Clinical Study Protocol

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: Version 1.0, 11 April 2023

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TAKEDA PHARMACEUTICALS

PROTOCOL

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 Identifier:	TAK-620-1024
Compound:	Maribavir (TAK-620)
Date:	11 April 2023
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1.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc. (TDCA) 95 Hayden Avenue Lexington, MA 02421 Telephone: +1 (617) 679-7000	**Compound:** Maribavir (TAK-620)
Study Identifier: TAK-620-1024	**Phase:** 1
Protocol 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 Design:

This single-center, open-label study in healthy adult participants will be conducted at Celerion in the United States (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 pharmacokinetic (PK) exposure of a single dose of maribavir pediatric formulation.

In Part 2, the gastric acid-reducing effect of multiple doses of a proton pump inhibitor (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. The schedules of assessments are shown in the Schedule of Study Procedures (Section 3.0).

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 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 treatment-emergent adverse events (TEAEs), vital signs, electrocardiograms (ECGs), and clinical laboratory evaluations.

The CRU will contact all participants (including participants who terminate the study early) 7 (± 4) days after the last dose of investigational drug (ID)/study drug by telephone or other methods per CRU standards to determine if any adverse event (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.

Study 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 PK 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 PPI rabeprazole, on the PK exposure of a single dose of 200 mg maribavir pediatric formulation administered orally as water suspension.

Study Secondary Objective:

Part 1 and Part 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.

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.

Study Participant Population: Healthy male and female participants aged 18 to 55 years, inclusive, with a

Body Mass Index (BMI) of 18.0-30.0 kg/m^2, inclusive, at the screening visit.	
Planned Number of Participants: Thirty-two (32) participants will be enrolled; 18 participants in Part 1 and 14 participants in Part 2. Participants will only participate in one study part.	**Planned Number of Sites:** 1
Dose Levels: **Part 1:** 200 mg maribavir commercial tablet or pediatric powder-for-oral suspension **Part 2:** 200 mg maribavir pediatric powder-for-oral suspension 20 mg rabeprazole tablet	**Route of Administration:** Oral
Duration of Treatment: **Part 1:** A single dose of maribavir on Day 1 in each treatment period **Part 2:** Once daily (QD) doses of rabeprazole for 5 days (Days 1 to 5) in Treatment Period 2 A single dose of maribavir on Day 1 of Treatment Period 1 and on Day 5 of Treatment Period 2	**Planned Study Duration:** Approximately 41 days (Part 1) and 43 days (Part 2) including screening period of up to 28 days and follow-up.

Criteria for Inclusion:

Participants must fulfill the following inclusion criteria before the first dose to be eligible for participation in the study:

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent to participate in the study.
3. Age 18 to 55 years, inclusive at the time of consent, at the screening visit. The date of signature of the informed consent is defined as the beginning of the screening period.
4. Male, or non-pregnant, non-breastfeeding female who agrees to comply with any applicable contraceptive requirements of the protocol or female of non-childbearing potential. Additional details are outlined in Appendix D.
5. BMI between 18.0 and 30.0 kg/m^2, inclusive with a body weight >50 kg (110 lbs), at the screening visit.
6. Healthy as determined by the Investigator or designee on the basis of screening evaluations and medical history. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry (includes thyroid-stimulating hormone [TSH] and free thyroxin [FT_4] at the screening visit), and urinalysis.
7. Hemoglobin for males ≥135.0 g/L and females ≥120.0 g/L, at the screening visit and on Day -1 of Treatment Period 1.
8. Ability to swallow a dose of maribavir or rabeprazole.

Criteria for Exclusion:

Participants must not be enrolled in the study if they meet any of the following criteria before the first dose:

1. History or presence of gastritis, gastrointestinal (GI) tract disorder, hepatic disorder or cholecystectomy, history of treated or untreated *Helicobacter pylori*, ulcer disease or other clinical condition which, in the opinion of the Investigator or designee, may affect the absorption, distribution, metabolism, or elimination of the study drugs.
2. History of any hematological, hepatic, respiratory, cardiovascular, renal, neurological or psychiatric disease, gall bladder removal, or current recurrent disease that could affect the action, absorption, or disposition of the study drugs, or clinical or laboratory assessments.
3. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or make the participant unlikely to fully complete the study, or any condition that presents undue risk from the study drugs or procedures.
4. Known or suspected intolerance or hypersensitivity to maribavir or rabeprazole (Part 2 only), closely related compounds, or any of the stated ingredients and excipients.
5. Significant illness, as judged by the Investigator or designee, within 2 weeks of the first dose of the ID.
6. Has diarrhea within 4 hours of the first dose of the ID.
7. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the first dose of the ID.
8. Within 30 days prior to the first dose of the ID:
    - Have used any investigational product (if elimination half-life is <6 days, otherwise 5 half-lives).
    - Have been enrolled in a clinical study (including vaccine studies) that, in the Investigator or designee's opinion, may impact this Takeda-sponsored study.
    - Have had any substantial changes in eating habits, as assessed by the Investigator or designee.
9. Systolic blood pressure >140 mmHg or <90 mmHg, and/or diastolic blood pressure >90 mmHg or <50 mmHg, at the screening visit.
10. Twelve-lead ECG demonstrating heart-rate corrected QT interval (QTc) >450 msec at the screening visit. If QTc exceeds 450 msec, the ECG should be repeated two more times and the average of the three QTc values should be used to determine the participant's eligibility.
11. Known history of alcohol or other substance abuse within the last year.
12. Male participants who consume more than 21 units of alcohol per week or three units per day. Female participants who consume more than 14 units of alcohol per week or two units per day (one alcohol unit = one beer or one wine [5 oz/150 mL] or one liquor [1.5 oz/40 mL] or 0.75 oz alcohol).
13. A positive screen for alcohol or drugs of abuse at the screening visit or on Day -1 of Treatment Period 1. Urine samples are to be tested for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, and phencyclidine.
14. A positive human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibody screen at the screening visit.
15. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch). Ex-users must self-report that they have stopped using tobacco for at least 3 months prior to receiving the first dose.
16. Routine consumption of more than two units of caffeine per day or participants who experience caffeine withdrawal headaches (One caffeine unit is contained in the following items: one 6-oz [180 mL] cup of

coffee, two 12-oz [360 mL] cans of cola, one 12-oz cup of tea, three 1-oz [85 g] chocolate bars). Decaffeinated coffee, tea, or cola are not considered to contain caffeine.

17. Current use of any prescription medication with the exception of hormonal contraceptives and hormonal replacement therapy. Current use is defined as use within 30 days of the first dose. Current use of any over-the-counter medication (including over-the-counter multi-vitamin, herbal, or homeopathic preparations) within 14 days of the first dose. Hormonal contraceptives (refer to Appendix D) and hormonal replacement therapy may be permitted if the female participant has been on the same stable dose for at least 3 months prior to first dose. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic interaction with maribavir and/or rabeprazole (Part 2 only).
18. Current use of antacids, PPIs, or H_2 antagonists within 14 days of the first dose, except for on-study rabeprazole.
19. Inability or unwillingness to consume 100 percent of the high-fat, high calorie meal (including participants with lactose or gluten intolerance).
20. Female participants with a positive pregnancy test at the screening visit or on Day -1 of Treatment Period 1 or who are lactating.
21. Participants on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.
22. Recent history (within 1 month) of oral/nasal cavity infections, history of gastroesophageal reflux, asthma treatment with albuterol, or zinc supplementation.
23. Participants with dry mouth syndrome or burning mouth syndrome or participants suffering from dysgeusia.

Main Criteria for Evaluation and Analyses:

Primary Endpoints (Part 1 and Part 2):

The following PK parameters in plasma will be analyzed for maribavir:

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

Secondary Endpoints (Part 1 and Part 2):

Safety endpoints will include the following:

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

Exploratory Endpoints:

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.

Part 1 and Part 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})

- Area under the curve from the last quantifiable concentration to infinity, calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞} ($AUC_{extrap\%}$)
- 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})
- Area under the concentration-time curve from time 0 to 12 (AUC_{12h})
- Projected trough concentration at 12 hours postdose after twice daily (BID) dosing (C_{τ})

Statistical Considerations:

Pharmacokinetic analysis

PK analysis will be based on the PK set. For both Part 1 and Part 2 of the study, individual maribavir plasma concentrations and PK parameters will be listed by participant and treatment and summarized by treatment (maribavir plasma concentrations and PK parameters) and nominal time (maribavir plasma concentrations). PK parameters (including but not limited to AUC_{last}, AUC_{∞}, C_{max}, $AUC_{extrap\%}$, AUC_{12h}, t_{max}, λ_z, CL/F, V_z/F, t_{lag}, $t_{½z}$, C_{12h}, and C_{τ}) will be computed using standard non-compartmental analysis (NCA) analysis. Additionally, the primary PK endpoints will be descriptively analyzed, and graphically displayed. Selected plasma PK parameters may be statistically analyzed, as appropriate. PK analysis will be fully specified in the Clinical Pharmacology Analysis Plan (CPAP).

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% confidence intervals (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 be then 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).

Additionally, analysis of t_{max} and t_{lag} will be performed by nonparametric Wilcoxon Signed-Rank test.

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 be then back transformed to provide point estimates and 90% CIs for the ratios of Treatment E (test) versus Treatment D (reference).

Additionally, analysis of t_{max} and t_{lag} will be performed by nonparametric Wilcoxon Signed-Rank test.

Safety analysis:

The safety data will be summarized descriptively for TEAEs, potentially clinically significant (PCS) clinical laboratory tests, vital signs, and 12-lead ECG. Concomitant medications will also be summarized by treatment.

Baseline will be the last assessment before the first dose. TEAEs are defined as those with a start date on or after the first dose, or with a start date before the date of first dose of maribavir but increasing in severity after the first dose.

Palatability analysis:

In Part 1, palatability data collected from the palatability questionnaire will be summarized descriptively using the Palatability Set (Part 1 only) for Treatments B and C (pediatric formulation) only. Percentages will be reported, based on the number of participants in the Palatability Set with any response to the corresponding question in each treatment.

Additional exploratory analyses may be conducted and reported separately.

Sample Size Justification:

The sample size for Part 1 and Part 2 is based on precision.

Table 11.a shows the estimated 90% 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.

As shown in Table 11.a, 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.

2.0 STUDY SCHEMATIC

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 powder-for-oral suspension under fasting conditions.

Treatment C: Maribavir single dose (200 mg) pediatric formulation administered as powder-for-oral suspension under fed conditions.

CRU: Clinical Research Unit, ID: Investigational drug, N: Sample size

Table 2.b Study Schematic for Part 2

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

Treatment D: Maribavir single dose (200 mg) pediatric formulation administered as powder-for-oral suspension.

Treatment E: Maribavir single dose (200 mg) pediatric formulation administered as powder-for-oral 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 dose, oral, fast	Day 1
B and D	Maribavir pediatric powder-for-oral suspension	200 mg (1 x 200-mg)	Single dose, oral, fast	Day 1
C	Maribavir pediatric powder-for-oral suspension	200 mg (1 x 200-mg)	Single dose, oral, fed: following a high-fat/high-calorie meal	Day 1
E	Rabeprazole tablet	20 mg (1 x 20-mg)	Once daily, oral, fast	Days 1 through Day 5
	Maribavir pediatric powder-for-oral suspension	200 mg (1 x 200-mg)	Single dose, oral, fast, 2 hours after rabeprazole dose	Day 5

3.0 SCHEDULE OF STUDY PROCEDURES

Table 3.a Relative Bioavailability and Food Effect (Part 1)

Study Procedures [a]	S [b]	Treatment Period 1 only	Study Days in Each Treatment Period [c]															ET [d]	F/U [e]
Days →		-1	1													1 or 2	2		
Hours →		C-1	0	0.08	0.25	0.5	1	1.5	2	3	4	5	6	8	12	16 [f]	24		
Administrative Procedures																			
Informed Consent	X																		
Inclusion/Exclusion Criteria	X	X																	
Medical History	X																		
Safety Evaluations																			
Physical Examination	X	X															X [g]	X	
Height	X																		
Weight	X	X																	
Vital Signs (PR and BP)	X		X [h]														X	X	
Vital Signs (T and RR)	X																X [g]	X	
12-Lead Safety ECG	X		X [h]														X	X	
Hem, Serum Chem [i], and UA	X	X	X [j]														X [g]	X [k]	
Serum Pregnancy Test (♀ only)	X	X	X [j]																
Serum FSH (PMP ♀ only)	X																		
Urine Drug and Alcohol Screen	X	X																	
HIV/Hepatitis Screen	X																		
AE Monitoring	X	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►	X
ConMeds Monitoring	X	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►	X
Study Drug Administration / PK																			
Maribavir Administration [l]			X																
Blood for Maribavir PK			X [m]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Other Procedures																			
Palatability assessment [n]				X															
Confinement in the CRU [o]		◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►	
Visit	X																		

a: For details on procedures, refer to Section 9.0.
b: Within 28 days prior to the first dosing of the investigational drug.
c: There will be a washout period of a minimum of 72 hours between each dosing.
d: To be performed prior to early termination from the study.
e: The CRU will contact all participants (including participants who terminate the study early) 7 (± 4) days after the last dose of investigational drug/study drug by telephone or other methods per CRU standards, to determine if any AE has occurred or concomitant medications have been taken since the last study visit. If clinically significant findings are observed upon discharge, participants may return to the CRU for re-evaluating per Investigator's discretion.
f: The 16-hour postdose on the day of dosing will be either on the same day or the day after dosing, depending on the time of dosing.
g: To be performed in Treatment Period 3 only.
h: To be performed within 2 hours prior to dosing.
i: Samples for serum clinical chemistry will be obtained following a fast of at least 8 hours, however, in case of dropouts or rechecks, participants may not have fasted for 8 hours prior to the serum chemistry sample is taken.
j: To be performed prior to the dosing in Treatment Period 2 and Treatment Period 3 only.
k: To be performed at early termination only if termination was due to any AE.
l: In Treatments A and B, participants will be dosed under fasting conditions. In Treatment C, participants will receive a meal 30 minutes prior to dosing; the meal will be entirely consumed within 25 minutes.
m: To be performed within 1 hour prior to maribavir dosing.
n: To be performed only in Treatments B and C, when participants will receive the pediatric formulation. The palatability questionnaire will be provided to the participants for preview during check-in.
o: Participants will be admitted to the CRU on Day -1 of Treatment Period 1, at the time indicated by the CRU, and will stay until completion of study procedures on Day 2 of Treatment Period 3, or early termination from the study.

♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, ET =Early termination, FSH = Follicle-stimulating hormone, F/U = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, PK = Pharmacokinetics, PMP = Postmenopausal, PR = Pulse rate, RR = Respiration rate, S = Screening, T = Temperature, UA = Urinalysis.

Table 3.b Gastric Acid-reducing Effect of Rabeprazole (Part 2)

Study Procedures [a]	S [b]	Study Days in Treatment Period 1 [c]														
Days →		-1	1												1 or 2	2
Hours →		C-I	0	0.25	0.5	1	1.5	2	3	4	5	6	8	12	16 [e]	24
Administrative Procedures																
Informed Consent	X															
Inclusion/Exclusion Criteria	X	X														
Medical History	X															
Safety Evaluations																
Physical Examination	X	X														
Height	X															
Weight	X	X														
Vital Signs (PR and BP)	X		X [f]													X
Vital Signs (T and RR)	X															
12-Lead Safety ECG	X		X [f]													X
Hem, Serum Chem [g], and UA	X	X														
Breath *H. pylori* Test		X														
Serum Pregnancy Test (♀ only)	X	X														
Serum FSH (PMP ♀ only)	X															
Urine Drug and Alcohol Screen	X	X														
HIV/Hepatitis Screen	X															
AE Monitoring	X	←	—	—	—	—	—	—	—	—	—	—	—	—	→	
ConMeds Monitoring	X	←	—	—	—	—	—	—	—	—	—	—	—	—	→	
Study Drug Administration																
Maribavir Administration			X													
Blood for Maribavir PK			X [k]	X	X	X	X	X	X	X	X	X	X	X	X	X
Other Procedures																
Confinement in the CRU [d]		←	—	—	—	—	—	—	—	—	—	—	—	—	→	
Visit	X															

Table 3.b Gastric Acid-reducing Effect of Rabeprazole (Part 2) (continued)

Study Procedures [a]	Study Days in Treatment Period 2 [b]																	ET [h]	F/U [i]
Days →	1	2-4	5													5 or 6	6		
Hours →			-2	0	0.25	0.5	1	1.5	2	3	4	5	6	8	12	16 [e]	24		
Safety Evaluations																			
Physical Examination																	X	X	
Vital Signs (PR and BP)				X [f]													X	X	
Vital Signs (T and RR)																	X	X	
12-Lead Safety ECG				X [f]													X	X	
Hem, Serum Chem [g], and UA	X [f]			X [f]													X	X [j]	
Serum Pregnancy Test (♀ only)	X [f]																		
Urine Drug and Alcohol Screen	X [f]																		
AE Monitoring	←																→		X
ConMeds Monitoring	←																→		X
Study Drug Administration																			
Rabeprazole Administration	X	X	X																
Maribavir Administration				X															
Blood for Maribavir PK				X [k]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Other Procedures																			
Confinement in the CRU [d]	←																→		

a: For details on procedures, refer to Section 9.0.
b: Within 28 days prior to the first dosing of the investigational drug.
c: There will be a washout period of a minimum of 72 hours between dosing in Treatment Period 1 and first dose in Treatment Period 2.
d: Participants will be admitted to the CRU on Day -1 of Treatment Period 1, at the time indicated by the CRU, and will stay until completion of study procedures on Day 6 in Treatment Period 2, or early termination from the study.
e: The 16-hour postdose on the day of maribavir dosing will be either on the same day or the day after maribavir dosing, depending on the time of maribavir dosing.
f: To be performed within 2 hours prior to dosing.
g: Samples for serum clinical chemistry will be obtained following a fast of at least 8 hours, however, in case of dropouts or rechecks, participants may not have fasted for 8 hours prior to the serum chemistry sample is taken.
h: To be performed prior to early termination from the study.
i: The CRU will contact all participant (including participants who terminate the study early) 7 (± 4) days after the last dose of investigational drug/study drug by telephone or other methods per CRU standards, to determine if any AE has occurred or concomitant medications have been taken since the last study visit. If clinically significant findings are observed upon discharge, participants may return to the CRU for re-evaluating per Investigator's discretion.
j: To be performed at early termination only if termination was due to any AE.
k: To be performed within 1 hour prior to maribavir dosing.

♀ = Females, AE = Adverse events, BP = Blood pressure, CI = Check-in, Chem = Chemistry, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, ET = Early termination, FSH = Follicle-stimulating hormone, F/U = Follow-up, *H. pylori* = *Helicobacter pylori*, Hem = Hematology, HIV = Human immunodeficiency virus, PK = Pharmacokinetics, PMP = Postmenopausal, PR = Pulse rate, RR = Respiration rate, S = Screening, T = Temperature, UA = Urinalysis.

4.0 INTRODUCTION

4.1 Maribavir Background

Maribavir (LIVTENCITY™) is a potent and selective, orally bioavailable antiviral drug with a novel mechanism of action against cytomegalovirus (CMV) [1].

LIVTENCITY™ (maribavir) is approved for the treatment of adults with post-transplant CMV infection/disease that is refractory (with or without genotypic resistance) to treatment with ganciclovir, valganciclovir, cidofovir, or foscarnet by the US Food and Drug Administration (FDA), the European Medicines Agency, Medicines and Healthcare Products Regulatory Agency (United Kingdom), Ministry of Food and Drug Safety (Republic of Korea), Health Canada, and Therapeutics Goods Administration (Australia). The US FDA approval also includes pediatric patients ≥12 years of age weighing at least 35 kg.

The current approved maribavir dosing regimen for adults is 400 mg BID, administered as 2x200 mg film-coated tablets. Maribavir tablets can be taken with or without food [1].

Clinical efficacy of maribavir has been demonstrated in one Phase 2 study and one Phase 3 study for the treatment of CMV infection or disease in adult transplant recipients, resistant or refractory to prior therapies. Maribavir had similar efficacy at clearing CMV viremia at doses ≥400 mg BID (400, 800, or 1200 mg BID) and overall exhibited a favorable safety and tolerability profile [2]. The most frequent TEAEs associated with maribavir were dysgeusia and GI TEAEs, including diarrhea, nausea, and vomiting which were generally mild or moderate.

Clinical pharmacology of maribavir in adults

Maribavir is a potent member of the benzimidazole ribosides. It is the first and only antiviral agent that targets CMV UL97 protein kinase and its natural substrates. Maribavir inhibits viral DNA assembly and egress of viral capsids from the nucleus of infected cells [3]. Maribavir is a weak base (pKa of 5.2), and it is considered a Biopharmaceutics Classification System (BCS) class II drug, with high solubility at acidic pH but moderate to low solubility in neutral pH (0.8 mg/mL in water) [4].

Following oral tablet administration, maribavir is rapidly and well absorbed with mean peak plasma concentrations (C_{max}) achieved between 1- and 3-hours postdose. Total exposure to maribavir, as measured by AUC, is approximately dose-proportional following a single dose from 50 to 1600 mg or multiple doses from 300 to 2400 mg per day, and maribavir demonstrates stationary PK. A Phase 1 study evaluating the effect of food on maribavir PK (Study TAK-620-1025) has shown that, compared to fasting conditions, low-fat/low-calorie or high-fat/high-calorie meals did not affect maribavir AUC (12.2% reduction) in a statistically significant level, and only modestly reduced C_{max} (by ~23.5%), which was not considered clinically meaningful. Maribavir displays high plasma protein binding (98% in vitro and 98.5% to 99% ex vivo), independently of plasma concentrations. The mean elimination half-life ($t_{1/2z}$) of maribavir is estimated to be between 4 and 5 hours in adult transplant patients. Maribavir is primarily eliminated by hepatic metabolism through cytochrome P450 (CYP) 3A4 and, to a

lesser extent, CYP1A2, leading to the formation of a primary metabolite, VP44469, which is much less active than maribavir in inhibition of the CMV UL97 protein. Renal clearance of maribavir is negligible (<2% of total clearance).

Clinical drug-drug interactions (DDI) studies have shown that maribavir dose adjustment is only required when maribavir is co-administered with a strong or moderate CYP3A4 inducer [5]. However, caution should be exercised when maribavir is given with concomitant sensitive substrates of CYP1A2, P-glycoprotein, breast cancer resistance protein, and immunosuppressants tacrolimus, cyclosporine, everolimus or sirolimus. In addition, the effect of concomitant administration of PPI on maribavir PK was quantified in the population PK model developed for maribavir in adults. Model-derived estimates of steady-state AUC_{τ} and C_{max} for CMV patients following 400 mg BID maribavir were approximately 10% and 22.5% lower in the presence of concomitant PPI compared to without PPI comedication. However, these gastric acid-reducing effects of PPIs are not considered clinically significant. The most current information regarding the drug metabolism, PK, efficacy, and safety of maribavir is detailed in the Investigator's Brochure (IB) for maribavir [4].

Clinical use of Maribavir in Pediatric Patients

There are currently no approved agents for the treatment of CMV infections in pediatric transplant patients <12 years of age [5]. A Phase 3 study for maribavir in children and adolescents with CMV infection/disease who have undergone a hematopoietic stem cell transplant or solid organ transplant is being planned (Study TAK-620-2004). This study will include participants of three age-based cohorts: ≥12 to <18 years (Cohort 1), ≥6 to <12 years (Cohort 2), and 0 to <6 years (Cohort 3). The dose selection in pediatric transplant participants will be based on full extrapolation, ie, matching pediatric PK exposure to that observed at the therapeutic doses in adults. Based on population PK simulations with allometrically scaled PK parameters for pediatric participants receiving maribavir tablet formulation, it is expected that 400 mg BID dosing in participants with body weight >25 kg and 200 mg BID dosing in participants with body weight from 10 to 25 kg would generate matching target PK exposures to 400 mg BID in adults. For participants in Cohort 3, there is a significant need for a pediatric specific formulation.

Maribavir has a strong and lingering bitter taste at clinically relevant doses. In order to have a palatable formulation for pediatric use, a taste-masking strategy that minimizes the availability of maribavir in the oral cavity was implemented. Two previously developed powder-for-oral suspension pediatric candidate formulations were evaluated in adult healthy participants in Study TAK-620-1019. This study was designed to be conducted in two parts. However only Part 1 of the study was conducted, as both pediatric candidate formulations had a bitter taste, with an acceptability rate lower than a preferred value of 80%. In addition, following administration of maribavir 200 mg 32.5% and 36.1% maribavir loaded powder-for-oral suspension formulations (Treatments B and C), the geometric mean C_{max} and AUC_{∞} values were 32% and 38%, and 16% and 20% lower, respectively, compared to that of maribavir tablet formulation (Treatment A), as shown in Table 4.a. Both candidate formulations were generally safe and well tolerated.

Table 4.a Statistical Comparison of Maribavir PK Parameters by Treatment - Part 1 of the Study TAK-620-1019

PK Parameter (unit)	Treatment	N	Geometric LS means	Treatment comparison	Ratio (%) of geometric LS means	90% CI of the ratio (%)
C_{max}	A	18	10.6			
(µg/mL)	B	19	7.19	B versus A	67.76	(59.50, 77.16)
	C	20	6.61	C versus A	62.29	(54.73, 70.90)
AUC_{∞}	A	18	51.2			
(h*µg/mL)	B	19	42.8	B versus A	83.52	(76.12, 91.64)
	C	20	41.2	C versus A	80.36	(73.26, 88.16)
AUC_{last}	A	18	48.7			
(h*µg/mL)	B	19	39.6	B versus A	81.27	(73.88, 89.40)
	C	20	38.0	C versus A	78.00	(70.92, 85.79)

Treatment A=maribavir 200 mg tablet; Pivotal clinical (Phase 3) formulation
Treatment B=maribavir 200 mg pediatric powder-for-oral suspension formulation, 32.5% drug loading
Treatment C=maribavir 200 mg pediatric powder-for-oral suspension formulation, 36.1% drug loading
ANOVA: analysis of variance; AUC_{∞}: area under the curve extrapolated to infinity; AUC_{last}: area under the curve from the time of dosing to the last measurable concentration; CI: confidence interval; C_{max}: maximum concentration; LS: least squares; N: sample size, PK: pharmacokinetic
Source: Study TAK-620-1019 clinical study report, Table 14.2.5.3.1

The new proposed candidate pediatric formulation which will be used in this study, consists of the same maribavir granular powder as the formulation used in the Study TAK-620-1019 (Treatment C). However additional sweetener and flavored excipients (eg, sucralose and berry citrus punch) were added to improve palatability. Prior to this study, a taste assessment study (Study TAK-620-1021) conducted in a sensory healthy panelist confirmed that the new proposed pediatric formulation provided considerably less bitter taste, although residual bitterness could persist in the aftertaste.

This improved pediatric formulation is considered more suitable for the pediatric Phase 3 study, and no further masking strategy attempts will be considered given that many options have been already explored. In this study (TAK-620-1024), the palatability of the proposed pediatric formulation will be assessed as an exploratory objective.

The maribavir pediatric formulation is designed to be reconstituted with water prior to administration to form an oral suspension suitable for younger children. Two dose strengths, compositionally proportional (ie, 50 mg and 200 mg) will be available to allow dose adjustment in pediatrics. Only the 200-mg dose strength will be tested in this study, one of the expected doses to be administered BID to children ≤6 years. Food intake and concomitantly administered PPIs (mainly omeprazole) were shown to have no clinically meaningful effects on the rate and extent of absorption of maribavir administered as the adult tablet formulation. However, considering the presence of the pH-sensitive coating polymer in addition to maribavir being a

BCS II drug, and to reduce risks of untoward effects on maribavir PK in the Phase 3 pediatric study, it will be important to evaluate the effects of food and gastric acid-reducing effect of PPI on the new pediatric formulation.

The effect of a high-fat, high-calorie meal on maribavir PK will be analyzed. The gastric acid-reducing effect of PPI will be evaluated with a PPI agent presenting minimal risk of potential metabolism-based DDI with maribavir to avoid confounding factors. Omeprazole is a commonly used PPI in pediatrics; however, it is metabolized by several CYP enzymes including CYP2C19, CYP3A4, and CYP1A2, the latter two also shared by maribavir [7]. Unlike other PPI, rabeprazole is mainly metabolized by non-enzymatic pathways [7-9]. Rabeprazole has also demonstrated similar gastric acid-reducing capacity compared to other PPI such as omeprazole [10]. Thus, to solely evaluate the gastric acid-reducing effect of PPI on maribavir PK, rabeprazole will be used in this study.

Safety Profile

Maribavir has been administered across a broad range of oral doses from 50 to 2400 mg/day. Clinical safety data has been obtained from 19 Phase 1 studies in adult healthy participants, special populations (participants with renal and hepatic impairment, and stable renal transplant recipients), and HIV-infected participants. No death or other serious adverse events (SAEs) was reported in Phase 1 studies with maribavir. The most common TEAE in single- and multiple-dose Phase 1 studies was taste disturbance (dysgeusia). ECG, vital signs, and laboratory findings did not suggest any treatment-emergent abnormalities related to maribavir. A definitive QT study in healthy participants demonstrated no clinically significant repolarization effect of maribavir administered orally at single doses of 100 mg and 1200 mg. In addition, no other significant ECG effects of maribavir were found. Maribavir (400 mg BID) was shown to increase the whole blood trough concentration of tacrolimus by 57% in a clinical drug-drug interaction study.

In two Phase 2 studies for CMV infection treatment (Studies SHP620-202 and SHP620-203) maribavir was well-tolerated with no safety concerns at all doses evaluated, ie, 400, 800, and 1200 mg BID. In Study SHP620-202, the most frequent TEAEs (occurred in ≥20% of maribavir-treated participants) were dysgeusia, followed by nausea, vomiting, diarrhea, fatigue, and anemia. In Study SHP620-203, the most frequent TEAEs (occurred in ≥20% of maribavir-treated participants) were dysgeusia, followed by nausea, diarrhea and vomiting. Analyses of clinical laboratory, vital signs, and ECG data did not identify any clinically meaningful differences across the maribavir treatment groups.

In a pivotal Phase 3 study for the treatment of CMV infection that is refractory or resistant to prior treatment (Study SHP620-303), maribavir 400 mg BID was well tolerated and safe. Dysgeusia was the most frequently reported TEAE overall. Other frequently reported TEAEs >10% included nausea, diarrhea, vomiting, fatigue, and pyrexia. The TEAE of immunosuppressant drug level increased was reported in 21 participants in the maribavir group (9.0%).

In another pivotal Phase 3 study for the treatment of CMV infection (Study SHP620-302), maribavir 400 mg BID was also well tolerated and safe. Nausea was the most frequently reported TEAE overall. Other frequently reported TEAEs >10% included diarrhea, vomiting, anaemia, neutropenia, thrombocytopenia, pyrexia, dysgeusia, and headache. TEAE of immunosuppressant drug level increased (2.9%) were also reported.

To date, maribavir has shown an overall favorable safety profile in placebo-controlled studies, open-label studies, and in studies that compared maribavir with other CMV therapies (ganciclovir, valganciclovir) for prophylaxis and for CMV treatment in hematopoietic stem-cell transplant and solid organ transplant recipients.

Refer to the latest version of the maribavir IB for the most detailed and most current information regarding the drug metabolism, PK, efficacy, and safety of maribavir [4].

4.2 Rabeprazole Background

Rabeprazole is used for the short-term (4 – 8 weeks) treatment of erosive or ulcerative esophagitis in patients with gastroesophageal reflux disease. Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole PPIs) that suppress gastric acid secretion by inhibiting the gastric H^+/K^+-ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric PPI [11].

The antisecretory effect of rabeprazole begins within 1 hour after oral administration of a 20 mg dose. The median inhibitory effect of rabeprazole on 24-hour gastric acidity is 88% of maximal after the first dose. Rabeprazole (20 mg) inhibits basal and peptone meal-stimulated acid secretion versus placebo by 86% and 95%, respectively, and increases the percent of time out of a 24-hour period that the gastric pH is >3 from 10% to 65%, after 7 days of QD dosing. This relatively prolonged pharmacodynamic action compared to the short PK $t_{½z}$ (1-2 hours) reflects the sustained inactivation of the H^+/K^+-ATPase. There were no significant changes in the PK parameters (t_{max}, C_{max}, AUC, and $t_{½z}$) following rabeprazole administration (20 mg and 40 mg, n=6) for 7 days when assessed for Day 1 and Day 7. Potential PK interactions (ie, increased or decreased drug absorption) can occur as a result of the increased gastric pH levels from rabeprazole administration [11].

Following a 20 mg oral administration, peak plasma concentrations (C_{max}) of rabeprazole occur over a range of 2.0 to 5.0 hours (t_{max}). The rabeprazole C_{max} and AUC are linear over an oral dose range of 10 mg to 40 mg. There is no appreciable accumulation when doses of 10 mg to 40 mg are administered every 24 hours; the PK of rabeprazole is not altered by multiple dosing [11].

The most common side effects with rabeprazole include pain, pharyngitis, flatulence, infection, and constipation.

Refer to the full prescribing information for more detailed background on rabeprazole [11].

4.3 Rationale for the Proposed Study

In this study, the relative bioavailability of a new maribavir pediatric candidate formulation will be compared to the approved maribavir tablet formulation, and the food effect as well as the gastric acid-reducing effect of concomitantly administered rabeprazole on the PK of maribavir in pediatric formulation in healthy adult participants will be evaluated. The results of this study will be critical to provide information relevant for further evaluation of maribavir in the youngest cohort of pediatric patients (≤6 years of age) with CMV infection/disease in the maribavir pediatric Phase 3 study (Study TAK-620-2004).

4.4 Benefit/Risk Profile

To date, maribavir has been safe and well tolerated in placebo-controlled studies, open-label studies, and in studies that compared maribavir with other CMV therapies (ganciclovir, valganciclovir) for prophylaxis and for CMV treatment in stem cell transplant and SOT patients. Always refer to the latest version of the maribavir IB for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, PK, efficacy, and safety of maribavir [9].

The dose of rabeprazole to be administered in this study is not anticipated to induce any potential risk to participants taking part in this study, as it will be administered according to the dosing recommendations found in the full prescribing information for rabeprazole [11].

There will be no direct health benefit for study participants from receipt of the study drugs. An indirect health benefit to the healthy participants enrolled in this study is the free medical tests performed at screening and during the study.

The inclusion and exclusion criteria, screening, and safety monitoring practices employed by this protocol (ie, 12-lead ECG, vital signs, clinical laboratory tests, AE questioning, and physical examination) are adequate to monitor the participant's safety.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

Not applicable.

5.2 Study Objectives

5.2.1 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 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 PPI rabeprazole, on the PK exposure of a single dose of 200 mg maribavir pediatric formulation administered orally as water suspension.

5.2.2 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.

5.2.3 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.

5.3 Endpoints

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

5.3.2 Secondary Endpoints

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

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

5.3.3 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})
- Area under the curve from the last quantifiable concentration to infinity, calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞} ($AUC_{extrap\%}$)
- 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})
- Area under the concentration-time curve from time 0 to 12 (AUC_{12h})
- Projected trough concentration at 12 hours postdose after BID dosing (C_{τ})

6.0 STUDY DESIGN AND DESCRIPTION

6.1 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. The schedules of assessments are shown in the Schedule of Study Procedures (Section 3.0).

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 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.

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.

6.2 Dose Escalation

Not applicable.

6.3 Stopping Rules

Not applicable.

6.4 Rationale for Study Design, Dose, and Endpoints

6.4.1 Rationale of Study Design

This study is being conducted to assess the relative bioavailability, food effect, and the gastric acid-reducing effect of a PPI on the PK of maribavir pediatric formulation.

The study is designed according to the FDA guidance on bioavailability and food effect studies for new drug applications (NDA) but as well to the FDA guidance entitled Evaluation of gastric-pH dependent drug interactions with acid reducing agents [12].

The study is conducted in two parts, which may be conducted concurrently.

In Part 1, participants will be randomized to treatment sequences to minimize assignment bias. There will be a washout period of a minimum of 72 hours between dosing in each treatment period. The washout period is considered sufficient to prevent carryover effects of the preceding treatment.

In Part 2, participants will receive both treatments in a single fixed order. Rabeprazole has a prolonged effect on acid secretion due to the irreversible nature of its binding to H^+/K^+-ATPase pump. Therefore rabeprazole will be administered in Treatment Period 2 to prevent the risk of confounding carryover of residual gastric acid suppression effect on the PK evaluation of maribavir alone.

A crossover design is used to reduce the residual variability as every participant acts as their own control. There will be a washout period of a minimum of 72 hours between dosing in Treatment Period 1 and the first dosing in Treatment Period 2. The washout period is considered sufficient to prevent carryover effects of the preceding treatment.

6.4.2 Rationale for Dose

A single dose of 200 mg maribavir pediatric candidate formulation will be used as this is one of the expected doses to be administered BID to children ≤6 years.

A dose of 20 mg rabeprazole will be used as this is within the recommended dose range per labeling of ACIPHEX® [11]. Rabeprazole 20 mg inhibits basal and peptone meal-stimulated acid secretion by 86% and 95%, respectively, versus placebo, and increases the percent of time out of a 24-hour period that the gastric pH is >3 from 10% to 65%, following QD dosing for 7 days. In additional, following 5 days of QD 20 mg rabeprazole, the intragastric pH was maintained above 4.0 for a mean of 12.1 hour [11]. This study will therefore evaluate the effect of rabeprazole on the PK of maribavir following 5 days of rabeprazole 20 mg QD. Maribavir will be administered 2 hours after rabeprazole dosing, which is within the range of rabeprazole t_{max}, to maximize the inhibitory effect on gastric acid excretion on the day of coadministration.

6.4.3 Rationale for Endpoints

6.4.3.1 Pharmacokinetic Endpoints

The PK endpoints are standard for this type of study.

6.4.3.2 Safety Endpoints

The key safety endpoints are typical for Phase 1 studies and will be assessed through monitoring of TEAEs, vital signs, ECGs, laboratory assessments, and physical examinations.

6.4.4 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the critical component is the blood collection for plasma concentrations of maribavir, and is to be collected as close to the scheduled times defined in this protocol as possible.

6.5 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

The dose and administration of maribavir and rabeprazole to any participant may not be modified. If necessary, a participant may be discontinued for the reasons described in Section 7.5 and Section 7.6.

6.6 Study Beginning and End/Completion

6.6.1 Definition of Beginning of the Study

The beginning of the study will be defined as the beginning of the screening (ie, signing of the informed consent form [ICF]) by the first participant.

6.6.2 Definition of End of the Study

The end of study is defined as the date of the last scheduled procedure. If there is an unresolved AE or concomitant medication, or an assessment date that is after the end of study, the date of study completion will be inclusive of that resolution/assessment date.

A study participant is considered to have completed the study if the participant completed dosing, did not discontinue or terminate the study early, and has completed most of the scheduled procedures in all periods including the last scheduled procedure ie, the follow-up contact, as outlined in the Schedule of Study Procedures (Section 3.0).

6.6.3 Definition of Study Discontinuation

Celerion reserves the right to terminate the study in the interest of participant welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

6.6.4 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination from the study:

- New safety information of maribavir and/or rabeprazole that indicates a change in the known product risk-benefit profile, such that the risk is no longer acceptable for study participants.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.

6.6.5 Criteria for Premature Termination or Suspension of a Site

Not applicable.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS

7.1 Inclusion Criteria

Participants must fulfill the following inclusion criteria before the first dose to be eligible for participation in the study:

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent to participate in the study.
3. Age 18 to 55 years, inclusive at the time of consent, at the screening visit. The date of signature of the informed consent is defined as the beginning of the screening period.
4. Male, or non-pregnant, non-breastfeeding female who agrees to comply with any applicable contraceptive requirements of the protocol or female of non-childbearing potential. Additional details are outlined in Appendix D.
5. BMI between 18.0 and 30.0 kg/m^2, inclusive with a body weight >50 kg (110 lbs), at the screening visit.
6. Healthy as determined by the Investigator or designee on the basis of screening evaluations and medical history. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry (includes TSH and FT_4 at the screening visit), and urinalysis.
7. Hemoglobin for males ≥135.0 g/L and females ≥120.0 g/L, at the screening visit and on Day -1 of Treatment Period 1.
8. Ability to swallow a dose of maribavir or rabeprazole.

7.2 Exclusion Criteria

Participants must not be enrolled in the study if they meet any of the following criteria before the first dose:

1. History or presence of gastritis, GI tract disorder, hepatic disorder or cholecystectomy, history of treated or untreated *Helicobacter pylori*, ulcer disease or other clinical condition which, in the opinion of the Investigator or designee, may affect the absorption, distribution, metabolism, or elimination of the study drugs.
2. History of any hematological, hepatic, respiratory, cardiovascular, renal, neurological or psychiatric disease, gall bladder removal, or current recurrent disease that could affect the action, absorption, or disposition of the study drugs, or clinical or laboratory assessments.

3. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or make the participant unlikely to fully complete the study, or any condition that presents undue risk from the study drugs or procedures.
4. Known or suspected intolerance or hypersensitivity to maribavir or rabeprazole (Part 2 only), closely related compounds, or any of the stated ingredients and excipients.
5. Significant illness, as judged by the Investigator or designee, within 2 weeks of the first dose of the ID.
6. Has diarrhea within 4 hours of the first dose of the ID.
7. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the first dose of the ID.
8. Within 30 days prior to the first dose of the ID:
    - Have used any investigational product (if elimination half-life is <6 days, otherwise 5 half-lives).
    - Have been enrolled in a clinical study (including vaccine studies) that, in the Investigator or designee's opinion, may impact this Takeda-sponsored study.
    - Have had any substantial changes in eating habits, as assessed by the Investigator or designee.
9. Systolic blood pressure >140 mmHg or <90 mmHg, and/or diastolic blood pressure >90 mmHg or <50 mmHg, at the screening visit.
10. Twelve lead-ECG demonstrating QTc >450 msec at the screening visit. If QTc exceeds 450 msec, the ECG should be repeated two more times and the average of the three QTc values should be used to determine the participant's eligibility.
11. Known history of alcohol or other substance abuse within the last year.
12. Male participants who consume more than 21 units of alcohol per week or three units per day. Female participants who consume more than 14 units of alcohol per week or two units per day (one alcohol unit = one beer or one wine [5 oz/150 mL] or one liquor [1.5 oz/40 mL] or 0.75 oz alcohol).
13. A positive screen for alcohol or drugs of abuse at the screening visit or on Day -1 of Treatment Period 1. Urine samples are to be tested for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, and phencyclidine.
14. A positive HIV, HBsAg, or HCV antibody screen at the screening visit.
15. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch). Ex-users must self-report that they have stopped using tobacco for at least 3 months prior to receiving the first dose.

16. Routine consumption of more than two units of caffeine per day or participants who experience caffeine withdrawal headaches (One caffeine unit is contained in the following items: one 6-oz [180 mL] cup of coffee, two 12-oz [360 mL] cans of cola, one 12-oz cup of tea, three 1-oz [85 g] chocolate bars). Decaffeinated coffee, tea, or cola are not considered to contain caffeine.
17. Current use of any prescription medication with the exception of hormonal contraceptives and hormonal replacement therapy. Current use is defined as use within 30 days of the first dose. Current use of any over-the-counter medication (including over-the-counter multi-vitamin, herbal, or homeopathic preparations) within 14 days of the first dose. Hormonal contraceptives (refer to Appendix D) and hormonal replacement therapy may be permitted if the female participant has been on the same stable dose for at least 3 months prior to first dose. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic interaction with maribavir and/or rabeprazole (Part 2 only).
18. Current use of antacids, PPIs, or H_2 antagonists within 14 days of the first dose, except for on-study rabeprazole.
19. Inability or unwillingness to consume 100 percent of the high-fat, high-calorie meal (including participants with lactose or gluten intolerance).
20. Female participants with a positive pregnancy test at the screening visit or on Day -1 of Treatment Period 1 or who are lactating.
21. Participants on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.
22. Recent history (within 1 month) of oral/nasal cavity infections, history of gastroesophageal reflux, asthma treatment with albuterol, or zinc supplementation.
23. Participants with dry mouth syndrome or burning mouth syndrome or participants suffering from dysgeusia.

7.3 Excluded Medications, Supplements, Dietary Products

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 7.2. After the first dose, acetaminophen (up to 2 g per 24-hour period) may be administered at the discretion of the Investigator or designee. Hormonal contraceptives (refer to Appendix D) and hormonal replacement medication may be permitted if the female participant has been on the same stable dose for at least 3 months prior to the first dose.

If deviations occur, the Investigator or designee in consultation with the Sponsor if needed will decide on a case-by-case basis whether the participant may continue participation in the study.

All medications taken by participants during the course of the study will be recorded.

Use of excluded agents (prescription or non-prescription) or dietary products is outlined in Table 7.a and Section 7.4.

Table 7.a Excluded Medications, Supplements, and Dietary Products

Category	Prohibited Between Screening and the First Dosing (Day -28 to predose [Day 1 of Treatment Period 1])	Prohibited After the First Dosing (Day 1) to Follow-Up
Alcohol	From 48 hours prior to the first dosing.	From the first dosing until the end of PK collection in Treatment Period 3 (Part 1) and Treatment Period 2 (Part 2).
Xanthine and/or caffeine	From 72 hours prior to the first dosing.	
Medications	See Section 7.1and Section 7.2.	See Section 7.1 and Section 7.2.
Nicotine- and tobacco-containing products	From 3 months prior to the first dosing.	From the first dosing until the end of PK collection in Treatment Period 3 (Part 1) and Treatment Period 2 (Part 2).
Food		
Grapefruit/Seville orange	From 14 days prior to the first dosing.	From the first dosing until the end of PK collection in Treatment Period 3 (Part 1) and Treatment Period 2 (Part 2).
Pine nuts	From 7 days prior to the first dosing.	

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Water (except water provided with each dosing) will be restricted between one hour prior to and one hour after each dosing, but will be allowed *ad libitum* at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

In Treatments A, B, and D, participants will fast overnight for at least 10 hours prior to dosing. Participants will continue the fast for at least four hours postdose.

In Treatment C, participants will fast overnight for at least 10 hours until 30 minutes prior to their scheduled morning dose, when they will be given a high-fat/high-calorie meal, as presented in Table 7.b which will be entirely consumed within 25 minutes. Participants will fast for at least four hours postdose.

In Treatment E, participants will fast overnight for at least 10 hours prior to maribavir dosing on Day 5. Participants will continue the fast for at least four hours post maribavir dose. For all other doses in Treatment Period 2, participants will be required to fast for at least one hour prior to rabeprazole dosing and until at least two hours after rabeprazole dosing.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, participants will be required to fast from all food and drink (including gum, mints, etc). Only water will be allowed between meals and snacks.

Each meal and/or snacks served at the CRU will be standardized and will be similar in caloric content and composition (except for the meal served as part of Treatment C) and will be taken at approximately the same time in each treatment period.

Table 7.b Examples of High-Fat/High-Calorie Meals and Breakdown of Calories and Contents

	High-Fat/High-Calorie Meal (Treatment C)
Total calories (kCal)	800-1000
Protein calories (kCal) (% of total calories; weight)	150 (19%; 38 grams)
Carbohydrate calories (kCal) (% of total calories; weight)	250 (31%; 63 grams)
Fat calories (kCal) (% of total calories; weight)	500-600 (50%; 55-65 grams)
Example of breakfast	• Eight ounces of whole milk • Two eggs fried in butter • Two strips of bacon • Two slices of toast with butter • Four ounces of hash brown potatoes (This meal's fat content accounts for approximately 50% of total kCal)
The high-fat/high-calorie meal proposed here for this study is based on FDA-recommended high-fat meal [13].	

7.4.2 Activity

Participants will remain ambulatory or seated upright for the first four hours post maribavir dose, except when they are supine or semi reclined for study procedures. There is no posture restriction around the dosing of rabeprazole when administered alone.

However, should AEs occur at any time, participants may be placed in an appropriate position or will be permitted to lie down on their right side.

Participants will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

7.5 Criteria for Discontinuation or Withdrawal of a Participant

The primary reason for discontinuation or withdrawal of the participant from the study or maribavir or rabeprazole dosing should be recorded in the case report form (CRF) using the following categories

1. AE: The participant has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the participant's health or the participant is unwilling to continue because of the AE.

   Liver Function Test (LFT) Abnormalities:

   Maribavir or rabeprazole should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a participant's laboratory profile has returned to normal/baseline status, see Section 9.2.8), if the following circumstances occur at any time during treatment:

   - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN), or
   - ALT or AST >5 × ULN and persists for more than two weeks, or
   - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN, or
   - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
2. Significant protocol deviation: The discovery post-enrollment that the participant failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the participant's health.
3. Lost to follow-up: Attempts to contact the participants were unsuccessful. Attempts to contact the participant must be documented in the participant's source documents.
4. Voluntary withdrawal: The participant (or participant's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the CRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category). If a participant chooses to withdraw from study participation due to personal concerns related to the Coronavirus disease 2019 (COVID-19) pandemic (other than a COVID-19-related AE), this should be specified as the reason for participant withdrawal in the CRF.
5. Study termination: The Sponsor, Institutional Review Board (IRB), or regulatory agency terminates the study.
6. Pregnancy: as described in Appendix D.

7. Participants may be withdrawn from the study by the Investigator or designee for the following reasons:
    - Difficulties in blood collection.
    - Positive urine drug or alcohol test.
8. Other. The specific reasons for discontinuation should be entered into the CRF including unavoidable circumstances such as COVID-19. Participants may be withdrawn from the study at any time at the discretion of the Investigator or Sponsor for safety reasons which should be entered into the CRFs.

7.6 Procedures for Discontinuation or Withdrawal of a Participant

The Investigator may discontinue a participant's study participation at any time during the study when the participant meets the study termination criteria described in Section 7.5. In addition, a participant may discontinue his or her participation without giving a reason at any time during the study. Should a participant's participation be discontinued, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures scheduled for the end-of-study or early termination as described in Section 3.0.

7.7 Participant Replacement

Replacement of discontinued or withdrawn participants due to any reason will be assessed on a case-by-case basis by the Sponsor and Investigator to ensure a minimum of 12 PK-evaluable participants complete the study in each study part.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Investigational Drug

Product Name:	Maribavir (TAK-620)
Strength:	200-mg
Dose:	200 mg
Dosage Form/Formulation:	Tablet (commercial formulation)
	Pediatric powder-for-oral suspension formulation
Dosing Regimen:	Single dose
Route of Administration:	Oral

Interacting Drug (Part 2 only)

Product Name:	Rabeprazole
Strength:	20-mg
Dose:	20 mg
Dosage Form/Formulation:	Tablet
Dosing regimen:	Multiple dose (QD)
Route of Administration:	Oral
Preference for generic or brand name:	Generic.

8.1.1 Clinical Study Drug Labeling

Maribavir and rabeprazole containers will be affixed with a clinical label in accordance with local regulatory requirements.

8.1.2 Clinical Study Drug Inventory and Storage

The Sponsor will supply sufficient quantities of maribavir to allow completion of this study. Celerion will supply sufficient quantities of rabeprazole to allow completion of this study (Part 2).

The same lot number will be used throughout the study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report. Study drugs will be stored according to the product labels provided with the product.

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied.

8.1.3 Clinical Study Drug Blinding

This is an open-label study.

8.1.4 Randomization Code Creation and Storage (Part 1)

In Part 1, a computerized randomization scheme will be created by a Celerion statistician. Treatments A, B, and C will be randomized to one of six sequences as indicated in Table 8.a.

Table 8.a Randomization Sequences in Part 1

Sequences	Number of participants (N)	Treatment Period 1	Treatment Period 2	Treatment Period 3
1	3	A	B	C
2	3	A	C	B
3	3	B	A	C
4	3	B	C	A
5	3	C	A	B
6	3	C	B	A

Treatment A: Maribavir single dose (200 mg) administered as commercial tablet under fasting conditions.
Treatment B: Maribavir single dose (200 mg) administered as powder-for-oral suspension under fasting conditions.
Treatment C: Maribavir single dose (200 mg) administered as powder-for-oral suspension under fed conditions.

8.1.5 Assignment to Treatments (Part 2)

Each participant will be assigned a unique identification number upon at the screening visit. Participants who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number, different from the screening number, and will receive the corresponding product.

Participants will receive each treatment on one occasion.

8.1.6 Clinical Study Blind Maintenance/Unblinding Procedure

Not applicable

8.1.7 Accountability and Destruction of Sponsor-Supplied Drugs

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drug will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

9.0 STUDY PROCEDURES

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the participants in non-technical terms. Participants will be required to read, sign, and date an ICF, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Participants will be given a copy of their signed ICF.

9.1.1.1 Assignment of Screening and Randomization Numbers

Each participant will be assigned a unique identification number upon screening. Participants who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number at the time of the first dose, different from the screening number and will receive the corresponding product, according to a randomization sequence (Section 8.1.4).

If replacement participants are used, the replacement participant number will be 100 more than the original (eg, Participant No. 1201 will replace Participant No. 1101).

9.1.1.2 Study Drug Assignment

All participants will receive the treatments as detailed in Section 8.1.

9.1.2 Inclusion and Exclusion

Please refer to Section 7.1 and Section 7.2.

9.1.3 Medical History/Demography

Medical history and demographic data, including name, sex, age, race, ethnicity, and history of tobacco use will be recorded.

9.1.4 Concomitant Medications

Concomitant medications will be prohibited as listed in Section 7.3. All medications taken by participants during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

The Schedule of Study Procedures (Section 3.0) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the Investigator or designee and/or the Sponsor for reasons related to participant safety.

For this study, collection of blood for maribavir PK is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior to or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

9.2.1 Full Physical Exam

A full physical examination will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Additional physical examinations may be performed at other times, if deemed necessary by the Investigator or designee.

9.2.2 Height and Weight

Body height (cm) and weight (kg) will be reported as outlined in the Schedule of Study Procedures (Section 3.0).

9.2.3 BMI

BMI will be calculated based on the height and weight measured at screening.

9.2.4 Vital Signs

Single measurements of temperature, respiration rate, blood pressure, and pulse rate, will be measured as outlined in the Schedule of Study Procedures (Section 3.0). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure and pulse rate measurements will be performed with participants in a supine position, except when they are semi-reclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the Investigator or designee. Participants should be in the appropriate position for at least five minutes prior to obtaining vital signs.

Blood pressure and pulse rate will be measured within two hours prior to Day 1 dosing in each treatment period for the predose time point. At all other predose time points, vital signs will be collected within two hours prior to dosing. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

9.2.5 12-Lead ECG

Single 12-lead ECGs will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Additional ECGs may be taken at any other times, if deemed necessary by the Investigator or designee.

At screening, if QTc exceeds 450 msec, the ECG should be repeated two more times and the average of the three QTc values should be used to determine the participant's eligibility.

ECGs will be performed with participants in a supine position. All ECG tracings will be reviewed by the Investigator or designee. The participant must be resting in the supine position for at least five minutes prior to collecting the ECG.

At all predose time points, ECGs will be collected within two hours prior to dosing. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

9.2.6 Study Drug Administration

The study drugs will be provided as described in Section 8.1.

Treatments are described in Table 2.c.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each participant, as appropriate.

All tablets will be administered with approximately 240 mL of water. When maribavir pediatric powder-for-oral suspension formulation is administered, a total of approximately 240 mL of water will be used, taking into account the volume of maribavir pediatric powder-for-oral suspension (20 mL) as described in the pharmacy manual.

Participants will be instructed not to crush, split, or chew the tablets.

Dosing should occur at approximately the same time in each treatment period. For Treatment C, a meal will be provided 30 minutes prior to dosing. For Treatment E, doses of rabeprazole on Days 2-5 will be administered ±1 hour of the time of rabeprazole dosing on Day 1.

The exact clock time of dosing will be recorded.

A qualified designee will be responsible for monitoring the administration of the assigned doses. For tablets, a mouth check will be performed by the qualified designee to ensure that the participants have swallowed the study drugs. Once a participant has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the participant's mouth. Participant's hands will also be verified to ensure that the study drug was ingested.

9.2.7 AE Monitoring

Participants will be monitored throughout the study for TEAEs and/or procedures as described in Section 10.0.

9.2.8 Laboratory Procedures and Assessments

All tests listed below will be performed as outlined in the Schedule of Study Procedures (Section 3.0). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator or designee.

9.2.8.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Hemoglobin	Red blood cell count
Hematocrit	Platelet count
Total and differential leukocyte count	

Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, participants may not have fasted for 8 hours prior to when the serum chemistry sample being taken.

Chemistry evaluations will consist of the following standard chemistry panel:

Blood Urea Nitrogen	Albumin
Bilirubin (total and direct)	Sodium
Alkaline phosphatase	Potassium
AST	Chloride
ALT	Glucose (fasting)
FT_4 **	Creatinine *
TSH **	

* At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

** At screening only

Urinalysis

Urinalysis will consist of the following tests:

pH	Bilirubin
Specific gravity	Blood *
Protein *	Nitrite *
Glucose	Urobilinogen
Ketones	Leukocyte esterase *

* If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

Other

HIV test	Urine drug screen - Opiates (includes morphine, heroin [diacetylmorphine], codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone) - Amphetamines - Barbiturates - Benzodiazepines - Cocaine - Cannabinoids - Methadone - Phencyclidine
HBsAg	
HCV	
Urine alcohol screen	
Serum pregnancy test (for females only)	
Follicle stimulating hormone (FSH; for postmenopausal females only)	
COVID-19 (Severe acute respiratory syndrome-Coronavirus-1 [SARS-CoV-2] polymerase chain reaction test or equivalent)	

9.3 PK Samples

Samples for maribavir PK assessment will be collected as outlined in the Schedule of Study Procedures (Section 3.0).

Instructions for PK sample collection, processing, and shipping will be provided in separate documents.

Primary specimen collection parameters are provided in Table 9.a and allowed windows for PK sample collection are provided in Table 9.b.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for PK	Blood	Plasma	Plasma sample for PK analysis	Mandatory

Table 9.b PK Sampling Collection Window

Sample Collection Time	Sampling Window
Predose	< -1 hour
>0 - ≤4 hours postdose	± 5 minutes
>4 - ≤24 hours postdose	± 15 minutes

9.3.1 PK Measurements

Samples from all participants will be analyzed even if the participants do not complete the study. Samples for determination of maribavir in plasma will be analyzed using validated bioanalytical methods.

PK parameters of maribavir will be calculated from the individual concentration-time profiles from all evaluable participants using NCA methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

9.3.1.1 Plasma for PK Measurements

The following PK parameters will be calculated from plasma concentrations of maribavir, unless otherwise specified:

AUC_{last}:	Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration.
AUC_{∞}:	Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
AUC_{12h}:	Area under the concentration-time curve from time 0 to 12 hours postdose.
$AUC_{extrap\%}$:	Area under the curve from the last quantifiable concentration to infinity, calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞}.
CL/F:	Apparent clearance after oral administration, calculated using the observed value of the last quantifiable concentration.
C_{max}:	Maximum observed concentration.
C_{12h}:	Concentration at 12 hours postdose.
C_{τ}:	Projected trough concentration at 12 hours postdose after BID dosing.
t_{max}:	Time to first occurrence of C_{max}.
t_{lag}:	Lag time to first quantifiable concentration in plasma.
λ_z:	Terminal disposition phase rate constant.
$t_{½z}$:	Terminal disposition phase half-life.
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.

No value for AUC_{∞}, $AUC_{extrap\%}$, CL/F, V_z/F, λ_z, or $t_{½z}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

PK parameters will not be calculated for subjects with less than five consecutive postdose time points with quantifiable concentrations.

Additional PK parameters may be estimated as appropriate.

9.3.2 Biomarker Measurements

Not applicable.

9.3.3 PGx Measurements

Not applicable.

9.4 Palatability

In Part 1, all participants who receive the maribavir pediatric formulation will undergo a palatability assessment as outlined in the Schedule of Study Procedures (Section 3.0).

Each participant performing the palatability evaluation will verbally respond to a series of questions asked by a trained clinical staff member utilizing the participant's fluent language (ie, English or U.S. Spanish). Participant will be isolated from other participants during the evaluation session and will be asked not to talk amongst themselves to discuss results to not influence their responses.

9.5 Confinement

Participants will be housed on Day -1 of Treatment Period 1, at the time indicated by the CRU, until completion of study procedures on Day 2 of Treatment Period 3 (Part 1) and Day 6 of Treatment Period 2 (Part 2) as outlined in the Schedule of Study Procedures (Section 3.0).

At all times, a participant may be required to remain at the CRU for longer at the discretion of the Investigator or designee.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation participant who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of maribavir or rabeprazole or a concomitant medication.
- Be considered unfavorable by the Investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc.) should NOT be recorded as an AE unless related to a study procedure. However, if the participant experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a participant has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, Investigators should ensure that the AE term recorded captures the change from Baseline in the condition (eg, "worsening of…").
- If a participant has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the participant experiences a worsening or complication of an AE after the first administration of maribavir or rabeprazole or after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the participant experiences a change in the severity of an AE that is not associated with a change in study drug, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the participant's medical condition should not be recorded as AEs but should be documented in the participant's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of ID/study drug, to or by a study participant, at a dose above that which is assigned to that individual participant according to the study protocol. It is up to the Investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the (e)CRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the participant should be treated symptomatically.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

COVID-19-related disease and COVID-19 pneumonia should be reported as Medically Significant AE.

AEs that fulfill one or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Section 10.1 and Section 10.1.1).

10.1.2 Adverse Events of Special Interest

Adverse events of special interest (AESIs) for maribavir include:

- Dysgeusia
- GI-related events (ie, nausea, vomiting, and diarrhea).

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild:	An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate:	An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe:	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning Causality of AEs

The relationship of each AE to the study drug will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

In addition, relationship (causality) to COVID-19 should be determined for all AEs. The relationship should be assessed as related if the Investigator considers that there is reasonable possibility that an event is due to COVID-19. Otherwise, the relationship should be assessed as not related.

Similarly, relationship (causality) to COVID-19 vaccines should be determined for all AEs. The relationship should be assessed as related if the Investigator considers that there is reasonable possibility that an event is due to COVID-19 vaccines. Otherwise, the relationship should be assessed as not related. If the AE has relationship to vaccination, specific verbatim term should be used, eg, post-vaccination fever, vaccination site burning.

In addition, if the causality assessment done by the Investigator determines that AEs are related or possible related to COVID-19 or the COVID-19 vaccine, the events should be assessed as not related to the study drug. If the AE is related to COVID-19 vaccination, specific verbatim term(s) should be used, eg, post-vaccination fever, vaccination site burning.

10.2.3 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the participant and/or Investigator.

10.2.4 End Date

The end date of the AE is the date at which the participant recovered, the event resolved but with sequelae or the participant died.

10.2.5 Pattern of Adverse Event (Frequency)

Episodic AEs (eg, headache) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.2.6 Action Taken With Study Treatment

- Drug withdrawn – the study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping the study drug
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – the study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the participant died, dosing with the study drug had not yet started or dosing with the study drug was already stopped before the onset of the AE.

10.2.7 Outcome

- Recovered/resolved – participant returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the participant died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the participant died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/resolved with sequelae – the participant recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the participant's participation in the study.

10.2.8 Collection and Reporting of AEs, SAEs, AESIs, and Abnormal LFTs

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, AESIs, and Abnormal LFTs) will commence at the time the participant signs the informed consent. Routine collection of AEs will continue until the follow-up contact on Day 7 (±4) days, after the last dose. For participants who discontinue prior to the administration of the study drug, AEs will be followed until the participant discontinues study participation.

10.2.8.2 Reporting AEs

At each treatment period, the Investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling?" may be asked. Participants may report AEs occurring at any other time during the study. Participants experiencing an SAE prior to the first exposure to maribavir must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin prior to the first exposure to the study drug, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All participants experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the CRF, whether or not the Investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (Investigator's opinion of the causal relationship between the event and administration of the study drug).
- Relationship to COVID-19.
- Relationship to COVID-19 vaccine.
- Action taken with study drug.
- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

When an SAE occurs through the AE collection period it should be reported according to the procedure outlined below:

A Takeda SAE form must be completed, in English and signed by the Investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Participant identification number.
- Investigator's name.
- Name of the study drug.
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 14.1.1.

Any SAE spontaneously reported to the Investigator following the AE collection period should be reported to the Sponsor if considered related to study participation.

Reporting of SAEs that begin before first administration of the study drug will follow the same procedure for SAEs occurring on treatment.

SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the Investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.2.8.4 Reporting AESIs

AESIs for maribavir include dysgeusia and GI-related events (ie, nausea, vomiting, and diarrhea).

10.2.8.5 Reporting of Abnormal LFTs

If a participant is noted to have ALT or AST elevated >3×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases CRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a participant is noted to have ALT or AST >3×ULN and total bilirubin >2×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.8.3. The Investigator must contact the Medical Monitor to discuss the relevant participant details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.2.8 must also be performed. In addition, an LFT Increases CRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

10.2.9 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, Investigators, and IRBs in accordance with national regulations. Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required

by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an ID or that would be sufficient to consider changes in the ID administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

Detailed methodology for data summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

11.1.1 Analysis Sets

11.1.1.1 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 NCA will be included in PK set.

11.1.1.2 Safety Set

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

11.1.1.3 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.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Continuous demographic data (ie, age, weight, height, and BMI) will be listed and summarized using appropriate summary statistics. Categorical demographic data (ie, gender, race, and ethnicity) will also be listed and tabulated.

11.1.3 PK Analysis

PK analysis will be based on the PK set. For both Part 1 and Part 2 of the study, individual maribavir plasma concentrations and PK parameters will be listed by participant and treatment and summarized by treatment (maribavir plasma concentrations and PK parameters) and nominal time (maribavir plasma concentrations). PK parameters (including but not limited to AUC_{last}, AUC_{∞}, C_{max}, $AUC_{extrap\%}$, AUC_{12h}, t_{max}, λ_z, CL/F, V_z/F, t_{lag}, $t_{½z}$, C_{12h}, and C_{τ}) will be computed using standard NCA analysis. Additionally, the primary PK endpoints will be descriptively analyzed, and graphically displayed. Selected plasma PK parameters may be statistically analyzed, if appropriate. PK analysis will be fully specified in the CPAP.

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 be then 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).

Additionally, analysis of t_{max} and t_{lag} will be performed by nonparametric Wilcoxon Signed-Rank test.

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 be then back transformed to provide point estimates and 90% CIs for the ratios of Treatment E (test) versus Treatment D (reference).

Additionally, analysis of t_{max} and t_{lag} will be performed by nonparametric Wilcoxon Signed-Rank test.

11.1.4 Pharmacodynamic Analysis

Not applicable.

11.1.5 Safety Analysis

Dosing dates and times will be listed by participant.

Safety analysis will be based on safety data set.

TEAEs will be tabulated. Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

11.1.5.1 AEs

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities® (MedDRA®) available at Celerion and summarized by treatment for the number of participants reporting the TEAE and the number of TEAEs reported. Summaries in terms of severity, seriousness, and relationship to maribavir and/or rabeprazole will also be provided. Treatment-emergent SAEs and AESIs will be summarized separately in a similar fashion. A

by-participant AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

TEAEs are defined as those with a start date on or after the first dose, or with a start date before the date of first dose of maribavir but increasing in severity after the first dose.

11.1.5.2 Clinical Laboratory Evaluation

Clinical laboratory results will be summarized by treatment and point of collection time and a shift table describing out of normal range shifts will be provided.

Individual results meeting PCS criteria for safety clinical laboratory assessments will be listed and summarized. The number and percentages of participants with at least one postdose result considered as a PCS will be provided. More detail will be provided in the SAP.

11.1.5.3 Vital Signs

Vital signs assessments will be summarized by treatment and point of time of collection.

Vital signs results meeting PCS criteria for vital signs assessments will be listed and summarized. The number and percentages of participants with at least one postdose result considered as a PCS will be provided. More detail will be provided in the SAP.

11.1.5.4 Other Safety Parameters

ECGs will be summarized by treatment and point of time of collection. ECG results meeting PCS criteria for safety ECGs will be listed and summarized. The number and percentages of participants with at least one postdose result considered as a PCS will be provided. More detail will be provided in the SAP.

Medical history, including concurrent conditions, will be coded using the MedDRA® and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary and will be summarized by treatment.

11.1.6 Exploratory Analysis

In Part 1, palatability data collected from the palatability questionnaire will be summarized descriptively using the Palatability Set for Treatments B and C (pediatric formulation) only. Percentages will be reported, based on the number of participants in the Palatability Set with any response to the corresponding question in each treatment.

Additional exploratory analyses may be conducted and reported separately.

11.2 Interim Analysis and Criteria for Early Termination

Not applicable.

11.3 Determination of Sample Size

The sample size for Part 1 and Part 2 is based on precision.

Table 11.a shows the estimated 90% CI for the 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.

Table 11.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	
	$AUC_{0-\infty}$ 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_{∞}: area under the curve 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.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Due to COVID-19, monitoring visits may also be conducted remotely. Source documents will be reviewed for verification of data recorded on the CRFs. Source documents are defined as original documents, data, and records. The Investigator and study site guarantee access to source documents by the Sponsor or its designee and by the IRB.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, participant medical records, informed consent documentation, and review of CRFs and associated source documents. It is important that the Investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The Investigator or study personnel should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study participants. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the Investigator should consult with the sponsor or designee (and IRB) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

For COVID-19-related protocol deviations, the specific protocol deviation, the reason for the deviation, and the relationship to COVID-19 should be documented using CRU standard processes.

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the participant, or confound interpretation of primary study assessment.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies (such as FDA), including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare Products Regulatory Agency - MHRA, the Pharmaceuticals and Medical Devices Agency of Japan - PMDA). If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The Investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP [14]. Each Investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

13.1 IRB Approval

IRBs must be constituted according to the applicable state and federal/local requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The Sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the IB, a copy of the ICF, a copy of the palatability questionnaire, and, if applicable, participant recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and participant informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study (ie, before shipment of the Sponsor-supplied drug or study specific screening activity). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The Sponsor will ship drug/notify site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from competent authority to begin the study. Until the site receives drug/notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by participants, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the Investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the Sponsor or its designee.

Participant incentives should not exert undue influence for participation. Payments to participants must be approved by the IRB and Sponsor.

13.2 Participant Information, Informed Consent, and Participant Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the participant's personal and personal health information for purposes of conducting the study. The ICF and the participant information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The Investigator is responsible for the preparation, content, and IRB approval of the ICF and, if applicable, the participant authorization form. The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) must be approved by both the IRB and the Sponsor prior to use.

The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) must be written in a language fully comprehensible to the prospective participant. It is the responsibility of the Investigator to explain the detailed elements of the ICF, participant authorization form (if applicable), and participant information sheet (if applicable) to the participant. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. In the event the participant is not capable of rendering adequate written informed consent, then the participant's legally acceptable representative may provide such consent for the participant in accordance with applicable laws and regulations.

The participant, or the participant's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the participant, or the participant's legally acceptable representative, determines he or she will participate in the study, then the ICF and participant authorization form (if applicable) must be signed and dated by the participant, or the participant's legally acceptable representative, at the time of consent and prior to the participant entering into the study. The participant or the participant's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The Investigator must also sign and date the ICF and participant authorization (if applicable) at the time of consent and prior to participant entering into the study; however, the Sponsor may allow a designee of the Investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, participant authorization form (if applicable), and participant information sheet (if applicable) will be stored in the Investigator's site file. The Investigator must document the date the participant signs the informed consent in the participant's medical record. Copies of the signed ICF, the signed participant authorization form (if applicable), and participant information sheet (if applicable) shall be given to the participant.

All revised ICFs must be reviewed and signed by relevant participants or the relevant participant's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the participant's medical record, and the participant should receive a copy of the revised ICF.

13.3 Participant Confidentiality

The Sponsor and designees affirm and uphold the principle of the participant's right to protection against invasion of privacy. Throughout this study, a participant's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited participant attributes, such as sex, age, or date of birth, and participant initials may be used to verify the participant and accuracy of the participant's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, MHRA, PMDA), the Sponsor's designated auditors, and the appropriate IRBs to review the participant's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports. Access to a participant's original medical records requires the specific authorization of the participant as part of the informed consent process (see Section 13.2).

Copies of any participant source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, participant name, address, and other identifier fields not collected on the participant's CRF).

13.4 Publication, Disclosure, and Clinical Study Registration Policy

13.4.1 Publication and Disclosure

The Investigator is obliged to provide the Sponsor with complete test results and all data derived by the Investigator from the study. During and after the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Study Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it Sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with Investigator's city, state (for Americas / United States Investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the Investigator name, address, and phone number to the callers requesting trial information. Once participants receive Investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established participant screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the Sponsor.

Any Investigator who objects to the Sponsor providing this information to callers must provide the Sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Study Results Disclosure

Takeda will post the results of clinical studies on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

13.5 Insurance and Compensation for Injury

Each participant in the study must be insured in accordance with the regulations applicable to the site where the participant is participating. If a local underwriter is required, then the Sponsor or Sponsor's designee will obtain clinical study insurance against the risk of injury to study participants. Refer to the study site agreement regarding the Sponsor's policy on participant compensation and treatment for injury. If the Investigator has questions regarding this policy, he or she should contact the Sponsor or Sponsor's designee.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. Fax: +1 484-595-8155 Email: GPSE@Takeda.com

14.1.2 INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the IB, package insert and any other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council on Harmonisation, E6[R2] Good Clinical Practice: Consolidated Guideline [14].
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix A).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

14.1.3 Study-Related Responsibilities

The Sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified for specific study-related activities will perform these activities in full or in partnership with the Sponsor.

14.1.4 List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{12h}	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
$AUC_{extrap\%}$	Percent of AUC_{∞} extrapolated
AUC_{last}	Area under the concentration-time curve, from time 0 to the last quantifiable concentration.
BCS	Biopharmaceutics Classification System
BID	Twice daily
BMI	Body mass index
bpm	Beats per minute
C_{12h}	Concentration at 12 hours postdose
C_{τ}	Projected concentration at 12 hours postdose
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent clearance after oral administration
cm	Centimeter
C_{max}	Maximum observed concentration
CMV	Cytomegalovirus
COVID-19	Coronavirus disease 2019
CPAP	Clinical Pharmacology Analysis Plan
CRF	Case report form
CRU	Clinical Research Unit
CSR	Clinical study report
CV	Coefficient of variance
CYP	Cytochrome P450
DDI	Drug-drug interactions
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram

FSH	Follicle stimulating hormone
FT_4	Free thyroxine
g	Gram
GCP	Good Clinical Practice
GI	Gastrointestinal
GMR	Geometric mean ratio
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Investigational drug
IRB	Institutional Review Board
kg	Kilogram
L	Liter
LFT	Liver function test
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
NCA	Non-compartmental analysis
NDA	New drug applications
PCS	Potentially clinically significant
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PPI	Proton pump inhibitor
QD	once daily
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction

$t_{½z}$	Terminal disposition phase half-life
TEAE	Treatment-emergent adverse event
t_{lag}	Lag time to first quantifiable concentration in plasma
t_{max}	Time to first occurrence of C_{max}
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
USA	United States of America
V_z/F	Apparent volume of distribution during the terminal disposition phase after oral administration
WHO	World Health Organization
λ_z	Terminal disposition phase rate constant

15.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the MedDRA®. Drugs will be coded using the WHO Drug Dictionary.

15.1 CRFs (Electronic and Paper)

Celerion standard CRFs will be supplied. CRFs are produced, stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the Investigator. The final signed CRFs are provided to the Sponsor in the format as decided upon between Celerion and the Sponsor (eg, electronically, compact disc, flashdrive, Secure File Transfer Protocol). This will be documented in the Data Management Plan (if applicable).

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The Investigator must review the CRFs for completeness and accuracy and must sign and date the appropriate CRFs as indicated. Furthermore, the Investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRFs.

After the lock of the clinical study database, any change of, modification of, or addition to the data on the CRFs should be made by the Investigator with use of change and modification records of the CRFs. The Investigator must review the data change for completeness and accuracy, and must sign and date.

CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The Sponsor or its designee will be permitted to review the participant's medical and hospital records pertinent to the study to ensure accuracy of the CRFs. The completed CRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the Sponsor.

15.2 Record Retention

The Investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating participants, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, participant authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of CRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Any source documentation printed on

degradable thermal sensitive paper should be photocopied by the site and filed with the original in the participant's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the Investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the Investigator and Sponsor.

Refer to the Clinical Study Site Agreement for the Sponsor's requirements on record retention. The Investigator and the head of the institution should contact and receive written approval from the Sponsor before disposing of any such documents.

16.0 REFERENCES

1. LIVTENCITY™ (maribavir milled tablets): US Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215596lbl.pdf.
2. Avery RK, Alain S, Alexander BD, Blumberg EA, Chemaly RF, et al. Maribavir for refractory cytomegalovirus infections with or without resistance post-transplant: results from a phase 3 randomized clinical trial. Clin Infect Dis. 2022 Sept 10;75(4):690-701. doi:10.1093/cid/ciab988.
3. Biron KK, Harvey RJ, Chamberlain SC, Good SS, Smith A, et al. 2002. Potent and selective inhibition of human cytomegalovirus replication by 1263W94, a benzimidazole L-riboside with a unique mode of action. Antimicrob Agents Chemother; 2002 Aug;46(8):2365-72. doi: 10.1128/AAC.46.8.2365-2372.2002.
4. SHP620 (Maribavir). Investigator's Brochure Edition 22.0 (24 Jan 2023).
5. LIVTENCITY EPAR SmPC. Summary of Product characteristics. https://www.ema.europa.eu/en/documents/product-information/livtencity-epar-product-information_en.pdf.
6. Genentech, Inc. Valcyte (valganciclovir hydrochloride) [package insert]. U.S. Food and Drug Administration website. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=dc548ff9-e8ea-4d6e-b9b4-e31f53ac4078 Revised June 2017. Accessed January 10, 2023.
7. Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors--emphasis on rabeprazole. Aliment Pharmacol Ther. 1999 Aug;13 Suppl 3:27-36. doi: 10.1046/j.1365-2036.1999.00022.
8. Vo L, Simonian HP, Doma S, Fisher RS, Parkman HP. The effect of rabeprazole on regional gastric acidity and the postprandial cardia/gastro-oesophageal junction acid layer in normal subjects: a randomized, double-blind, placebo-controlled study. Aliment Pharmacol Ther; 2005 Jun 1;21(11):1321-30. doi: 10.1111/j.1365-2036.2005.02489.x.
9. Dash RP, Rais R, Srinivas NR. Stereoselective and non-stereoselective pharmacokinetics of rabeprazole – an overview. Xenobiotica; 2018 Apr;48(4):422-432.
10. Miner JR P, Katz PO, Chen Y, Sostek M. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. Am J Gastroenterol; 2003 Dec;98(12):2616-20. doi: 10.1111/j.1572-0241.2003.08783.
11. ACIPHEX® (rabeprazole sodium) Delayed-Release Tablets, for oral use, prescribing information published on FDA website (document revised: 12/2014). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020973s035204736s005lbl.pdf.
12. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Guidance for Industry: Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing

Agents: Study Design, Data Analysis, and Clinical Implications. March 2023. Available at: https://www.fda.gov/media/166156/download.

13. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Guidance for Industry: Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations. June 2022. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-effects-food-drugs-inds-and-ndas-clinical-pharmacology-considerationsand.
14. ICH harmonized guideline Integrated addendum to ICH 6[R1]: Guideline for Good Clinical Practice E6[R2], Step 4 version, November 2016. Available at: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf.

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the Investigator may participate in this study.

The Investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
1. Personally conduct or supervise the staff that will assist in the protocol.
2. If the Investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the Investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential participants, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to participants. Make at least yearly reports on the progress of the study to the IRB, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each participant who participates in the study, and document the date of consent in the participant's medical chart. Valid informed consent is the most current version approved by the IRB. Each ICF should contain a participant authorization section that describes the uses and disclosures of a participant's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a participant authorization, then the Investigator must obtain a separate participant authorization form from each participant or the participant's legally acceptable representative.

9. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
12. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix B Elements of the Participant Informed Consent

In seeking informed consent, the following information shall be provided to each participant:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the participant's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of participants involved in the study.
7. A description of the participant's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the participant may receive.
11. A description of any reasonably foreseeable risks or discomforts to the participant and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the participant or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the participant will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB, and the monitor may inspect the records. By signing a written ICF, the participant or the participant's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the participant for participating in the study.
17. The anticipated expenses, if any, to the participant for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (Investigator), participant's rights, and IRB and whom to contact in the event of a research-related injury to the participant.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant otherwise is entitled, and that the participant or the participant's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.
20. The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant.
21. A statement that the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the study.
22. The foreseeable circumstances or reasons under which the participant's participation in the study may be terminated.
23. A written participant authorization (either contained within the ICF or provided as a separate document) describing to the participant the contemplated and permissible uses and disclosures of the participant's personal information (including personal health information) for purposes of conducting the study. The participant authorization must contain the following statements regarding the uses and disclosures of the participant's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer participants the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the ID(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that participants agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the participant's identity will remain confidential in the event that study results are published.

24. Female participants of childbearing potential (eg, nonsterilized, premenopausal female participants) who are sexually active must use highly effective contraception (as defined in the informed consent) from signing the informed consent and throughout the duration of the study, and for 1 month after the last dose. If a participant is found to be pregnant during study, dosing will be discontinued.
25. Male participants must use an effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 3 months after the last dose.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

Takeda will collect and retain personal information of Investigator, including his or her name, address, and other personally identifiable information. In addition, Investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of Investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting Investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in Investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Participants

From signing of informed consent, throughout the duration of the study, and for 3 months after last dose of study drug, nonsterilized** male participants who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

Female Participants and Their Males Partners

From signing of informed consent, throughout the duration of the study, and for 1 month after last dose of study drug, female participants of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective/effective method of contraception (from the list below). In addition they must be advised not to donate ova during this period.

Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential, ie fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as “those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:

   Non-Hormonal Methods:

   - Intrauterine device.
   - Bilateral tubal occlusion.

- Vasectomy, provided that partner is the sole sexual partner of the study participant and that the vasectomised partner has received medical assessment of the surgical success.
- True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the participant. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose of study drug until 1 month after last dose of study drug for female participants of childbearing potential* and 3 months after the last dose of study drug for male participants.

Hormonal Methods:

- Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;

  Oral

  Intravaginal (eg, ring)

  Transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation1 initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;

  Oral

  Injectable

  Implantable

  Intrauterine device

2. In addition, effective methods of contraception (there may be a higher than 1% failure rate) are:
   - Female participant: Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom).
   - Female participant: Progestogen only hormonal contraception, where inhibition of ovulation is not the primary mode of action PLUS condom with or without spermicide.
   - Male participant with female partner of childbearing potential: A barrier method (condom with or without spermicidal cream or jelly).
3. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.

- Withdrawal.
- No method at all.
- Use of female and male condoms together.
- Cap/diaphragm/sponge without spermicide and without condom.
- Sexual abstinence is NOT an acceptable method of contraception, unless it is true sexual abstinence.

4. Participants will be provided with information on highly effective/effective methods of contraception as part of the participant informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
5. During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all participants (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:

   f) contraceptive requirements of the study

   g) reasons for use of barrier methods (ie, condom) in males with pregnant partners

   h) assessment of participant compliance through questions such as

      i. Have you used the contraception consistently and correctly since the last visit?

      ii. Have you forgotten to use contraception since the last visit?

      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")

      iv. Is there a chance you could be pregnant?

6. In addition to a negative serum hCG pregnancy test at the screening visit, female participants of childbearing potential must also have confirmed menses in the month before first dose of study drug (no delayed menses; with the exception of female participants using a protocol acceptable contraception method that has a known side effect of delayed or irregular menses), and, a negative serum hCG pregnancy test prior to receiving any dose of study drugs. In addition, participants must also have a negative serum hCG pregnancy test within 28 days prior to receiving first dose of study drug.

General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- contraceptive requirements of the study.
- reasons for use of barrier methods (ie, condom) in males with pregnant partners.

- assessment of participant compliance through questions such as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
  - Is there a chance you could be pregnant?

Pregnancy

If a female participant is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male participant during the study or for 3 months after the last dose, should also be recorded following authorization from the participant's partner.

If the female participant and/or female partner of a male participant agrees to the primary care physician being informed, the Investigator should notify the primary care physician of her or her male partner (ie, male participant) participation in a clinical study at the time she became pregnant and provide details of study drug the female participant or her male partner (ie, male participant) received.

All pregnancies, including female partners of male participants, in participants on active study drug (including comparator, if applicable) will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the Sponsor. An evaluation after the birth of the child will also be conducted.