Clinical Study Protocol

NCT Number: NCT05382104

Title: A Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food on Maribavir (TAK-620) Pharmacokinetics in Healthy Adult Participants

Study Number: TAK-620-1025

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TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food on Maribavir (TAK-620) Pharmacokinetics in Healthy Adult Participants

Study Identifier: TAK-620-1025

Compound: Maribavir (TAK-620)

Date: 27 April 2022

Version/Amendment Number: Initial version

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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-620-1025	**Phase:** 1
Protocol Title: A Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food on Maribavir (TAK-620) Pharmacokinetics in Healthy Adult Participants	
Study Design: This is a single-center, open-label, single-dose, randomized, 3-period, 6-sequence, crossover study in healthy adult participants. Study schematic and dose regimens are shown in Table 2.a and Table 2.b. The schedule of assessments is shown in Schedule of Study Procedures (Section 3.0). A single dose of 400 mg maribavir (commercial [marketed] tablet formulation) will be administered orally under 3 different feeding conditions: 1) Fasting (Treatment A), 2) Fed following a low-fat/low-calorie meal (Treatment B), and 3) Fed following a high-fat/high-calorie meal (Treatment C). There will be a washout period of a minimum of 72 hours between each investigational drug (ID) dosing. Pharmacokinetic (PK) sample collections will be conducted predose and up to 36 hours postdose in each treatment period. Safety and tolerability will be assessed throughout the study by treatment-emergent adverse events (TEAEs), vital signs, electrocardiograms (ECGs), and clinical laboratory evaluations. The clinical research unit (CRU) will contact all participants (including participants who terminate the study early) 7 (±4) days after the last ID administration by telephone or other methods per CRU standards to determine if any adverse event (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-evaluation per Investigator's discretion.	
Study Primary Objectives: To assess the relative bioavailability of a single oral dose of 400 mg maribavir commercial (marketed) tablet formulation administered with a low-fat/low-calorie meal relative to administration under fasting conditions. To assess the relative bioavailability of a single oral dose of 400 mg maribavir commercial (marketed) tablet formulation administered with a high-fat/high calorie meal relative to administration under fasting conditions. **Study Secondary Objective:** To evaluate the safety and tolerability of a single oral dose of 400 mg maribavir commercial (marketed) tablet formulation when administered under fasting conditions, with a low-fat/low-calorie meal and with a high-fat/high-calorie meal. **Study Exploratory Objective:** To evaluate other PK parameters of a single oral dose of 400 mg maribavir commercial (marketed) tablet formulation when administered under fasting conditions, with a low-fat/low-calorie meal and with a high-fat/high-calorie meal.	
Study Participant Population: Healthy male and female participants aged 19 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 (30) participants will be enrolled.	**Planned Number of Sites:** 1
Dose Level: 400 mg (2 x 200 mg) commercial (marketed) tablet	**Route of Administration:** Oral
Duration of Treatment: Single-dose	**Planned Study Duration:** Approximately 42 days 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 of the ID 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 19-55 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. 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 thyroxine [FT_4] at the screening visit), and urinalysis.
6. 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.
7. BMI between 18.0 and 30.0 kg/m^2, inclusive with a body weight >50 kg (110 lbs), at the screening visit.
8. Ability to swallow a dose of the ID.

Criteria for Exclusion:

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

1. History or presence of gastritis, gastrointestinal (GI) tract, 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 ID.
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 ID, 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 ID or procedures.
4. Known or suspected intolerance or hypersensitivity to the ID, 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 diastolic blood pressure >90 mmHg or <50 mmHg, at the screening visit.
10. Twelve-lead ECG demonstrating corrected QT interval (QTc) >450 msec at the screening visit. If QTc exceeds 450 msec, the ECG should be repeated 2 more times and the average of the 3 QTc values should be used to determine the 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 3 units per day. Female participants who consume more than 14 units of alcohol per week or 2 units per day (1 alcohol unit=1 beer or 1 wine [5 oz/150 mL] or 1 liquor [1.5 oz/40 mL] or 0.75 oz alcohol).
13. A positive 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 antibody (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 of the ID.
16. Routine consumption of more than 2 units of caffeine per day or participants who experience caffeine withdrawal headaches (1 caffeine unit is contained in the following items: one 6 oz [180 mL] cup of coffee, two 12 oz [360 mL] cans of cola, one 12 oz cup of tea, three 1 oz [85 g] chocolate bars). Decaffeinated coffee, tea, or cola are not considered to contain caffeine.
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 of the ID. 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 of the ID. Hormonal contraceptives (refer to Appendix D) and hormonal replacement therapy may be permitted if the participant has been on the same stable dose for at least 3 months prior to first dose of the ID. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic interaction with the ID.
18. Current use of antacids, proton pump inhibitors, or H_2 antagonists within 14 days of the first dose of the ID.
19. Inability or unwillingness to consume 100 percent of high-fat meal or low-fat meal (including participants with lactose or gluten intolerance).
20. Recent history (within 1 month) of oral/nasal cavity infections, history of gastroesophageal reflux, asthma treatment with albuterol, or zinc supplementation.
21. Participants with dry mouth syndrome or burning mouth syndrome or participants suffering from dysgeusia.

Main Criteria for Evaluation and Analyses:

Primary Endpoints:

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:

- 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:

Exploratory PK endpoints include (if applicable, but are not limited to) additional PK parameters for maribavir as follows:

- Concentration at 12 hours postdose (C_{12})
- Area under the concentration-time curve from time 0 to 12 (AUC_{12})
- 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})

Statistical Considerations:

Pharmacokinetic analysis:

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 (C_{max}, AUC_{last}, AUC_{∞}, AUC_{12}, $AUC_{extrap\%}$, C_{12}, t_{max}, λ_z, $t_{½z}$, CL/F, V_z/F, and t_{lag}) will be computed using standard non-compartmental analysis (NCA). Actual time of sampling will be used to calculate the PK parameters. The PK endpoints will be presented descriptively. All individual concentration data and PK parameters will be listed with summary statistics such as geometric mean, median, arithmetic mean, standard deviation (SD), coefficient of variation (CV), minimum and maximum. Individual plasma concentration/time curves will be presented in linear/linear and log/linear scale. At least 3 PK time points within the terminal log-linear phase will be used to estimate the terminal rate constant for each participant in each treatment period.

The appropriate PK analysis will be fully specified in the Clinical Pharmacology Analysis Plan (CPAP).

Estimation of food-effect:

A mixed-effect 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 (low-fat/low-calorie meal) versus Treatment A (fasting), and Treatment C (high-fat/high-calorie meal) versus Treatment A (fasting). 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 (low-fat/low-calorie meal) versus

Treatment A (fasting) and Treatment C (high-fat/high-calorie meal) versus Treatment A (fasting).

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, and potentially clinically significant values for clinical laboratory tests, vital signs, 12-lead ECG, and use of concomitant medications by treatment. Baseline will be the last assessment before the first dose of the ID. TEAEs are defined as those with a start date on or after the first dose of the ID, or with a start date before the date of first dose of the ID but increasing in severity after the first dose of the ID.

Exploratory analysis:

In a separate analysis, both non-compartmental and compartmental PK modeling will be used to project the steady-state AUC_{12}, C_{max} and C_{12} after theoretical regimens of multiple twice daily (BID) oral doses of 400 mg maribavir commercial (marketed) formulation under different dosing conditions (Treatment A, B, or C). The results from this analysis will not be listed in the clinical study report (CSR) and will be detailed in a separate report.

Additional exploratory analyses may be conducted and reported separately.

Sample Size Justification:

Thirty (30) participants will be enrolled to account for possible dropouts.

A total of 24 participants should complete all treatment periods of the study.

Sample size calculations is performed using R package PowerTOST and were based on the following:

- The intra-participant CV was assumed at 0.166 and 0.218, respectively for AUC_{∞} and C_{max}, which were estimated from the 90% CIs of the geometric mean ratio (GMR) of AUC_{∞}, and C_{max} in Study 1263-104.
- Reference data set is AUC_{∞} or C_{max} under fasting conditions; test data set is AUC_{∞} or C_{max} under fed conditions
- Assumed GMR for Test / Reference: 0.80, 0.85, 0.90, 0.95, or 1.00
- The estimated 90% CIs of the GMRs at 0.90, with N = 24, is within (0.80, 1.25) for both AUC_{∞} and C_{max}.

2.0 STUDY SCHEMATIC

Table 2.a Study Schematic

Pretreatment	Predose Assessments	Treatment Periods 1-2-3 (a)		Study Exit	Follow-up (b)
Screening	**Check-in**	**Dosing and Safety and PK Assessments**	**Safety and PK Assessments**	Day 2 of Treatment Period 3	7 (±4) days after last dose
Day -28 to first dosing of ID	Day -1 of Treatment Period 1	Day 1	Day 2		
	◄- - - - - - - Confinement (c) - - - - - -►				

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

(b) The CRU will contact all participants (including participants who terminate the study early) 7 (± 4) days after the last ID administration 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-evaluation per Investigator's discretion.

(c) Participants will start the confinement on Day -1 of Treatment Period 1 and will remain confined until Day 2 of Treatment Period 3. Participants may be admitted earlier for Coronavirus disease 2019 (COVID-19) testing not related to study protocol as per CRU requirements.

Table 2.b Study Treatments for Study Investigational Drug

Treatment	Investigational Drug	Dose	Dose Regimen	Days on Investigational Drug
Treatment A	Maribavir commercial (marketed) tablet formulation	400 mg (2 x 200-mg)	Single dose, oral, fast	Day 1
Treatment B	Maribavir commercial (marketed) tablet formulation	400 mg (2 x 200-mg)	Single dose, oral, fed: following a low-fat/low-calorie meal	Day 1
Treatment C	Maribavir commercial (marketed) tablet formulation	400 mg (2 x 200-mg)	Single dose, oral, fed: following a high-fat/high-calorie meal	Day 1

3.0 SCHEDULE OF STUDY PROCEDURES

Study Procedures [a]	**S** [b]	**Treatment Period 1 Only**	**Study Days in Each Treatment Period** [c]																**EOP3 or ET** [d]	**FU** [e]
Days →		**-1**	**1**														**2**	**2**		
Hours →		**C-1** [f]	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**3.5**	**4**	**5**	**6**	**8**	**12**	**16** [g]	**24**	**36**		
Administrative Procedures																				
Informed Consent	X																			
Inclusion/Exclusion Criteria	X	X																		
Medical History	X																			
Safety Evaluations																				
Physical Examination	X																		X	
Height	X																			
Weight	X	X																	X	
Vital Signs (PR and BP)	X		X [h]														X		X	
Vital Signs (T and RR)	X																		X	
12-Lead Safety ECG	X		X [h]							X [k]							X		X	
Hem, Serum Chem [i], and UA	X	X	X [j]														X [k]		X [l]	
FT_4 and TSH	X																			
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---------->																		X
ConMeds Monitoring	X	<----------X---------->																		
ID Administration / PK																				
Maribavir Administration			X [m]																	
Blood for Maribavir PK			X [n]	X	X	X	X	X	X		X	X	X	X	X	X	X	X		
Other Procedures																				
Confinement in the CRU [f]		<----------X---------->																		
Visit	X																			

a. The study procedures will be detailed in Section 9.0.
b. Screening will start within 28 days prior to the first ID administration on Day 1 of Treatment Period 1.
c. There will be a washout period of a minimum of 72 hours between each ID dosing.
d. To be performed at the end of Treatment Period 3 or 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 ID administration 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-evaluation per Investigator's discretion.
f. Participants will be admitted to the CRU 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. Participants may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol, as per CRU requirements.
g. The 16-hour postdose time point will be either on Day 1 or Day 2, depending on the time of dosing on Day 1.
h. To be performed within 2 hours prior to the ID 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 ID dosing, in Treatment Period 2 and Treatment Period 3 only.
k. To be performed in Treatment Period 3 only.
l. To be performed at early termination only, if termination was due to any AE.
m. In Treatment A, participants will be dosed fasted. In Treatments B and C, participants will receive a meal 30 minutes prior to dosing the ID; the meal will be entirely consumed within 30 minutes.
n. To be performed prior to the ID dosing.

Abbreviations: ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, ConMeds = Concomitant medication, COVID-19 = Coronavirus disease 2010, CRU = Clinical research unit, ECG = Electrocardiogram, EOP3 or ET = End of Treatment Period 3 or early termination, FSH = Follicle-stimulating hormone, FT_4 = Free thyroxine, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, ID = Investigational drug, PK = Pharmacokinetics, PMP = Premenopausal, PR = Pulse rate, RR = Respiration rate, S = Screening, T = Temperature, TSH = Thyroid stimulating hormone, UA = Urinalysis.

4.0 INTRODUCTION

4.1 Background

Maribavir is a potent and selective, orally bioavailable antiviral drug with a novel mechanism of action against cytomegalovirus (CMV) [1] and a favorable non-clinical and clinical safety profile. It is a potent member of a new class of drugs, the benzimidazole ribosides [2]. In side-by-side *in vitro* assays, it is 3- to 20-fold more potent than ganciclovir and cidofovir and at least 100-fold more potent than foscarnet [3-4]. Unlike currently available anti-CMV agents that inhibit CMV deoxyribonucleic acid (DNA) polymerase, maribavir inhibits viral DNA assembly and also inhibits egress of viral capsids from the nucleus of infected cells [2-7]. In both *in vitro* and *in vivo* studies, strains of CMV resistant to ganciclovir, foscarnet, or cidofovir, or resistant to combinations of these drugs, remained sensitive to maribavir.

LIVTENCITY (maribavir) is approved by the United States (US) Food and Drug Administration (FDA) for the treatment of adults and pediatric patients (12 years of age and older and weighing at least 35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet; the approved dosing regimen is 400 mg twice daily [8]. Prior to maribavir, no therapies were approved for the treatment of CMV infection or CMV disease in transplant recipients nor for CMV infection or disease that is resistant or refractory to currently available therapies. Maribavir's clinical efficacy has been demonstrated in two Phase 2 dose ranging clinical trials in adults and one Phase 3 clinical trial for the treatment of CMV infection or disease in transplant recipients, including those infections resistant or refractory to ganciclovir, valganciclovir, foscarnet, or cidofovir.

Previous Clinical Studies on the Effect of Food on Maribavir

Various maribavir solid oral formulations (capsule and tablet formulations I, II, III and IV) have been used in several Phase 1 studies over the course of maribavir clinical development. Tablet II was used in the dose-ranging Phase 2 studies, while Tablet IV was used in the pivotal Phase 3 studies. Tablet I and Tablet II were bioequivalent (Study 1263-104). Based on the cross-study analysis of data from studies 1263-104 and TAK-620-1019 which compared Tablet II and Tablet IV maribavir formulations following single dose administration, maribavir AUCs were similar, however relative bioavailability data have not been generated. Tablet II used unmilled maribavir drug substance while Tablet IV used milled particles. Two clinical studies were conducted to evaluate the food effects with varying fat content on the PK and relative bioavailability of maribavir after single oral administration of the Tablet II (Study 1263-104) and capsule formulations (Study CMAB1002). No food effect study has been performed with maribavir Tablet IV and commercial formulation.

Study 1263-104 was an open-label, single-dose, randomized, three-way crossover study in healthy male and female adult participants to evaluate the relative bioavailability of maribavir Tablet II relative to maribavir Tablet I and the effect of food on the bioavailability of the maribavir Tablet II (Study 1263-104 CSR and Goldwater et al., 2009 [9]).

Randomly assigned participants to 1 of 6 treatment sequence groups (5 participants per sequence) received the following 3 treatments (A, B, and C): maribavir 400 mg (4×100 mg) Tablet I - "fasted" (Treatment A); maribavir 400 mg (2×200 mg) Tablet II –"fasted" (Treatment B); and maribavir 400 mg (2×200 mg) Tablet II-"fed" (Treatment C; in the original clinical study report for Study 1263-104, the meal was referred to as "moderately high-fat breakfast"). Treatment A and B were received after overnight fast, while Treatment C was received after moderate fat breakfast. The treatments were separated by a 1-week washout period.

Out of 30 enrolled participants 28 participants completed all 3 treatments in this study. Blood samples for maribavir PK assessment were collected up to 24 hours postdose. Maribavir PK parameters for participants who received a single oral dose of maribavir 400 mg (Tablet II) under fed (moderate-fat breakfast) and fasted conditions are presented in Table 4.a. When maribavir Tablet II was administered with food, median t_{max} was prolonged from 1.5 hours to 2 hours, and C_{max} decreased 28%. However, the AUC_{last} and AUC_{∞} values, although 14% lower with food, were considered equivalent (90% CI within the 0.80 to 1.25 no-effect range).

Table 4.a Statistical Analysis of the Pharmacokinetic Parameters of Maribavir Following a Single Oral Dose of 400 mg Maribavir Tablet II Under Fed and Fasted Conditions (Study 1263-104)

Parameter	Tablet II Fed (N=29)	Tablet II Fasted (N=29)	Tablet II Fed / Tablet II Fasted[a] (90% CI) (N=28)
AUC_{last} (µg*h/mL)[b]	81.6	95.0	0.860 (0.802, 0.922)
AUC_{∞} (µg*h/mL)[b]	85.6	99.0	0.864 (0.804, 0.929)
C_{max} (µg/mL)[b]	11.4	15.9	0.722 (0.656, 0.793)
t_{max} (h)[c]	2.0 (1.0, 4.0)	1.5 (1.0, 4.0)	N/A[d]

ANOVA=analysis of variance; AUC=area under the plasma concentration-versus-time curve from time 0 to the last measurable concentration (AUC_{last}) and from time 0 to infinity (AUC_{∞}); CI=confidence interval; C_{max}=maximum measured plasma concentration; N/A=not applicable; t_{max}=time to C_{max}
[a] Least squares geometric mean ratio.
[b] Geometric mean.
[c] Median (minimum, maximum).
[d] The p-value for the ranked values of t_{max} from the ANOVA model was <0.001.
Source: Study 1263-104 CSR, Table 10.2.3.2, Table 10.2.3.3, and Table 10.2.3.4.

In summary, based on a modest decrease in C_{max} and no effect on AUC, controlling the timing of low-fat breakfast intake with respect to oral administration of maribavir Tablet II is not needed.

Study CMAB1002 was a single-dose, double-blind, randomized, placebo-controlled, dose-escalation study conducted in HIV-infected adult male participants (Study CMAB1002 CSR and Wang et al., 2003 [10]). During the initial 4 treatment periods, each participant received under fasted conditions 3 escalating single doses of maribavir capsules (100, 400, 800, or 1600 mg, administered as 100 mg capsules) and 1 dose of matching placebo, according to a

randomized assignment to treatment sequence. A minimum 5-day washout period separated each treatment period. To evaluate the effect of food on the PK of maribavir, participants who received maribavir 400 mg in Period 2 were to receive an additional 400 mg maribavir dose following consumption of a high-fat breakfast during a fifth (fed) treatment period. Participants assigned to placebo in Period 2 were not studied during the fifth period. Blood and urine PK samples were collected through 24 hours postdose.

Seventeen (17) participants were enrolled in the study. Thirteen (13) participants received maribavir 400 mg in a fasted condition and 10 of these 13 participants received maribavir 400 mg in a fed condition. Maribavir PK parameters following oral administration of 400 mg maribavir under fed and fasted conditions are presented in Table 4.b.

Table 4.b Statistical Analysis of the Pharmacokinetic Parameters of Maribavir Following a Single Oral Dose of 400 mg Maribavir Capsules Under Fed and Fasted Conditions (Study CMAB1002)

Parameter	Maribavir 400 mg Fed (N=10)	Maribavir 400 mg Fasted (N=13)	Maribavir 400 mg Fed/Fasted [a] (90% CI) (N=13)
AUC_{last} (µg*h/mL)[b]	52.01	69.99	0.734 (0.588, 0.917)
AUC_{∞} (µg*h/mL)[b]	53.09	71.85	0.729 (0.579, 0.918)
C_{max} (µg/mL)[b]	11.41	16.11	0.715, (0.609, 0.840)
$_{tmax}$ (h)[c]	3.5 (1.5, 5.0)	1.5 (1.0, 2.0)	N/A[d]

ANOVA=analysis of variance; AUC=area under the plasma concentration-versus-time curve from time 0 to the last measurable concentration (AUC_{last}) and from time 0 to infinity (AUC_{∞}); CI=confidence interval; C_{max}=maximum measured plasma concentration; N/A=not applicable; t_{max}=time to C_{max}
[a] Least squares geometric mean ratio.
[b] Geometric mean.
[c] Median (minimum, maximum).
[d] The p-value for the ranked values of t_{max} from the ANOVA model was 0.0015.
Note: The maribavir 100 mg capsule formulation was used in this study.
Source: Study CMAB1002 CSR, Table 10.2.11.2, Table 10.2.11.5, Table 10.2.11.6, and Table 10.2.11.7.

In summary, administration of maribavir capsules in HIV-infected adult participants following consumption of a standard high-fat breakfast delayed plasma total maribavir t_{max} by approximately 2 hours and plasma maribavir AUC_{∞} and C_{max} decreased by 27% and 28%, respectively.

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 18 Phase 1 studies in adult healthy volunteers, 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 for any participants in a Phase 1 study 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 demonstrated no clinically significant repolarization effect of maribavir administered orally at single doses of 100 mg and 1200 mg in healthy participants. 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 interaction study.

Initially developed for prophylaxes against CMV, maribavir had a favorable safety and tolerability profile in both the Phase 2 and Phase 3 trials for CMV prophylaxes. Most frequent TEAEs that appeared to be associated with maribavir were GI AE (eg, diarrhea, dysgeusia, nausea, and vomiting). These events were generally of mild or moderate intensity. There were no signals of clinically significant effects of maribavir on vital signs, ECG parameters, or laboratory findings in the studies conducted for CMV prophylaxis.

In 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, or 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 CMV treatment (SHP620 303), maribavir 400 mg BID was well tolerated and safe. Dysgeusia was the most frequently reported TEAE overall. Other frequently reported TEAEs greater than 10% included nausea, diarrhea, vomiting, fatigue, and pyrexia. In Study SHP620-303, the TEAE of immunosuppressant drug level increased was reported in 21 participants in the maribavir group (9.0%).

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 Investigator's Brochure for the most detailed and most current information regarding the drug metabolism, PK, efficacy, and safety of maribavir.

4.2 Rationale for the Proposed Study

At the end-of-phase-2 meeting with Japan's Pharmaceuticals and Medical Devices Agency (PMDA), PMDA requested a definitive food effect study be conducted with the commercial formulation of maribavir. High-fat/high-calorie meal typically elicits the most pronounced food effect on orally administered drugs and therefore is assessed in the food effect study, per recommendation of regulatory agencies. In addition, transplant recipients are often on a low-fat

diet. Therefore, the purpose of this study is to investigate the effect of food on maribavir PK administered as the commercial tablet formulation in healthy adult human participants under different food conditions. Thus, maribavir PK under three different food conditions will be evaluated:

- Fasted (Treatment A)
- Fed following a low-fat/low-calorie meal as defined by the FDA (Treatment B)
- Fed following a high-fat/high-calorie meal as defined by the FDA (Treatment C)

The low-fat/low-calorie meal should contain in total 400-500 kCal with 100-125 kCal from fat. "**The low-fat meal**" per the FDA draft guidance (Guideline for Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations) is referred to as **"moderate meal"** in the European Medicines Agency (EMA) guidance document (EMA Guideline on the Investigations of Drug Interactions) and as **"low-fat diet"** in the Japan's PMDA guidance (Guideline for Bioequivalence Studies of Generic Products) [10-13]. The fat content and total calorie counts are consistent in these three guidance documents. For the sake of consistency, this meal is referred to in this protocol as the "low-fat/low-calorie meal."

The high-fat/high-calorie meal should contain in total 800-1000 kCal with 500-600 kCal from fat, 250 kCal from carbohydrates, and 150 kCal from proteins (The FDA-recommended high-fat meal is generally consistent with the standardized high-fat meal recommended by the EMA/Committee for Medicinal Products for Human Use guideline [11-12]. Food effect studies conducted with the standard high-fat, high-calorie meal that conforms to FDA or EMA guidance are generally deemed acceptable by Japan PMDA.

4.3 Benefit-Risk Profile

Maribavir will be administered at the dose according to the product label and the adult dosing recommendations found therein [8].

There will be no direct health benefit for study participants from receipt of the ID. 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 protect the participant's safety.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

Not applicable.

5.2 Study Objectives

5.2.1 Study Primary Objectives

To assess the relative bioavailability of a single oral dose of 400 mg maribavir commercial (marketed) tablet formulation administered with a low-fat/low-calorie meal relative to administration under fasting conditions.

To assess the relative bioavailability of a single oral dose of 400 mg maribavir commercial (marketed) tablet formulation administered with a high-fat/high calorie meal relative to administration under fasting conditions.

5.2.2 Study Secondary Objective

To evaluate the safety and tolerability of a single oral dose of 400 mg maribavir commercial (marketed) tablet formulation when administered under fasting conditions, with a low-fat/low-calorie meal and with a high-fat/high-calorie meal.

5.2.3 Study Exploratory Objective

To evaluate other PK parameters of a single oral dose of 400 mg maribavir commercial (marketed) tablet formulation when administered under fasting conditions, with a low-fat/low-calorie meal and with a high-fat/high-calorie meal.

5.3 Endpoints

5.3.1 Primary Endpoints

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

- 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

Exploratory PK endpoints include (if applicable, but are not limited to) additional PK parameters for maribavir as follows:

- Concentration at 12 hours postdose (C_{12})
- Area under the concentration-time curve from time 0 to 12 (AUC_{12})
- 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})

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a single-center, open-label, single-dose, randomized, 3-period, 6-sequence, crossover study in healthy adult participants.

Study schematic and dose regimens are shown in Table 2.a and Table 2.b. The schedule of assessments is shown in Schedule of Study Procedures (Section 3.0).

A single dose of 400 mg maribavir (commercial [marketed] tablet formulation) will be administered orally under 3 different feeding conditions:

1) Fasting (Treatment A),
2) Fed following a low-fat/low-calorie meal (Treatment B), and
3) Fed following a high-fat/high-calorie meal (Treatment C).

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

PK samples will be collected predose and up to 36 hours postdose in each treatment period.

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 ID administration 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-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 effect of a low-fat/low-calorie and a high-fat/high-calorie meal on the PK profile of maribavir after a single oral dose.

Participants will be randomized to treatment sequences to minimize assignment bias. A crossover design is used to reduce the residual variability as every participant acts as their own control.

The washout period of 72 hours between doses is considered sufficient to prevent carryover effects of the preceding treatment.

6.4.2 Rationale for Dose

The 400 mg single oral dose of maribavir was selected as this is the recommended therapeutic single dose according to the LIVTENCITY (maribavir) US prescribing information [8]. Based on results from Study CMAB1002, food is expected to reduce maribavir exposure by approximately 27%. The current dose level is thus expected to provide a robust PK profile under the different dosing food conditions in this study.

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 the ID 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 ie, follow-up contact, as outlined in the Schedule of Study Procedures (Section 3.0).

A study participant is considered to have completed the study if the participant has completed 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 Completion

The end of the study is scheduled after completion of the evaluations in the follow-up contact for the last participant in the study.

This time period may change in the event that the study is terminated early or the last participant is lost to follow-up.

6.6.4 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.

6.6.5 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 of the study:

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

6.6.6 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 of the ID 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 19-55 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. 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.
6. 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.
7. BMI between 18.0 and 30.0 kg/m^2, inclusive with a body weight >50 kg (110 lbs), at the screening visit.
8. Ability to swallow a dose of the ID.

7.2 Exclusion Criteria

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

1. History or presence of gastritis, GI tract, 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 ID.
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 ID, 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 ID or procedures.
4. Known or suspected intolerance or hypersensitivity to the ID, 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 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 2 more times and the average of the 3 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 3 units per day. Female participants who consume more than 14 units of alcohol per week or 2 units per day (1 alcohol unit=1 beer or 1 wine [5 oz/150 mL] or 1 liquor [1.5 oz/40 mL] or 0.75 oz alcohol).
13. A positive 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 of the ID.
16. Routine consumption of more than 2 units of caffeine per day or participants who experience caffeine withdrawal headaches. (1 caffeine unit is contained in the following items: one 6 oz [180 mL] cup of coffee, two 12 oz [360 mL] cans of cola, one 12 oz cup of tea, three 1 oz

[85 g] chocolate bars). Decaffeinated coffee, tea, or cola are not considered to contain caffeine.

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 of the ID. 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 of the ID. Hormonal contraceptives (refer to Appendix D) and hormonal replacement therapy may be permitted if the participant has been on the same stable dose for at least 3 months prior to first dose of the ID. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic interaction with the ID.
18. Current use of antacids, proton pump inhibitors, or H_2 antagonists within 14 days of the first dose of the ID.
19. Inability or unwillingness to consume 100 percent of high-fat meal or low-fat meal (including participants with lactose or gluten intolerance).
20. Recent history (within 1 month) of oral/nasal cavity infections, history of gastroesophageal reflux, asthma treatment with albuterol, or zinc supplementation.
21. 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 of the ID, 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 of the ID.

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.

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

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

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Water (except water provided with each dosing) will be restricted between 1 hour prior to and 1 hour after each dosing of the ID, 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 Treatment A, participants will fast overnight for at least 10 hours prior to dosing of the ID. Participants will continue the fast for at least 4 hours postdose.

In Treatment B, participants will fast overnight for at least 10 hours until 30 minutes prior to their scheduled morning dose of the ID, when they will be given a low-fat/low-calorie meal, as presented in Table 7.b which will be entirely consumed within 30 minutes. Participants will fast for at least 4 hours postdose.

In Treatment C, participants will fast overnight for at least 10 hours until 30 minutes prior to their scheduled morning dose of the ID, when they will be given a high-fat/high-calorie meal, as presented in Table 7.b which will be entirely consumed within 30 minutes. Participants will fast for at least 4 hours postdose.

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 B and Treatment C) and will be taken at approximately the same time in each treatment period.

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

	Low-Fat/Low-Calorie Meal (Treatment B)	**High-Fat/High-Calorie Meal (Treatment C)**
Total calories (kCal)	400-500	800-1000
Protein calories (kCal) (% of total calories; weight)	110 (27%; 27 grams)	150 (19%; 38 grams)
Carbohydrate calories (kCal) (% of total calories; weight)	190 (47%; 47 grams)	250 (31%; 63 grams)
Fat calories (kCal) (% of total calories; weight)	100-125 (25%; 11-14 grams)	500-600 (50%; 55-65 grams)
Saturated and unsaturated fat (grams)	4 g; 6 g	
Example of breakfast	• Eight ounces milk (1% fat) • One boiled egg • One packet flavored instant oatmeal made with water (This low-fat breakfast contains approximately 387 kCal and has 10 grams of fat)	• 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)

7.4.2 Activity

Participants will remain ambulatory or seated upright for the first 4 hours postdose, except when they are supine or semi reclined for study procedures.

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 ID 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:

   ID 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 ID 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 2 weeks, or
   - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio >1.5, or
   - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

   QTcF interval:

   ID should be discontinued immediately with appropriate clinical follow-up if a QTcF interval >500 msec or if there is an increase of QTcF >60 msec above baseline detected by ECG and confirmed with a repeat ECG. Appropriate clinical follow-up includes a repeat ECG.

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 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, IRB/IEC, 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 the COVID-19 pandemic. 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 24 PK-evaluable participants complete the study.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Investigational Drug

Product Name:	Maribavir (TAK-620)
Strength:	200-mg
Dose:	400 mg
Dosage Form/Formulation:	Tablet (commercial [marketed] form)
Dosing Regimen:	Single dose
Route of Administration:	Oral

8.1.1 Clinical Investigational Drug Labeling

ID containers will be affixed with a clinical label in accordance with local regulatory requirements.

8.1.2 Clinical Investigational Drug Inventory and Storage

The same lot number will be used throughout the study. The lot numbers and expiration dates (where available) of the IDs supplied will be recorded in the final report. IDs 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 IDs supplied.

8.1.3 Clinical Investigational Drug Blinding

This is an open-label study.

8.1.4 Randomization Code Creation and Storage

A computerized randomization scheme will be created by a Celerion statistician.

Treatments A, B, and C will be randomized to 1 of 6 sequences as indicated in (Table 8.a).

Table 8.a Randomization Sequence

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

Treatment A = maribavir tablet (2 x 200 mg), fasting
Treatment B = maribavir tablet (2 x 200 mg), fed - following a low-fat/low-calorie meal
Treatment C = maribavir tablet (2 x 200 mg), fed - following a high-fat/high-calorie meal.

8.1.5 Clinical Study Blind Maintenance/Unblinding Procedure

Not applicable.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

Records will be made of the receipt and dispensing of the IDs supplied. At the conclusion of the study, any unused ID 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 of the ID, different from the screening number and will receive the corresponding product, according to a randomization sequence.

If replacement participants are used, the replacement participant number will be 100 more than the original (eg, Participant No. 101 will replace Participant No. 1).

9.1.1.2 Investigational 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 Examination

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 the screening visit.

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 (e.g. nausea, dizziness) or if deemed necessary by the Investigator or designee. Participants should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

Blood pressure and pulse rate will be measured within 2 hours prior to Day 1 dosing in each treatment period for the predose time point. 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 2 more times and the average of the 3 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 5 minutes prior to collecting the ECG.

ECGs will be measured within 2 hours prior Day 1 dosing in each treatment period for the predose time point. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

9.2.6 Investigational Drug Administration

The ID will be provided as described in Section 8.1.

Treatments are described in Table 2.b.

The ID will be administered orally with approximately 240 mL of water.

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

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 B and Treatment C, a meal will be provided 30 minutes prior to the ID dosing.

The exact clock time of the ID dosing will be recorded.

A qualified designee will be responsible for monitoring the administration of the assigned doses. A mouth check will be performed by the qualified designee to ensure that the participants have swallowed the ID. 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 ID 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 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 Sampling Collection Window

Sample Collection Time	Sampling Window
Predose	< -1 hour
>0 - ≤4 hours postdose	± 5 minutes
>4 - ≤36 hours postdose	± 15 minutes

9.3.1 PK Measurements

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

Pharmacokinetic 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_{12}:	Area under the concentration-time curve from time 0 to 12
$AUC_{extrap\%}$:	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_{12}:	Concentration at 12 hours postdose.
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.

No PK parameters will be calculated for participants with detectable concentrations at 4 or fewer consecutive time points.

Individual and mean plasma concentration-curves (both linear and log-linear) will be included in the final report.

Additional PK parameters may be estimated as appropriate.

9.3.2 Biomarker Measurements

Not applicable.

9.3.3 PGx Measurements

Not applicable.

9.3.4 Confinement

Participants will be housed on Day -1 of Treatment Period 1, at the time indicated by the CRU, until after the 36-hour blood draw and/or study procedures of Treatment Period 3 as outlined in the Schedule of Study Procedures (Section 3.0). Participants may be admitted earlier for COVID-19 testing not related to study protocol as per CRU requirements.

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 the ID 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 the ID or after any change in ID, 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 ID, 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 investigational 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.

AEs that fulfill 1 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 for maribavir include:

- Dysgeusia
- GI-related events

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 ID 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 ID. 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 ID is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping the ID.
- Unknown – only to be used if it has not been possible to determine what action has been taken.

- Not applicable – the ID was stopped for a reason other than the particular AE eg, the study has been terminated, the participant died, dosing with the ID had not yet started or dosing with the ID 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, Special Interest AEs, and Abnormal Liver Function Tests (LFTs)

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, 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 of the ID. For participants who discontinue prior to the administration of the ID, 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 the ID 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 ID, 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 ID 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 ID).
- Relationship to COVID-19.
- Relationship to COVID-19 vaccine.
- Action taken with ID.
- 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 ID.
- 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 ID 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 Special Interest AEs

Adverse events of Special Interest for maribavir include dysgeusia and GI-related events.

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 or IECs, 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 or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. 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 products 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 or IEC 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 1 dose of maribavir, did not vomit or had diarrhea within 4 hours of the ID dosing, and have 5 or more postdose time points with evaluable postdose maribavir concentration values that enable NCA.

11.1.1.2 Safety Set

All participants who received at least 1 dose of maribavir will be included in the safety evaluations.

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

Statistical analysis of PK data will be based on the PK set.

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 (C_{max}, AUC_{last}, AUC_{∞}, AUC_{12}, $AUC_{extrap\%}$, C_{12}, t_{max}, λ_z, $t_{½z}$, CL/F, V_z/F, and t_{lag}) will be computed using standard NCA. Actual time of sampling will be used to calculate the PK parameters. The PK endpoints will be presented descriptively. All individual concentration data and PK parameters will be listed with summary statistics such as geometric mean, median, arithmetic mean, SD, CV, minimum and maximum. Individual plasma concentration/time curves will be presented in linear/linear and log/linear scale. At least 3 PK time points within the terminal log-linear phase will be used to estimate the terminal rate constant for each participant in each treatment period.

The appropriate PK analysis will be fully specified in the CPAP.

11.1.3.1 Food-effect estimation

A mixed-effect 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 (low-fat/low-calorie meal) versus Treatment A (fasting), and Treatment C (high-fat/high-calorie meal) versus Treatment A (fasting). 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 (low-fat/low-calorie meal) versus Treatment A (fasting) and Treatment C (high-fat/high-calorie meal) versus Treatment A (fasting).

11.1.3.2 Non-Parametric Analysis

Analysis of t_{max} and t_{lag} will be performed by nonparametric Wilcoxon Signed-Rank test. This analysis will be based on the PK data set.

11.1.3.3 Exploratory Analysis

In a separate analysis, both non-compartmental and compartmental PK modeling will be used to simulate and to project the steady-state AUC_{12}, C_{max} and C_{12} after theoretical regimens of multiple BID oral doses of 400 mg maribavir commercial (marketed) formulation under different dosing conditions (Treatment A, B, or C). The results from the exploratory analysis will not be listed in the CSR and will be detailed in a separate report.

Additional exploratory analyses may be conducted and reported separately.

11.1.4 Pharmacodynamic Analysis

Not applicable.

11.1.5 Safety Analysis

All safety data will be populated in the individual CRFs.

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 the ID 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 of the ID, or with a start date before the date of first dose of the ID but increasing in severity after the first dose of the ID.

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 potentially clinically significant (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 listed by participant.

11.2 Interim Analysis and Criteria for Early Termination

Not applicable.

11.3 Determination of Sample Size

A total of 24 participants should complete all treatment periods of the study.

Sample size calculations is performed using R package PowerTOST and were based on the following:

- The intra-participant CV was assumed at 0.166 and 0.218, respectively for AUC_{∞} and C_{max}, which were estimated from the 90% CIs of the GMR of AUC_{∞}, and C_{max} in Study 1263-104.
- Reference data set is AUC_{∞} or C_{max} under fasting conditions; test data set is AUC_{∞} or C_{max} under fed conditions
- Assumed GMR for Test / Reference: 0.80, 0.85, 0.90, 0.95, or 1.00
- The estimated 90% CI of the GMR at 0.90, with N = 24, is within (0.80, 1.25) for both AUC_{∞} and C_{max}

Accounting for possible dropouts, a total of 30 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 or IEC.

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, ID, 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 or IEC, as required) 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 (ie, 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. 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 and/or IEC Approval

IRBs and IECs 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 or IEC. If any member of the IRB or IEC 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 or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, 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 or IEC for approval. The IRB's or IEC'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 or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) 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 or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, 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 or IEC, and submission of the Investigator's final status report to IRB or IEC. All IRB and IEC 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 or IEC 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 informed consent form, 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 informed consent form 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 informed consent form 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 or IEC approval of the informed consent form and, if applicable, the participant authorization form. The informed consent form, participant authorization form (if applicable), and participant information sheet (if applicable) must be approved by both the IRB or IEC and the Sponsor prior to use.

The informed consent form, 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 informed consent form, 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 or IEC. 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 informed consent form 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 informed consent form 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 informed consent form, 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 informed consent form, the signed participant authorization form (if applicable), and participant information sheet (if applicable) shall be given to the participant.

All revised informed consent forms 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 informed consent form.

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, Medicines and Healthcare products Regulatory Agency, PMDA), the Sponsor's designated auditors, and the appropriate IRBs and IECs 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: +1 224-554-1052

14.1.2 Investigator Agreement

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, 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.
- 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_{12}	Area under the concentration-time curve, from time 0 to 12
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.
BID	Twice daily doses
BMI	Body mass index
bpm	Beats per minute
C_{12}	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
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EMA	European Medicines Agency
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
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Investigational drug
IEC	Independent Ethics Committee
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
PCS	Potentially clinically significant
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
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
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 World Health Organization 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 principal 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 principal 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 informed consent forms, participant authorization forms regarding the use of personal health information (if separate from the informed consent forms), 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

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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.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. 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.
4. 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.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC 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/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. 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/IEC. Each informed consent form 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 informed consent form 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.

10. 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.
11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
13. 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/IEC, and the monitor may inspect the records. By signing a written informed consent form, 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/IEC 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 informed consent form 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/IECs;

    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 of the ID. If a participant is found to be pregnant during study, ID 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 of the ID.
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 and IECs.

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 ID.
- 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 the ID, 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 Male Partners

From signing of informed consent, throughout the duration of the study, and for 1 month after last dose of the ID, 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 the ID until 1 month after last dose of the ID for female participants of childbearing potential* and 3 months after the last dose of the ID 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 the ID 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 the ID 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:
   a) contraceptive requirements of the study
   b) reasons for use of barrier methods (ie, condom) in males with pregnant partners
   c) 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 the ID (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 the ID. In addition, participants must also have a negative serum hCG pregnancy test within 28 days prior to receiving first dose of the ID.

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 the ID the female participant or her male partner (ie, male participant) received.

All pregnancies, including female partners of male participants, in participants on active ID (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.