Statistical Analysis Plan

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

Document Version and Date: Original Version (15-June-2022)

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

STATISTICAL ANALYSIS PLAN

Study Number: TAK-620-1025

Celerion Study Number: CA36719

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

Phase: 1

Version: Final

Date: 15-June-2022

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Based on:

Protocol Version: Original

Protocol Date: 27-Apr-2022

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original Version	15-June-2022	Not Applicable

Approval Signatures

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

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

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LIST OF IN-TEXT TABLES

ABBREVIATIONS

AE	adverse event
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, calculated using the observed value of the last quantifiable concentration
$AUC_{extrap\%}$	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_{∞}
AUC_{last}	area under the concentration-time curve, from time 0 to the time of the last quantifiable concentration
BLQ	below the limit of quantitation
BMI	body mass index
C_{12}	concentration at 12 hours postdose
CI	confidence interval
CL/F	apparent clearance after oral administration, calculated using the observed value of the last quantifiable concentration
C_{max}	maximum observed concentration
COVID-19	Coronavirus disease 2019
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRU	clinical research unit
CS	clinically significant
CSR	clinical study report
CV	coefficient of variation
CV%	percent coefficient of variation
DMP	data management plan
ECG	electrocardiogram
ET	early termination
Geom CV%	geometric coefficient of variation
Geom Mean	geometric mean
GI	gastrointestinal
GMR	geometric mean ratio
ICF	informed Consent Form
ID	investigational drug
LLN	lower limit of normal
LSM	least-squares mean
Mean	arithmetic mean
MedDRA®	Medical Dictionary for Regulatory Activities®
n	number of observations
NCA	non-compartmental analysis
PCS	potentially clinically significant
PK	pharmacokinetic(s)

PT	preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
$t_{½z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TFL	tables, figures and listings
t_{lag}	lag time to first quantifiable concentration in plasma
t_{max}	time to first occurrence of C_{max}
ULN	upper limit of normal
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
WHO	World Health Organization
λ_z	terminal disposition phase rate constant

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objectives

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.

1.1.2 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.

1.1.3 Exploratory Objective

To evaluate other pharmacokinetic (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.

1.2 Endpoints

1.2.1 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_{∞})*

1.2.2 Secondary Endpoints

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

1.2.3 Exploratory Endpoints

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})*

1.3 Estimand(s)

Not applicable

2.0 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.

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 investigational drug (ID) dosing.

(b) 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 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

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.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not applicable.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

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

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

- *The intra-participant coefficient of variation (CV) was assumed at 0.166 and 0.218, respectively for AUC_∞ and C_{max}, which were estimated from the 90% confidence intervals (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% 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.

5.0 ANALYSIS SETS

5.1 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 non-compartmental analysis (NCA).

Details on criteria for excluding participants from the PK analysis will be described in the Clinical Pharmacology Analysis Plan (CPAP).

5.2 Safety Set

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

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All PK analyses will be conducted using Phoenix® WinNonlin® Version 8.3.4, or higher. All statistical analyses will be conducted using SAS® Version 9.4 or higher. All data recorded on the case report form (CRF) will be listed by participant. All tables, figures, and listings (TFL) shells and numbering list will be included and specified in the TFL shells document.

All concentration and PK parameter data and their descriptive statistics (with the exception of the number of observations) will be presented to 3 significant digits. The number of observations (n) will be presented as an integer (no decimal places).

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

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

- A predose (0 hr) concentration is greater than 5% of that participant's maximum concentration value in that period
- A participant did not meet inclusion/exclusion criteria that may have an effect on the PK (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)
- A participant vomits or has diarrhea within 4 hours of dosing
- A participant that has less than 5 postdose timepoint with evaluable postdose maribavir concentration values

- A participant deviates substantially from the protocol defined study procedures including but not limited to dosing, dose timing, sample collection, meal timing, etc. (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)

  Note: additional details for excluding participants and/or PK parameters will be detailed in the CPAP.

The details on PK parameter calculations (individual PK parameters for each participant for each period) and TFLs will be outlined in the CPAP and TFL Shells document, as applicable, including specifics on the following:

- Insufficient data to determine a reliable $t_{1/2z}$ value and other λ_z-dependent parameters
- PK parameters presented by treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables
- Concentration data presented by treatment, including the units, precision, and summary statistics that will be presented in end-of-text tables
- Concentration data file used for PK analysis
- PK parameter WinNonlin® output file used to generate the TFLs
- PK parameter ratios for C_{max}, AUC_{last}, and AUC_{∞}, for each comparison of interest presented in end-of-text tables
- Linear mixed-effects model results presented in in-text and end-of-text tables
- Nonparametric analysis of t_{max} and t_{lag} for each comparison of interest presented in end-of-text tables
- Arithmetic mean concentration-time figures presented as in-text and end-of-text figures
- Individual concentration-time figures and listings presented in Appendices 16.2.6 and 16.2.5, respectively of the clinical study report (CSR)

Safety data will be summarized by randomized treatment sequence or by treatment and time point, as applicable. For the categorical variables, the count and percentages of each possible value will be tabulated, where applicable. The denominator for the percent calculation will be the number of non-missing observations in the safety set for each treatment or sequence. Counts and percentages will be presented as integers. For continuous variables, n, mean, SD, minimum, median, and maximum values will be tabulated. The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer.

Baseline, unless specified otherwise, is defined as the last observation prior to dosing in each period.

6.1.1 Handling of Treatment Misallocations

Participants with misallocated treatments will be analyzed per the treatment they received rather than per the treatment regimen to which they were randomized.

6.2 Study Information

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

6.3 Disposition of Participants

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

6.4 Demographic and Other Baseline Characteristics

6.4.1 Demographics

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

6.4.2 Medical History and Concurrent Medical Conditions

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

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

6.5 Medication History and Concomitant Medications

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

6.6 Efficacy Analysis

Not applicable.

6.7 Safety Analysis

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

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

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

6.7.1 Adverse Events

All AEs captured in the database will be listed in by-participant data listings including verbatim term, coded term, severity (mild, moderate, severe), relationship to ID (related or not related), relationship to COVID-19 and COVID-19 vaccine, frequency, and action relative to the ID as recorded in the CRF. Study procedure taken due to AE will also be listed. All AEs occurring during this study will be coded using the MedDRA® version specified in the DMP. Only TEAEs will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after the first dose of ID administered in the study. Each TEAE will be attributed to the treatment prior to and the closest to the AE based on the AE onset date and time.

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

TEAEs will be tabulated by treatment (including overall), SOC, and preferred term. Summary tables will include number of participants reporting the TEAE as percent of safety set by treatment and overall. The most commonly reported non-serious TEAEs (i.e., those events reported by >5% of participants in any treatment, excluding serious adverse events (SAEs) will also be summarized. The denominators for percent calculations will be the number of participants dosed for each treatment. In addition, TEAEs will be summarized as number of TEAEs and percentage of TEAEs for each treatment and overall.

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

An overview summary of TEAEs table, including number of participants with TEAEs, SAEs, treatment-related TEAEs, treatment-related SAEs, TEAEs by severity, and AEs leading to discontinuation will be provided.

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

6.7.2 Adverse Events of Special Interest

Adverse events of special interest will be identified in the data listings, and will be discussed in the CSR, but will not be summarized separately. Adverse events of special interest for maribavir include dysgeusia and gastrointestinal (GI)-related events.

6.7.3 Clinical Laboratory Evaluation

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

Table 6.a Collection of Laboratory Samples

Clinical Laboratory Panels	Time Point		
	Period	CRF/Listing Day and Hour	Table
	Screening		NA

Clinical Laboratory Panels	Time Point		
	Period	CRF/Listing Day and Hour	Table
Serum Chemistry, Hematology, Urinalysis	1	Day -1 PRE-DOSE	Baseline
	2	Day 1 PRE-DOSE	Period 2 Predose
	3	Day 1 PRE-DOSE Day 2 Hour 24	Period 3 Predose Period 3 Day 2

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

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

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

If a value fails the reference range, it will automatically be compared to a laboratory clinically significant (CS) range. If the value falls within the CS range, it will be noted as “N” for not clinical significant. If the value fails the CS range, it will be flagged with a “Y” which prompts the investigator to determine how the out-of-range value should be followed using 4 Investigator flags: "N", not clinically significant, "R", requesting a recheck, "^", checking at the next scheduled visit, or "Y", clinically significant. Additionally, the investigator will provide a 4th flag when the 3rd flag indicates “R” or “^”. This 4th flag is intended to capture final CS (+)/NCS (-) when the 3rd flag does not document significance.

Individual postdose serum chemistry or hematology results that meet Takeda’s PCS criteria, including recheck, unscheduled, and ET results, will be listed and tabulated. A participant’s value will be considered PCS if it meets one of the criteria described in Appendix A and if it is worse than the participant’s baseline value. The number and percentages of participants with at

least one postdose result considered PCS will be provided. A participant mapping table will also be provided to show which participants with worsened postdose values met each category. All clinical laboratory PCS values will also be listed in by-participant data listings.

6.7.4 Vital Signs

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

Table 6.b Collection of Vital Signs

Parameter	Time Point		
	Period	CRF/Listing Day and Hour	Table
Blood Pressure, Heart Rate	Screening		NA
	1, 2, 3	Day 1 PRE-DOSE Day 2 Hour 24	Baseline Hour 24
	3	Day 2 Hour 36	Hour 36
Respiration, Temperature	Screening		NA
	3	Day 2 Hour 36	NA

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

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

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

6.7.5 12-Lead ECG

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

Table 6.c Collection of ECG Measurements

Parameter	Time Point		
	Period	CRF/Listing Day and Hour	Table
HR, PR, QRS, QT, QTcF, RR	Screening		NA
	1, 2, 3	Day 1 PRE-DOSE Day 2 Hour 24	Baseline Hour 24
	3	Day 1 Hour 3.5 Day 2 Hour 36	Hour 3.5 Hour 36

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

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

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

6.7.6 Physical Examinations

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

6.7.7 Overdose

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

6.7.8 Extent of Exposure and Compliance

The dates, times, and doses of maribavir will be listed by participant and study period.

6.8 Pharmacokinetic Analyses

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

Table 6.d Collection of Blood Samples for Pharmacokinetic Analysis

Analytes	Matrix	Periods	Scheduled Time (Hours)[#]
Maribavir	Plasma	1, 2, and 3	Predose (0) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, and 36 hours postdose

[#] The actual date and time of sample collection will be recorded on the source document in the CRF.

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

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

The PK parameters will be calculated from plasma maribavir concentration-time profiles using NCA methods where all calculations will be based on actual sampling times after maribavir dosing. The PK parameters will be summarized by treatment for each study part using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, maximum, Geom mean, and Geom CV%. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from descriptive statistics.

6.8.1 Food-effect Estimation

A linear mixed-effects model will be applied to ln-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).

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

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

6.8.2 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 set. The difference of medians (treatment effect) and the corresponding 90% CI will be estimated using the Hodges-Lehmann method and Walsh Averages. The t_{max} and t_{lag} parameters will not be ln-transformed. The comparisons of interest are the same as in the linear mixed-effects model.

6.8.3 Exploratory Analysis

In a separate analysis, not conducted by Celerion, *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 twice daily (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.

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

Not applicable.

6.10 Preliminary Analyses

Preliminary PK analyses will be completed as described in the CPAP and Section 6.8 of the SAP, with the following changes: 1) QCed data will be used (not QAed); 2) nominal times (not actual sampling times) will be used for the calculation of PK parameters; and 3) tables and figures will be created using Phoenix® WinNonlin® Version 8.3.4 or higher, except for the tables presenting the linear mixed-effects model data which will be generated using SAS® Version 9.4 or higher.

6.11 Interim Analyses

Not applicable.

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

Not applicable.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

The analyses described in this SAP do not differ from those specified in the protocol.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Not applicable.

9.2 Data Handling Conventions

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

Appendix A Criteria for Identification of PCS Safety Laboratory Values

Hematology—Criteria for PCS Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Conventional	<0.8 × LLN	>1.2 × ULN
Hematocrit	Conventional	<0.8 × LLN	>1.2 × ULN
RBC count	Conventional	<0.8 × LLN	>1.2 × ULN
WBC count	Conventional	<0.5 x LLN	>1.5 x ULN
Platelet Count	Conventional	<75 x 10^9/L	>600 x 10^9/L

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

Serum Chemistry—Criteria for PCS Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Conventional	--	>3x ULN
AST	Conventional	--	>3x ULN
GGT	Conventional	--	>3x ULN
Alkaline phosphatase	Conventional	--	>3x ULN
Total Bilirubin	Conventional	--	>1.5x ULN
Albumin	Conventional	<2.5 g/dL	--
Total protein	Conventional	<0.8x LLN	>1.2x ULN
Creatinine	Conventional		>1.5x ULN
Blood urea nitrogen	Conventional		>40 mg/dL
Sodium	Conventional	<130 mEq/L	>150 mEq/L
Potassium	Conventional	<3.0 mEq/L	>5.3 mEq/L
Glucose	Conventional	<50 mg/dL	>300 mg/dL
Chloride	Conventional	<75 mmol/L	>126 mmol/L
Calcium	Conventional	<7.7 mg/dL	>11.1 mg/dL
Bicarbonate	Conventional	<8.0 mmol/L	

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

Appendix B Criteria for PCS Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	<40	>115
Systolic blood pressure	mm Hg	<90	≥160
Diastolic blood pressure	mm Hg	<50	≥100
Systolic blood pressure change from baseline	mm Hg		>20, >30
Diastolic blood pressure change from baseline	mm Hg		>20, >30

Appendix C Criteria for PCS Values for Electrocardiograms

Parameter	Unit	Lower Criteria	Upper Criteria
Heart rate	bpm	<40	>115
PR	msec	≤80	≥200
QRS	msec	≤80	≥180
QTcF	msec	<300	>500 Or >450 and ≥30 msec change from baseline

9.3 Analysis Software

SAS® Version 9.4 or higher will be used for all statistical analyses provided in the CSR.

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