less than five postdose time points with quantifiable concentrations, instead of less than five **consecutive** postdose time points with quantifiable concentrations as stated in the protocol.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Not applicable.

9.2 Data Handling Conventions

PCS values must be more extreme than those seen at baseline (e.g. if the baseline value is below the low abnormal value, then the postdose PCS value must be lower). Safety laboratory, vital sign, and ECG values will be identified as PCS using the following criteria:

Appendix A Criteria for Identification of PCS Safety Laboratory Values

Hematology—Criteria for PCS Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	SI	<100 g/L	>200 g/L
Hematocrit	SI	≤0.6x LLN	>1.3x ULN
RBC count	SI	<3x 10^{12}/L	>7.5x 10^{12}/L
WBC count	SI	<0.5 x LLN	>2x ULN
Platelet Count	SI	<100x 10^{9}/L	>500x 10^{9}/L

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Chemistry—Criteria for PCS Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	SI	--	>2x ULN
AST	SI	--	>2x ULN
GGT	SI	--	>1.5x ULN
Alkaline phosphatase	SI	--	>1.5x ULN
Total Bilirubin	SI	--	>1.5x ULN
Albumin	SI	<LLN	--
Total protein	SI	<LLN	>ULN
Creatinine	SI		>1.5x ULN
Blood urea nitrogen	SI		>14.3 mmol/L
Sodium	SI	<130 mmol/L	>150 mmol/L
Potassium	SI	<3.0 mmol/L	>5.3 mmol/L
Glucose	SI	≤4.2 mmol/L	≥6.7 mmol/L
Chloride	SI	<98 mmol/L	>106 mmol/L
Calcium	SI	≤LLN and decrease from baseline of ≥0.25mmol/L	>ULN and increase from baseline of ≥0.25mmol/L
Bicarbonate	SI	<8.0 mmol/L	

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix B Criteria for PCS Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse Rate	bpm	≤45	≥100
Systolic blood pressure	mm Hg	≤90	≥140
Diastolic blood pressure	mm Hg	≤50	≥90
Systolic blood pressure change from baseline	mm Hg	≤-20	≥20
Diastolic blood pressure change from baseline	mm Hg	≤-20	≥20

Appendix C Criteria for PCS Values for Electrocardiograms

Parameter	Unit	Lower Criteria	Upper Criteria
Heart rate	bpm	≤45	≥100
PR	msec	≤80	≥200
QRS	msec	≤80	≥180
QTcF	msec	<300	>450 and >30 msec increase from baseline (F) or >430 and >30 msec increase from baseline (M)

9.3 Analysis Software

SAS® Version 9.4 or higher will be used for all statistical analysis provided in the clinical study report.