STATISTICAL ANALYSIS PLAN

NCT Number: NCT04131556

Study Title: A Phase 1, Open-label, Randomized, Crossover, Bioavailability, Dose Proportionality, and Food Effect Study Comparing the Pharmacokinetics and Palatability of Two Candidate Pediatric Powder-for-Oral-Suspension Formulations of Maribavir to the Current Maribavir Tablet Formulation Administered in Healthy Adult Subjects

Study Number: TAK-620-1019

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STATISTICAL ANALYSIS PLAN

TAK620 (SHP620), Maribavir
PHASE 1

A Phase 1, Open-label, Randomized, Crossover, Bioavailability, Dose Proportionality, and Food Effect Study Comparing the Pharmacokinetics and Palatability of Two Candidate Pediatric Powder-for-Oral-Suspension Formulations of Maribavir to the Current Maribavir Tablet Formulation Administered in Healthy Adult Subjects

PROTOCOL IDENTIFIER: TAK-620-1019

Study Sponsor(s): Shire Human Genetic Therapies, Inc. (Shire, [and affiliates]); Shire is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	18Dec2019	Not applicable

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ABBREVIATIONS

AE	adverse event
AUC	area under the curve
$AUC_{0\text{-inf}}$	area under the curve from the time of dosing to the last measurable concentration
$AUC_{0\text{-inf}}$%extrap	percent of $AUC_{0\text{-inf}}$ extrapolated
$AUC_{0\text{-last}}$	area under the curve from the time of dosing to the last measurable concentration
BLQ	below limit of quantitation
BMI	body mass index
CI	confidence interval
CL/F	apparent total body clearance following extravascular administration
C_{max}	maximum concentration occurring at time of maximum observed concentration sampled during a dosing interval
CSR	clinical study report
CV	coefficient of variation
ECG	electrocardiogram
IP	investigational product
PCI	potentially clinically important
PK	pharmacokinetic(s)
PT	Preferred Term
SD	standard deviation
SOC	System Organ Class
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{lag}	delay between the time of dosing and time of appearance of plasma concentration in the employed sampling scheme
t_{max}	time of maximum observed concentration sampled during a dosing interval

1. INTRODUCTION

This statistical analysis plan provides a technical and detailed elaboration of the statistical analyses of pharmacokinetic (PK), palatability, safety, and tolerability data as described in the TAK-620-1019 protocol amendment 1 dated 05 Nov 2019. Specifications for tables, figures, and listings are contained in a separate document.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

The primary objectives of Part 1 are:

- To assess the relative bioavailability of 2 candidate pediatric formulations of maribavir given as a single oral dose at 200 mg as compared to the Phase 3 adult maribavir 200 mg tablet formulation in healthy adult subjects.
- To assess the palatability of two candidate pediatric formulations of maribavir by using a questionnaire.

The primary objectives of Part 2 are:

- To assess the dose proportionality of 50 mg, 100 mg, and 200 mg of the selected pediatric formulation of maribavir.
- To assess the impact of food on the rate and extent of absorption of the selected pediatric formulation of maribavir given as 200 mg under fasted and fed conditions.
- To assess the palatability of the selected pediatric formulation of maribavir at various doses and with food.

2.1.2 Secondary Objective

The secondary objective for both Part 1 and Part 2 is:

- To assess the safety and tolerability of 2 candidate pediatric formulations and the adult tablet formulation of maribavir given as a single oral dose up to 200 mg in healthy adult subjects.

2.2 Endpoints

2.2.1 Pharmacokinetic Endpoints

Part 1 (Day 1, Day 4, and Day 7) and Part 2 (Day 1, Day 4, Day 7, and Day 10)

- Time of maximum observed concentration sampled during a dosing interval (t_{max})
- Maximum concentration occurring at t_{max} (C_{max})
- Area under the curve (AUC) from the time of dosing to the last measurable concentration ($AUC_{0\text{-}last}$)
- AUC extrapolated to infinity, calculated using the observed value of the last non zero concentration ($AUC_{0\text{-}inf}$)
- The percent of $AUC_{0\text{-}inf}$ extrapolated, calculated by $(1\text{-}AUC_{0\text{-}last}/AUC_{0\text{-}inf})*100$ ($AUC_{0\text{-}inf}$%extrap)
- Terminal half-life ($t_{1/2}$)
- Apparent total body clearance following extravascular administration calculated as dose divided by $AUC_{0\text{-}inf}$ (CL/F)
- Delay between the time of dosing and time of appearance of plasma concentration in the employed sampling scheme (T_{lag})
- Dose-normalized C_{max} (for Part 2 Treatments D, E, and F only, refer to Section 3.1 for treatment descriptions)
- Dose-normalized $AUC_{0\text{-}last}$ (for Part 2 Treatments D, E, and F only, refer to Section 3.1 for treatment descriptions)
- Dose-normalized $AUC_{0\text{-}inf}$ (for Part 2 Treatments D, E, and F only, refer to Section 3.1 for treatment descriptions)

2.2.2 Safety Endpoints

Part 1 and Part 2:

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

2.2.3 Palatability Endpoints

Part 1 and Part 2:

- To identify and characterize the sensory attributes of products, eg, basic tastes, texture and mouth feel and to assess the overall acceptability.

3. STUDY DESIGN

3.1 General Description

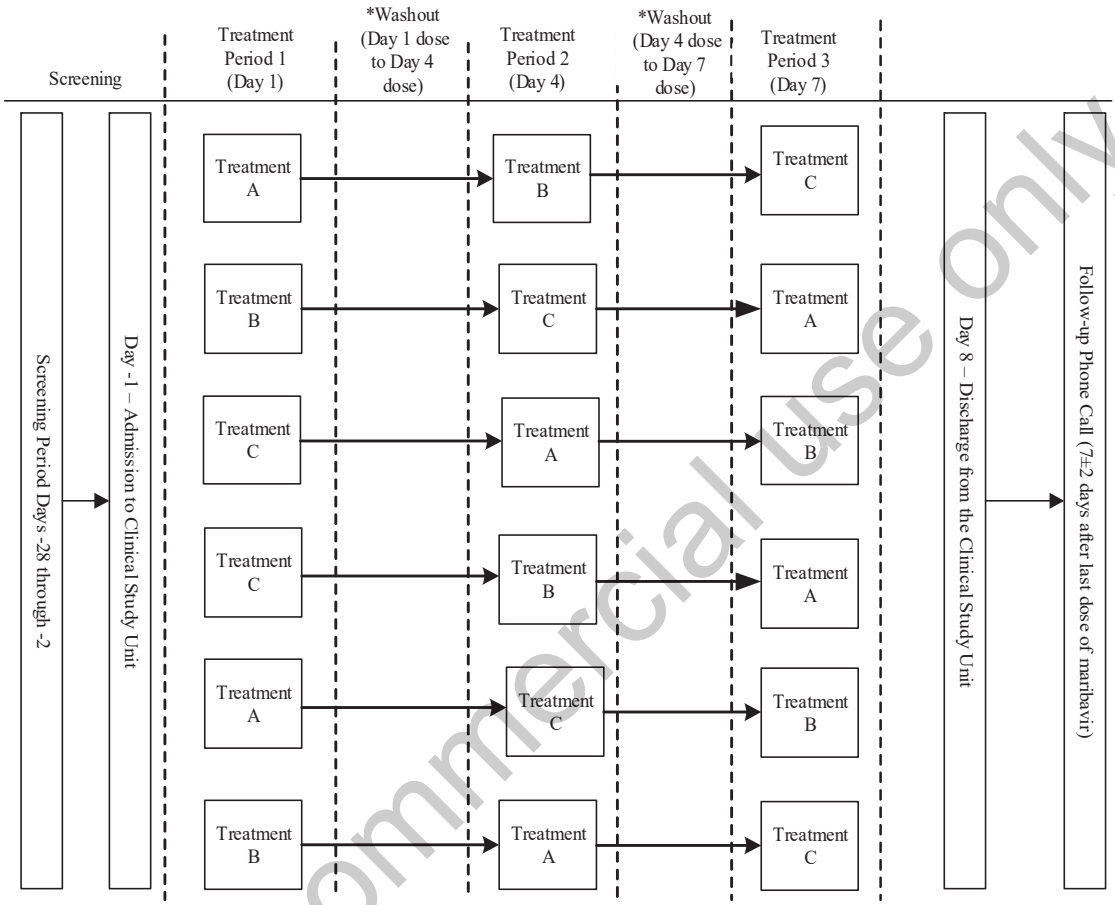
The study will be conducted sequentially in 2 parts:

- In Part 1, two pediatric candidate powder formulations will be compared with maribavir 200 mg tablet (current Phase 3 formulation) under fasted conditions with respect to their bioavailability and palatability, and one formulation will be selected for Part 2.
- In Part 2, dose proportionality of 50, 100, and 200 mg dose of the selected pediatric powder formulation will be assessed, as well as the impact of food (a high-fat meal) on the rate and extent of absorption of the selected pediatric formulation.

The pediatric formulation which will be assessed in Part 2 will be chosen based on the results of planned analysis (interim) of Part 1 PK and palatability data from two candidate pediatric formulations. The doses to be evaluated in Part 2 may be adjusted based on relative bioavailability of the selected pediatric formulation (powder for oral suspension) to the Phase 3 tablet formulation observed in Part 1. The planned analysis (interim) of Part 1 is described in Section 11. Final analysis will be performed after Part 2 is completed.

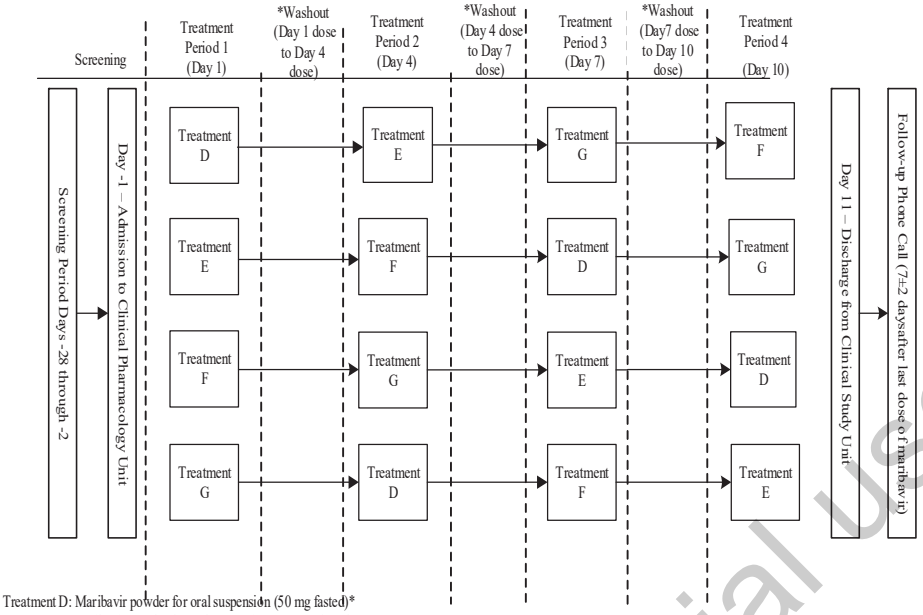
Study design flow charts for Part 1 and Part 2 are presented in Figure 1 and Figure 2, respectively.

Figure 1: Study Design Flow Chart Part 1



Treatment A: Maribavir 200mg tablet
Treatment B: Maribavir powder for oral suspension, 32.5% drug loading
Treatment C: Maribavir powder for oral suspension, 36.1% drug loading
*NOTE: Treatment will be dependent on randomization sequence.
*NOTE: There will be a drug washout of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4) and between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7)

Figure 2: Study Design Flow Chart Part 2



Treatment D: Maribavir powder for oral suspension (50 mg fasted)*
Treatment E: Maribavir powder for oral suspension (100 mg fasted)*
Treatment F: Maribavir powder for oral suspension (200 mg fasted)*
Treatment G: Maribavir powder for oral suspension (200 mg fed with a high-fat meal)*
*NOTE: Treatment will be dependent on randomization sequence. The doses to be evaluated in Part 2 may be adjusted based on relative bioavailability of the selected pediatric formulation (powder for oral suspension) to the Phase 3 tablet formulation observed in Part 1.
*NOTE: There will be a drug washout of a minimum of 72 hours and maximum of 73 hours between the administration of maribavir in Period 1 (Day 1) and the administration of maribavir in Period 2 (Day 4) between the administration of maribavir in Period 2 (Day 4) and the administration of maribavir in Period 3 (Day 7), and between the administration of maribavir in Period 3 (Day 7) and the administration of maribavir in Period 4 (Day 10)

3.2 Randomization

Part 1:

Subjects who meet all the inclusion criteria and none of the exclusion criteria on the morning of Day 1 will be randomized (1:1:1:1:1:1 ratio) to 1 of 6 sequences as shown in Table 1.

Table 1: Treatment Sequence Part 1: N=18

Sequence number (number of subjects per sequence)	Treatment Sequence
1 (n=3)	ABC
2 (n=3)	BCA
3 (n=3)	CAB
4 (n=3)	CBA
5 (n=3)	ACB
6 (n=3)	BAC

- Treatment A: maribavir 200 mg tablet- current Phase 3 formulation
- Treatment B: maribavir 200 mg powder for oral suspension, 32.5% drug loading
- Treatment C: maribavir 200 mg powder for oral suspension, 36.1% drug loading

Part 2:

Subjects who meet all the inclusion criteria and none of the exclusion criteria on the morning of Day 1 will be randomized (1:1:1:1 ratio) to 1 of 4 sequences as shown in Table 2.

Table 2: Treatment Sequence Part 2: N=20

Sequence number (number of subjects per sequence)	Treatment Sequence
1 (n=5)	DEGF
2 (n=5)	EFDG
3 (n=5)	FGED
4 (n=5)	GDFE

- Treatment D: maribavir powder for oral suspension (50 mg fasted)
- Treatment E: maribavir powder for oral suspension (100 mg fasted)
- Treatment F: maribavir powder for oral suspension (200 mg fasted)
- Treatment G: maribavir powder for oral suspension (200 mg fed with a high-fat meal)

The doses for Treatments D, E, F, and G may be adjusted based on relative bioavailability of the selected pediatric formulation (powder for oral suspension) to the Phase 3 tablet formulation observed in Part 1.

There is no stratification for this study for either part.

3.3 Blinding

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

3.4 Sample Size and Power Considerations

Sample size calculations were based on the following data:

- The intra-subject coefficient of variation (CV) is assumed at 0.166 and 0.218 respectively for $AUC_{0\text{-inf}}$ and C_{max}, which are estimated from the 90% confidence intervals (CIs) of the geometric mean ratio of $AUC_{0\text{-inf}}$, and C_{max} in Study 1263-104.

- Sample size estimation is performed using nQuery's two one sided test of equivalence in ratio of mean for crossover design study.
- True mean ratio: 1.00, 1.05
- Power: 80%, 90%
- One-sided α-level: 0.05 (corresponding to 90% CI)
- Bioequivalence range: 0.8-1.25

Table 3: Number of Subjects Required

True Ratio	Power	Intra-subject coefficient of variation	
		0.166	0.218
1.0	80%	12	18
	90%	14	22
1.05	80%	14	22
	90%	18	28

Note: sample size estimation is performed using nQuery's two one sided test of equivalence in ratio of mean for crossover design study.

Assuming a true mean ratio of 1.0 with intra-subject CV of 0.218, a total of 18 completers is required to achieve 80% study power to show that the 90% CIs for the geometric mean ratios of test formulation/reference formulation lie within the range of 0.80 to 1.25.

Therefore, for Part 1, three subjects in each sequence with a total of 18 subjects is required to randomize subjects to 1 of 6 sequences in a 1:1:1:1:1:1 treatment allocation. For Part 2, five subjects in each sequence with a total of 20 subjects is required to randomize subjects to 1 of 4 sequences in 1:1:1:1 treatment allocation. Subjects who withdraw early will be replaced and the replacement subject will receive the same treatment sequence as the subject being replaced.

4. STATISTICAL ANALYSIS SETS

4.1 Screened Set

The Screened Set consists of all subjects who have signed informed consent form. Subjects who were rescreened will be counted once in the Screened Set.

4.2 Enrolled Set

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

4.3 Randomized Sets

Part 1: The Randomized Set 1 consists of all subjects who were randomized to a treatment sequence in Part 1.

Part 2: The Randomized Set 2 consists of all subjects who were randomized to a treatment sequence in Part 2.

For analyses that will be performed using the randomized sets, the randomized treatment will be used regardless of the treatment actually received.

4.4 Safety Sets

Part 1: The Safety Set 1 consists of all subjects who received at least 1 dose of maribavir in Part 1.

Part 2: The Safety Set 2 consists of all subjects who received at least 1 dose of maribavir in Part 2.

Part 1 and 2 (Combined): The Total Safety Set includes subjects who received at least 1 dose of maribavir in either Part 1 or Part 2.

For analyses that will be performed using the safety sets, the treatment actually received will be used.

4.5 Pharmacokinetic Sets

Part 1: The PK Set 1 consists of subjects who received at least 1 dose of maribavir, did not vomit within 4 hours of dosing, and had at least 1 evaluable post-dose maribavir concentration value in Part 1.

Part 2: The PK Set 2 consists of subjects who received at least 1 dose of maribavir, did not vomit within 4 hours of dosing, and had at least 1 evaluable post-dose maribavir concentration value in Part 2.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

The number of subjects included in each statistical analysis set (ie, Randomized, Safety, and PK) will be summarized separately for Part 1 and Part 2.

The reasons for exclusion from the PK sets will be presented in the listings. The number and percentage of subjects who completed and prematurely discontinued the study, as well as subjects who completed dosing and prematurely discontinued the study drug, as recorded on the termination page of the electronic case report form, will be summarized separately for Part 1 and Part 2. Discontinuation reason will be specified. All subjects who prematurely discontinued the study or discontinued the study drug will be listed separately for Part 1 and Part 2.

Summaries and listing of subject disposition will be based on the randomized sets.

5.2 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented in tables for Part 1 and Part 2 Safety Set as well as PK Set separately. In addition, descriptive summaries of demographic and baseline characteristics will be presented in a table for the Total Safety Set by dose level regardless of the formulation. Demographics and other baseline characteristics data will be listed for Part 1 and Part 2 separately, and the listings will be based on the Safety Set for the corresponding part of the study.

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

Age will be calculated as the integer part of: (date of informed consent is signed – date of birth + 1)/365.25. Body mass index will be calculated as: weight (kg) / (height [m])^2. Height and weight at the last available measurement prior to first single dose of the investigational product (IP) will be used to calculate BMI.

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

5.3 Medical History

Medical history will be collected at the Screening Visit and will be coded using MedDRA Version 22.1 or newer (version to be delineated in the clinical study report [CSR]). Listings will be provided using the safety sets.

Medical history will be summarized separately for Part 1 and Part 2 by system organ class (SOC) and preferred term (PT), based on the Safety Set for the corresponding part. The summary of medical history will include the number and percentage of subjects who experienced the event and number of events experienced. System organ class will be sorted alphabetically, and within each SOC, PT will be sorted in the table Total column by descending order of frequency for each part of the study.

5.4 Prior Therapies, Procedures, and Medication

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

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

Prior medication usage presented by therapeutic class (according to Anatomical Therapeutic Chemical classification) and PT will be summarized based on the number and proportion of subjects separately for Part 1 and Part 2, based on the Safety Set for the corresponding part of the study. Multiple medication usage by a subject in the same category will be counted only once.

All prior therapies, procedures and medications will be listed separately for Part 1 and Part 2 based on the Safety Set for the corresponding part of the study.

5.5 Concomitant Therapies, Procedures, and Medications

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

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

Concomitant medication usage presented by therapeutic class (according to Anatomical Therapeutic Chemical classification) and PT will be summarized based on the number and proportion of subjects by treatment and overall separately for Part 1 and Part 2, based on the Safety Set for the corresponding part of the study. Multiple medication usage by a subject in the same category will be counted only once.

All concomitant therapies, procedures, and medications will be listed separately for Part 1 and Part 2 based on the Safety Set for the corresponding part of the study.

5.6 Exposure to Investigational Product

Exposure to IP will be summarized in terms of total planned dose in mg. Descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) will be presented to describe the exposure to IP by treatment separately for Part 1 and Part 2 based on the Safety Set for the corresponding part of the study.

Listings will be created by subject number and visit presenting the date and time of dose administration separately for Part 1 and Part 2 based on the Safety Set for the corresponding part of the study.

5.7 Treatment Compliance

Treatment compliance will be summarized in terms of number of subjects who completed the drug administration, who fasted 10 hours before study drug administration, and who fasted 4 hours after the study drug administration, by treatment separately for Part 1 and Part 2 based on the Safety Set for the corresponding part of the study.

For Treatment G in Part 2, a high-fat meal is to be consumed within 30 minutes prior to maribavir doses. A listing will be created by subject number and visit for meal consumption.

5.8 Protocol Deviations

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

Major/minor protocol deviations will be summarized by category and site for each treatment and overall separately for Part 1 and Part 2 based on the Safety Set. Major/minor protocol deviations will be listed based on the Safety Set separately for Part 1 and Part 2.

6. EFFICACY ANALYSES

Not applicable.

7. SAFETY ANALYSIS

The safety analysis will be performed using the safety sets. Safety variables include AEs, clinical laboratory data, vital signs, and ECG data. For clinical laboratory tests, vital signs, and ECG data, baseline is defined as the last value collected before the first single dose of each treatment.

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

7.1 Adverse Events

Adverse events will be coded using MedDRA Version 22.1 or newer (version to be delineated in the CSR).

An AE (classified by PT) that occurs after the first dose of IP, or that worsens in intensity or is reported with increased frequency following first dose of IP, will be considered a TEAE. If more than 1 AE with the same PT is reported before the date of the first dose of IP, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring after the first dose of IP under the PT.

Adverse events during the study will be assigned to the treatment(s) a subject has taken at the onset of the event. An AE with start date and time during the wash-out period or the 7 days follow-up period after last single dose of IP will be assigned to the prior treatment subject received. An AE that occurs more than 7 days after the date of the last single dose of IP will not be counted as a TEAE.

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

The number and percentage of subjects reporting TEAEs, as well as the number of events, will be tabulated by SOC and PT; by SOC, PT, and maximum severity. Treatment-emergent AEs considered related to IP will also be summarized by SOC and PT. If more than 1 AE occurs with the same PT for the same subject, then the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to IP. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending order of incidence.

Treatment-emergent AEs and related TEAEs will be summarized by PT by descending order of frequency. Non-serious TEAEs, serious TEAEs, TEAEs leading to discontinuation of IP, and TEAEs leading to death, will be summarized by SOC, PT, and treatment group.

Summaries of TEAEs will be presented separately for Part 1 and Part 2 using the corresponding Safety Set; additionally, summary of TEAEs will be presented for the Total Safety Set by dose level regardless of formulation.

Duration of an AE is calculated from the event start date time to the event stop date time. If both start and stop times are available, duration will be presented in hours with 1 decimal. If any of the start or end times are unavailable, duration will be presented in days as an integer. Listings of AEs will be presented by subject separately for Part 1 and Part 2 based on the corresponding Safety Set.

7.1.1 Selected Adverse Events

The following AEs (per PT) will be summarized for Part 1 as part of the planned (interim) analysis:

- Dysgeusia
- Nausea
- Vomiting
- Diarrhea
- Neutropenia

7.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline at each assessment time point for quantitative variables as well as shift tables from baseline to each visit for both quantitative and qualitative variables will be presented by treatment group separately for Part 1 and Part 2 for the following clinical laboratory variables.

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

Biochemistry Sodium, potassium, glucose, urea nitrogen, creatinine, calcium, chloride, thyroid stimulating hormone, free T_4, follicle-stimulating hormone, phosphate, protein, carbon dioxide, albumin, aspartate transaminase, alanine transaminase, gamma glutamyl transferase, alkaline phosphatase, total bilirubin, uric acid, and beta human chorionic gonadotropin.

Urinalysis pH, glucose, protein, blood, ketones, bilirubin, nitrites, leukocyte esterase, and specific gravity. Microscopic examination will be conducted if protein and/or blood is/are detected during urinalysis. At a minimum the microscopic examination will consist of red blood cells, white blood cells, casts, and bacteria.

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 4. The number and percentage of

subjects with post-baseline PCI values will be tabulated by treatment group separately for Part 1 and Part 2 based on the corresponding Safety Set; and will be tabulated based on the Total Safety Set by dose level regardless of formulation. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 post-baseline PCI value. Supportive listings of subjects with post-baseline PCI values will be provided including the subject number, site, baseline, and post-baseline values separately for Part 1 and Part 2.

Table 4: Criteria for Potentially Clinical Important Laboratory Tests

Parameter	Classification	Criteria: SI Units (Conventional Units)
Hematology		
Hemoglobin	LOW and DECREASE	<100 g/L (10g/dL) AND Decrease of ≥ 20 g/L (2.0 g/dL) from baseline value
	HIGH	>200 g/L (20g/dL)
Hematocrit	LOW and DECREASE	≤0.6 × LLN AND Decrease of ≥0.06 L/L (6.0%) from baseline value
	HIGH	>1.3 × ULN
RBC count	LOW	$<3 \times 10^{12}$/L
	HIGH	$>7.5 \times 10^{12}$/L
Platelets (thrombocytes)	LOW	$<0.6 \times$ LLN OR $<100 \times 10^9$/L (100×10^3/μL)
	HIGH	$>1.5 \times$ ULN OR $>500 \times 10^9$/L (500×10^3/μL)
WBC	LOW	$<0.5 \times$ LLN OR $<3.0 \times 10^9$/L (3×10^3/μL)
	HIGH	$>2 \times$ ULN OR $>16.0 \times 10^9$/L (16×10^3/μL)
Neutrophils	LOW	$<1.5 \times 10^9$/L (1.5×10^3/μL) OR < 40%
	HIGH	$>6.2 \times 10^9$/L (6.2×10^3/μL) OR > 70 %
Eosinophils	HIGH	$>0.5 \times 10^9$/L (0.5×10^3/μL) OR > 10.0%
Monocytes	HIGH	$>1.1 \times 10^9$/L (1.1×10^3/μL) OR >11 %
Basophils	HIGH	$>0.2 \times 10^9$/L (0.2×10^3/μL) OR > 2%
Lymphocytes	LOW	$<0.8 \times 10^9$/L (0.8×10^3/μL) OR < 22 %
	HIGH	$> 4.0 \times 10^9$/L (4.0×10^3/μL) OR > 44 %
Biochemistry		
Sodium	LOW	>5 mmol/L (5 mEq/L) below LLN
	HIGH	>5 mmol/L (5 mEq/L) above ULN
Potassium	LOW and DECREASE	Below LLN AND Decrease of >0.5 mmol/L (0.5 mEq/L) from baseline value
	HIGH and INCREASE	Above ULN AND Increase of > 0.5 mmol/L (0.5 mEq/L) from baseline value
Glucose (fasting)	LOW	≤4.2 mmol/L
	HIGH	≥6.7 mmol/L

Parameter	Classification	Criteria: SI Units (Conventional Units)
Blood urea nitrogen (BUN)	HIGH	>1.5 × ULN
Creatinine	HIGH and INCREASE	>150 µmol/L AND Increase > 30% from baseline value
Calcium	LOW and DECREASE	Below LLN AND Decrease of ≥0.25 mmol/L (1.0 mg/dL) from baseline value
	HIGH and INCREASE	Above ULN AND Increase of ≥ 0.25 mmol/L (1.0 mg/dL) from baseline value
Phosphate	LOW	>0.162 mmol/L (0.5 mg/dL) below LLN
	HIGH	>0.162 mmol/L (0.5 mg/dL) above ULN
Protein	LOW and DECREASE	Below LLN AND Decrease of ≥20 g/L (2.0 g/dL) from baseline value
	HIGH and INCREASE	Above ULN AND Increase of ≥20 g/L (2.0 g/dL) from baseline value
Albumin	LOW and DECREASE	Below LLN AND Decrease of ≥10 g/L (1.0 g/dL) from baseline value
	HIGH and INCREASE	Above ULN AND Increase of ≥10 g/L (1.0 g/dL) from baseline value
Aspartate transaminase	HIGH	>2 × ULN
Alanine transaminase (ALT)	HIGH	>2 × ULN
Gamma glutamyl transferase (GGT)	HIGH	>1.5 × ULN
Alkaline phosphatase (ALP)	HIGH	>1.5 × ULN
Total bilirubin	HIGH	>1.5 × ULN
Uric acid (with normal diet)	LOW and DECREASE	Below LLN AND Decrease of >0.119 mmol/L (2.0 mg/dL) from baseline value
	HIGH and INCREASE	Above ULN AND Increase of >0.119 mmol/L (2.0 mg/dL) from baseline value
Thyroid stimulating hormone	LOW	<0.5 µU/L
	HIGH	>5.0 µU/L
Urinalysis		
Urine glucose	HIGH	≥1+
Urine protein	HIGH	≥2+
Urine blood	HIGH	≥2+
Urine ketones	HIGH	≥2+
Urine bilirubin	HIGH	Positive
Urine nitrites	HIGH	Positive

Parameter	Classification	Criteria: SI Units (Conventional Units)
Urine leukocyte esterase	HIGH	Positive

Abbreviations: LLN=lower limit of normal value provided by the laboratory, RBC=Red Blood Cells, ULN=upper limit of normal value provided by the laboratory, WBC=White Blood Cells.

All laboratory data will be listed separately for Part 1 and Part 2 based on the corresponding Safety Set.

7.3 Vital Signs

Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, body temperature, and body weight) and their changes from baseline at each post-baseline visit and timepoint will be presented by treatment group separately for Part 1 and Part 2 based on the corresponding Safety Set.

Vital sign values will be considered PCI if they meet both the observed value criteria and the change from baseline criteria listed in Table 5. The number and percentage of subjects with PCI post-baseline values will be tabulated by treatment group separately for Part 1 and Part 2 based on the corresponding Safety Set; and will be tabulated based on the Total Safety Set by dose level regardless of formulation. The percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-baseline vital sign value. Supportive listings of subjects with post-baseline PCI values will be provided including the subject number, site, baseline, and post-baseline PCI values.

Table 5: Criteria for Potentially Clinically Important Vital Signs

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	Change from Baseline Value
Systolic blood pressure (mmHg)	High	≥140	Increase of ≥20
	Low	≤90	Decrease of ≥20
Diastolic blood pressure (mmHg)	High	≥90	Increase of ≥15
	Low	≤50	Decrease of ≥15
Pulse rate (beats per minute)	High	≥100	Increase of >15
	Low	≤45	Decrease of >15
Temperature (regardless of method)	High	>38.3°C or >100.9°F	
	Low	<35°C or <95°F	

Respiratory rate (breaths/min)	Low	<10	
	High	>25	
Weight (kg)	High	-	Increase of ≥5%
	Low	-	Decrease of ≥5%

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

All vital signs data will be listed separately for Part 1 and Part 2 based on the corresponding Safety Set.

7.4 Electrocardiogram (ECG)

Descriptive statistics for ECG variables (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc intervals) and their changes from baseline at each assessment time point will be presented by treatment group. QTc interval will be calculated using both Fridericia ($QTcF=QT/(RR)^{1/3}$) and Bazett ($QTcB=QT/(RR)^{1/2}$) corrections; and if RR is not available, it will be replaced with 60/heart rate in the correction formula. Electrocardiogram interpretation will be summarized by visit. A shift table from baseline to each visit for qualitative ECG results will be presented. Summaries will be presented separately for Part 1 and Part 2 based on the corresponding Safety Set.

Electrocardiogram variable values will be considered PCI if they meet or exceed the upper limit values listed in Table 6. The number and percentage of subjects with post-baseline PCI values will be tabulated by treatment group separately for Part 1 and Part 2 based on the corresponding Safety Set; and by dose level based on the Total Safety Set. The percentages will be calculated relative to the number of subjects with available baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-baseline ECG value. Listings of all subjects with post-baseline PCI value will be provided separately for Part 1 and Part 2 including the subject number, site, baseline, and post-baseline PCI values.

Table 6: Criteria for Potentially Clinically Significant ECG Values

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

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

All ECG results will be presented in data listings separately for Part 1 and Part 2.

7.5 Palatability

A palatability questionnaire will be completed following each dose administration to identify and characterize basic tastes, texture, and mouth feel and to assess the overall acceptability.

Palatability data will be summarized by treatment separately for Part 1 and Part 2 based on the corresponding Safety Set.

8. PHARMACOKINETIC ANALYSIS

All summaries and analyses of the PK data will be based on the Pharmacokinetic Set defined in Section 4.5.

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

8.1 Plasma Pharmacokinetic Concentrations

Blood samples will be drawn from each subject during this study for the determination of plasma concentration of maribavir. Serial blood samples will be collected at the following time points for each part of the study.

Collection of Blood Samples of Maribavir for Pharmacokinetic Analysis in Part 1

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
Maribavir	Plasma	1	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, and 24 hours post dose
	Plasma	4	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, and 24 hours post dose
	Plasma	7	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, and 24 hours post dose

Collection of Blood Samples of Maribavir for Pharmacokinetic Analysis in Part 2

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
Maribavir	Plasma	1	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, and 24 hours post dose
	Plasma	4	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, and 24 hours post dose
	Plasma	7	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, and 24 hours post dose
	Plasma	10	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, and 24 hours post dose

Plasma concentrations of maribavir will be measured using a validated analytical method. The following procedures will be used for plasma maribavir concentrations below the lower limit of quantification (LLOQ):

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

For each part, the concentration of maribavir in plasma will be summarized by treatment and scheduled sampling time using descriptive statistics (n, arithmetic mean, SD, median,

minimum, and maximum). Individual plasma concentration data will be presented in data listings by Part and Treatment.

For each part, individual concentrations of maribavir in plasma will be plotted by actual time on linear and semilogarithmic scales for each subject, displaying all treatments. Plots of mean maribavir plasma concentrations versus nominal time for all treatments will also be provided on linear and semilogarithmic scales for each part of the study.

8.2 Pharmacokinetic Parameters

Pharmacokinetic parameters of plasma maribavir will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times, except for interim PK analysis at the end of Part 1 where normal times will be used to allow for quick turnaround on PK data analysis and internal decision-making. The following PK parameters will be calculated using non-compartmental analysis using Phoenix WinNonlin version 8.0 or higher or SAS version 9.4 or higher (version to be delineated in the CSR). The PK parameters for maribavir will include, but may not be limited to:

Part 1 and Part 2 PK Parameters

Parameter	Description
C_{max}	Maximum observed drug concentration
t_{max}	Time of maximum observed concentration sampled during a dosing interval
$AUC_{0\text{-}last}$	AUC from time zero to the last measurable concentration in plasma
$AUC_{0\text{-}inf}$	AUC from time zero extrapolated to infinity, calculated using the observed value of the last non-zero concentration
$AUC_{0\text{-}inf}$%extrap	The percent of $AUC_{0\text{-}inf}$ extrapolated, calculated by $(1\text{-}AUC_{0\text{-}last}/AUC_{0\text{-}inf})$ *100
$t_{1/2}$	Terminal half-life
CL/F	Apparent total body clearance following oral administration, calculated as dose divided by $AUC_{0\text{-}inf}$
T_{lag}	Delay between the time of dosing and time of appearance of plasma concentration in the employed sampling scheme

Additional Part 2 PK Parameters

Parameter	Description
C_{max}/D^*	Dose-normalized C_{max}
$AUC_{0\text{-}last}/D^*$	Dose-normalized $AUC_{0\text{-}last}$
$AUC_{0\text{-}inf}/D^*$	Dose-normalized $AUC_{0\text{-}inf}$

*For Treatments D, E, and F only

Descriptive statistics (n, arithmetic mean, SD, median, minimum, maximum, and %CV) will be used to summarize the plasma PK parameters for maribavir by treatment for each part of the study. In addition, geometric mean, 95% CI of geometric mean and geometric CV% will be computed for C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ Individual plasma PK parameters will be presented in a data listing for each part of the study.

For Part 2, scatter plots of individual plasma maribavir C_{max} and AUCs (original and dose-normalized) versus dose will be provided.

8.3 Statistical Analysis of Pharmacokinetic Data

8.3.1 Part 1

Relative bioavailability

To evaluate the relative bioavailability of test treatment (Treatment B or C) versus reference treatment (Treatment A, i.e. current Phase 3 maribavir 200 mg tablet formulation), following the natural log-transformation, the PK parameters $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, and C_{max} will be analyzed using a linear mixed effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Point estimates and their associated 90% CIs will be constructed for the differences in the log-transformed parameters. The point estimates and their associated 90% CIs will be back-transformed to provide point estimates for the ratio of geometric least squares means and associated 90% CIs on the original scale. If the 90% CIs of the geometric mean ratios for both C_{max} and AUCs are within (0.8, 1.25), bioequivalence between the two formulations (test powder for oral suspension versus reference tablet) will be claimed. A forest plot will be generated to display the relative bioavailability results.

Statistical analysis of t_{max} and T_{lag} will be performed using a nonparametric test. The median difference of t_{max} and T_{lag} between treatments and 90% CIs of the median difference will be calculated from Hodges-Lehman estimate, and p-value will be produced from Wilcoxon signed rank test.

8.3.2 Part 2

Dose proportionality

Dose proportionality will be first assessed using the Power Model for (fasted) dose range tested in Part 2. The Power Model: $\log(Y_{ijk})=S_i + P_j + \beta x\log(D_k) + \varepsilon_{ijk}$, where D is the total number of doses, N are the total number of subjects and P the total number of periods and i=1,…..,N, j=1,….., P and k=1,…….., D. Y_{ijk} is the log-transformed response

variable, $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, or C_{max} on the k^{th} dose, in the j^{th} period, for the i^{th} subject. S_i is the random subject effect for the i^{th} subject, P_j is the fixed period effect for the j^{th} period, β was the slope and ε_{ijk} is the error. Dose proportionality is concluded when the 90% CIs of the slope β lie entirely within (1 + ln(0.8)/ln(r), 1 + ln(1.25)/ln(r)) where r is a ratio that describes the dose range and is defined as (highest dose/lowest dose). The fold increase with associated 90% CI in PK parameters when doubling the dose will be calculated.

Additionally, a linear mixed effect analysis of variance model with treatment, period, and sequence as fixed effects and subject within sequence as a random effect will be performed to fit log-transformed dose-normalized response variable, $AUC_{0\text{-inf}}/D$, $AUC_{0\text{-last}}/D$, or C_{max}/D, and to estimate all treatment differences and corresponding two-sided 90% CIs. The geometric mean ratios and 90% CI for each dose compared to the reference dose (50 mg dose) will be provided.

Food Effect

In Part 2, food effect will be assessed by comparison of Treatment G (200 mg selected maribavir formulation under fed condition) to Treatment F (200 mg selected maribavir formulation under fasted condition). The effect of food on maribavir PK parameters will be evaluated using an analysis of variance model on the natural log-transformed C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ with treatment, sequence, and period as fixed effects and subject within sequence as a random effect. Point estimates and 90% CIs for geometric mean ratios of C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ will be computed. If the 90% CIs for the geometric mean ratios falls within 0.8 and 1.25 limits, 'no food effect' on the exposure will be claimed. A forest plot will be generated to display the food effect on maribavir PK parameters.

Analysis of t_{max} and T_{lag} will be performed using nonparametric test. The median difference in t_{max} and T_{lag} between treatments and 90% CIs of the median difference will be calculated from Hodges-Lehman estimate, and p- value will be produced from Wilcoxon signed rank test.

9. PHARMACODYNAMIC ANALYSIS

Not applicable.

10. OTHER ANALYSES

No other analyses are planned for this study.

11. PLANNED ANALYSIS (INTERIM) AFTER PART 1

The formulation to be evaluated in Part 2 will be chosen based on the results from the Part 1 PK and palatability data from two candidate pediatric formulations. Thus, a selected set of analyses will be conducted after Part 1. If the number of replaced subject(s) is <=2, then planned analysis (interim) will be conducted based on the available Part 1 data without waiting for the replaced subject(s) to complete Part 1.

Evaluation of Part 1 PK will include performing noncompartmental analysis (NCA) by using nominal time to obtain PK parameters listed in Section 8.2. Statistical analysis of Part 1 PK parameters will be performed to compare the differences between test treatments (Treatment B or C) and reference treatment (Treatment A).

The disposition, demographics, AEs, SAEs, and selected AEs data will also be reviewed.

Palatability data from Part 1 will be reviewed.

Based on the results of the planned analysis of Part 1 data, the specific pediatric formulation will be chosen to be assessed in Part 2 of the study.

12. DATA HANDLING CONVENTIONS

12.1 General Data Reporting Conventions

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

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

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

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

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

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

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

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

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

8. Derived questionnaire scores, and other similar efficacy parameters recorded as integers, should be rounded to 1 decimal place for reporting.

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

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

12.2 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated or unscheduled assessments of safety parameters before the start of IP, then the results from the final safety assessment made prior to the start of IP will be used as baseline. If end of study assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating descriptive statistics. However, all post-baseline assessments will be used for PCS value determination, and all assessments will be presented in the data listings.

12.3 Handling of Missing, Unused, and Spurious Data

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

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

12.3.1.1 Incomplete Start Date

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

12.3.1.1.1 Missing Day and Month

- If the year of the incomplete start date is;
  - The same as the year of the date of the first dose of IP, then the day and month of

the date of the first dose of IP will be assigned to the missing fields.

- Before the year of the date of the first dose of IP, then December 31 will be assigned to the missing fields.
- After the year of the date of the first dose of IP, then 01 January will be assigned to the missing fields.

12.3.1.1.2 Missing Month Only

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

12.3.1.1.3 Missing Day Only

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

12.3.1.2 Incomplete Stop Date

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

12.3.1.2.1 Missing Day and Month

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

12.3.1.2.2 Missing Month Only

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

12.3.1.2.3 Missing Day Only

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

12.3.2 Missing Date Information for Adverse Events

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

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

12.3.2.1 Incomplete Start Date

Follow the same rules as in Section 12.3.1.1.

12.3.2.2 Incomplete Stop Date

Follow the same rules as in Section 12.3.1.2.

12.3.3 Missing Severity Assessment for Adverse Events

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

12.3.4 Missing Relationship to Investigational Product for Adverse Events

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

12.3.5 Character Values of Clinical Laboratory Variables

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

13. ANALYSIS SOFTWARE

Phoenix WinNonlin version 8.0 or higher will be used to perform the PK analysis.

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® (version to be delineated in the CSR) on a suitably qualified environment.

14. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

The following change is made to this statistical analysis:

- An additional summary for selected AEs (dysgeusia, nausea, vomiting, diarrhea, neutropenia) is added to support the planned (interim) analysis after Part 1.
- Planned analysis (interim) is updated as follows:

  The formulation to be evaluated in Part 2 will be chosen based on the results from the Part 1 PK and palatability data from two candidate pediatric formulations. Thus, a selected set of analyses will be conducted after Part 1. If the number of replaced subject(s) is <=2, then planned analysis (interim) will be conducted based on the available Part 1 data without waiting for the replaced subjects to complete Part 1.

15. REFERENCES

Not applicable

16. APPENDICES

16.1 Schedule of Activities

Table 7: Schedule of Assessments Part 1

Visit[a]	Screening	Treatment Period 1				Treatment Period 2			Treatment Period 3		Follow-up[l]
Study Day	**-28 to -2**	**-1**	**1[j]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demography	X										
Medical/medication history	X	X									
Physical examination[b]	X	X	X			X			X	X	
Randomization			X[k]								
Vital signs (blood pressure, pulse)[b,c]	X	X	X	X	X	X	X	X	X	X	
Oral temperature	X	X	X			X			X	X	
Height and weight[d]	X	X	X			X			X	X	
Electrocardiogram (12-lead)[b,e]	X	X	X	X		X	X		X	X	
Biochemistry, hematology, and urinalysis[b, f, m]	X	X		X			X			X	
HIV, HBsAg, and HCV antibodies	X										
Beta HCG Pregnancy test (females only)[b, g]	X	X								X	
FSH[h] test in perimenopausal women	X										
Urine drug and alcohol screening[i]	X	X									
Investigational Drug Administration			X			X			X		
Pharmacokinetic blood sampling[j, n]			X	X		X	X		X	X	
Palatability Assessment			X			X			X		
Admit to the CSU (Day -1)		X									
Discharge from the CSU (Day 8 after last assessment)										X	
Washout between treatment periods			X	X	X	X	X	X			
Adverse events/serious adverse events[b]	X	X	X	X	X	X	X	X	X	X	X

Visit[a]	Screening	Treatment Period 1				Treatment Period 2			Treatment Period 3		Follow-up[l]
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X

β-hCG=beta-human chorionic gonadotropin; CSU-clinical study unit; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PK=pharmacokinetic; SAE=serious adverse event; TSH=thyroid-stimulating hormone

[a] There will be a minimum of 72 hours and a maximum of 73 hours washout period between administration of the last dose of investigational product in Treatment Period 1 and Treatment Period 2. There will also be a minimum of 72 hours and a maximum of 73 hours washout period between administration of the last dose of investigational product in Treatment Period 2 and Treatment Period 3. Treatment Period 1 includes washout (Days 1 through 3), Treatment Period 2 includes washout (Days 4 through 6), and Treatment Period 3 is from Days 7 through 8.

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

[c] Vital signs will be obtained while subject is in the supine position on study days noted. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

[d] Height will be recorded at the screening visit only.

[e] Twelve-lead ECGs will be measured in the supine position. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

[f] Clinical laboratory assessments include serum biochemistry, TSH and FT_4, at (screening only), hematology, and urinalysis.

[g] Serum β-HCG test at Screening is required for all females. Urine pregnancy test is required for all females at subsequent scheduled time points.

[h] Females only, to confirm menopausal status.

[i] Drugs of abuse and alcohol at screening and Day-1

[j] See Table 8, Table 9, and Table 10 for detailed collection time points.

[k] Randomization is for Treatment Period 1, Day 1 only.

[l] There will be a follow-up telephone call approximately 7±2 days following the last dose of investigational product in Treatment Period 3 (Day 7). AEs/SAEs occurring up to the time of the follow-up telephone call will be captured. The follow-up telephone call should be completed for all subjects including those who withdraw or are removed from the study prior to Day 8 of Treatment Period 3.

[m] If screening occurs on Day -2, biochemistry, hematology and urinalysis is not required on Day -1

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

Table 8: Detailed Schedule of Assessments for Treatment Period 1 (Day 1), Part 1

Study Day	Day 1																Day 2
Hour (relative to dosing time)	**Predose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																
Randomization[b]	X																
Vital signs (blood pressure, pulse) [a, c]	X[e]								X								X
Oral Temperature[a]	X[e]																
Weight	X[e]																
Electrocardiogram (12-lead)[a,d]	X[e]								X								X
Biochemistry, hematology, and urinalysis[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[g]	X[e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[f]														

ECG=electrocardiogram; PK=pharmacokinetic; QTc=corrected QT interval

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

[b] Randomization will occur in Treatment Period 1, Day 1 only.

[c] Vital signs will be obtained while subject is in the supine position on study days noted. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

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

[e] These assessments should be performed within 30 minutes prior to dose administration.

[f] Palatability questionnaire should be given within 5 minutes of receiving dose

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

Table 9: Detailed Schedule of Assessments for Treatment Period 2 (Day 4), Part 1

Study Day	Day 4																Day 5
Hour (relative to dosing time)	**Pre-dose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Oral Temperature[a]	X[d]																
Weight	X[d]																
Electrocardiogram (12-lead)[a,c]	X[d]								X								X
Biochemistry, hematology, and urinalysis[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[f]	X[d]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

ECG=electrocardiogram; PK=pharmacokinetic; QTc=corrected QT interval

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

[b] Vital signs will be obtained while subject is in the supine position on study days noted. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

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

[d] These assessments should be performed within 30 minutes prior to dose administration.

[e] Palatability questionnaire should be given within 5 minutes of receiving dose

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

Table 10: Detailed Schedule of Assessments for Treatment Period 3 (Day 7), Part 1

Study Day	Day 7																Day 8
Hour (relative to dosing time)	Pre-dose	0	0.08	0.25	0.5	1	1.5	2	3	4	5	6	8	12	16	20	24
Physical examination[a]	X																X
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Electrocardiogram (12-lead)[a,c]	X[d]								X								X
Oral Temperature[a]	X[d]																X
Weight	X[d]																X
Biochemistry, hematology, and urinalysis[a]																	X
Pregnancy (females only)[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[f]	X[d]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

ECG=electrocardiogram; PK=pharmacokinetic; QTc=corrected QT interval

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

[b] Vital signs will be obtained while subject is in the supine position on study days noted. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

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

[d] These assessments should be performed within 30 minutes prior to dose administration.

[e] Palatability questionnaire should be given within 5 minutes of receiving dose

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

Table 11: Schedule of Assessments Part 2

Visit[a]	Screening	Treatment Period 1				Treatment Period 2			Treatment Period 3			Treatment Period 4		Follow-up[l]
Study Day	**-28 to -2**	**-1**	**1[j]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Informed consent	X													
Inclusion/ exclusion criteria	X	X												
Demography	X													
Medical/medication history	X	X												
Physical examination[b]	X	X	X			X			X			X	X	
Randomization			X[k]											
High-fat meal prior to dose administration			X[n]			X[n]			X[n]			X[n]		
Vital signs (blood pressure, pulse)[b,c]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Oral temperature	X	X	X			X			X			X	X	
Height and weight[d]	X	X	X			X			X			X	X	
Electrocardiogram (12-lead)[b,e]	X	X	X	X		X	X		X	X		X	X	
Biochemistry, hematology, and urinalysis[b, f, m]	X	X		X			X			X			X	
HIV, HBsAg, and HCV antibodies	X													
Pregnancy (females only)[b, g]	X	X											X	
FSH[h] test in perimenopausal women	X													
Urine drug and alcohol screening[i]	X	X												
Investigational Drug Administration			X			X			X			X		
Pharmacokinetic blood sampling[j, o]			X	X		X	X		X	X		X	X	
Palatability Assessment			X			X			X			X		
Admit to the CSU (Day -1)		X												
Discharge from the CSU (Day 11 after last assessment)													X	

Visit[a]	Screening	Treatment Period 1				Treatment Period 2			Treatment Period 3			Treatment Period 4		Follow-up[l]
Study Day	**-28 to -2**	**-1**	**1[j]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Washout between treatment periods			X	X	X	X	X	X	X	X	X			
Adverse events/serious adverse events[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

β-hCG=beta-human chorionic gonadotropin; CSU=clinical study unit; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PK=pharmacokinetic; SAE=serious adverse event; TSH=thyroid-stimulating hormone

[a] There will be a minimum of 72 hours and a maximum of 73 hours washout period between administration of the last dose of investigational product in Treatment Period 1 and Treatment Period 2. There will also be a 3-day washout period between administration of the last dose of investigational product in Treatment Period 2 and Treatment Period 3 and between administration of the last dose in Treatment 4. Treatment Period 1 includes washout (Days 1 through 3), Treatment Period 2 includes washout (Days 4 through 6), and Treatment Period 3 is from Days 7 through 9.

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

[c] Vital signs will be obtained while subject is in the supine position on study days noted. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

[d] Height will be recorded at the screening visit only.

[e] Twelve-lead ECGs will be measured in the supine position. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

[f] Clinical laboratory assessments include serum biochemistry, (TSH and FT_4 at screening only), hematology, and urinalysis.

[g] Serum β-HCG test at Screening is required for all females. Urine pregnancy test is required for all females at subsequent scheduled time points

[h] Females only, to confirm menopausal status

[i] Drugs of abuse and alcohol at screening, and drugs of abuse and alcohol Day -1.

[j] See Table 12, Table 13, Table 14, and Table 15 for detailed collection time points

[k] Randomization is for Treatment Period 1, Day 1 only.

[l] There will be a follow-up telephone call approximately 7±2 days following the last dose of investigational product in Treatment Period 43 (Day 10). Adverse events/SAEs occurring up to the time of the follow-up telephone call will be captured. The follow-up telephone call should be completed for all subjects including those who withdraw or are removed from the study prior to Day 11 of Treatment Period 4.

[m] If screening occurs on Day -2, biochemistry, hematology and urinalysis is not required on Day -1.

[n] Subjects in Part 2 will receive maribavir depending on his/her randomized assignment to treatment sequence following an overnight fast of at least 10 hours. The study subjects should start the high-fat meal 30 minutes before administration of the drug product. Trial subjects should eat this meal in 30 minutes or less and consume 100 percent of the meal.

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

Table 12: Detailed Schedule of Assessments for Treatment Period 1 (Day 1), Part 2

Study Day	Day 1																Day 2
Hour (relative to dosing time)	**Predose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																
Randomization[b]	X																
Vital signs (blood pressure, pulse)[a, c]	X[e]								X								X
Oral Temperature[a]	X																
Weight	X[e]																
Electrocardiogram (12-lead)[a,d]	X[e]								X								X
Biochemistry, hematology, and urinalysis[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[g,]	X[e, h]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[f]														

ECG=electrocardiogram; PK=pharmacokinetic; QTc=corrected QT interval

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

[b] Randomization will occur in Treatment Period 1, Day 1 only.

[c] Vital signs will be obtained while subject is in the supine position on study days noted. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

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

[e] These assessments should be performed within 60 minutes prior to dose administration.

[f] Palatability questionnaire should be given within 5 minutes of receiving dose

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

[h] The pre-dose PK sample for subjects on Treatment G should be collected after the high-fat breakfast and before dose administration.

Table 13: Detailed Schedule of Assessments for Treatment Period 2 (Day 4), Part 2

Study Day	Day 4																Day 5
Hour (relative to dosing time)	**Pre-dose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Oral Temperature[a]	X[d]																
Weight	X[d]																
Electrocardiogram (12-lead)[a,c]	X[d]								X								X
Biochemistry, hematology, and urinalysis[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[f]	X [d, g]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

ECG=electrocarodiogram; PK=pharmacokinetic; QTc=corrected QT interval

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

[b] Vital signs will be obtained while subject is in the supine position on study days noted. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

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

[d] These assessments should be performed within 60 minutes prior to dose administration.

[e] Palatability questionnaire should be given within 5 minutes of receiving dose

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

[g] The pre-dose PK sample for subjects on Treatment G should be collected after the high-fat breakfast and before dose administration.

Table 14: Detailed Schedule of Assessments for Treatment Period 3 (Day 7), Part 2

Study Day	Day 7																Day 8
Hour (relative to dosing time)	**Pre-dose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination [a]	X																
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Electrocardiogram (12-lead)[a,c]	X[d]								X								X
Oral Temperature[a]	X[d]																
Weight	X[d]																
Biochemistry, hematology, and urinalysis[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling[f]	X[d, g]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

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

[b] Vital signs will be obtained while subject is in the supine position on study days noted. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

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

[d] These assessments should be performed within 30 minutes prior to dose administration.

[e] Palatability questionnaire should be given within 5 minutes of receiving dose.

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

[g] The pre-dose PK sample for subjects on Treatment G should be collected after the high-fat breakfast and before dose administration.

Table 15: Detailed Schedule of Assessments for Treatment Period 4 (Day 10), Part 2

Study Day	Day 10																Day 11
Hour (relative to dosing time)	**Pre-dose**	**0**	**0.08**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**
Physical examination[a]	X																X
Vital signs (blood pressure, pulse)[a, b]	X[d]								X								X
Electrocardiogram (12-lead)[a,c]	X[d]								X								X
Oral Temperature[a]	X[d]																X
Weight	X[d]																X
Biochemistry, hematology, and urinalysis[a]																	X
Pregnancy (females only)[a]																	X
Investigational drug administration		X															
Pharmacokinetic blood sampling [f]	X[d, g]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Assessment			X[e]														

ECG=electrocarodiogram; PK=pharmacokinetic; QTc=corrected QT interval

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

[b] Vital signs will be obtained while subject is in the supine position on study days noted. Subjects should be in the appropriate position for at least 5 minutes prior to obtaining vital signs.

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

[d] These assessments should be performed within 60 minutes prior to dose administration.

[e] Palatability questionnaire should be given within 5 minutes of receiving dose

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

[g] The pre-dose PK sample for subjects on Treatment G should be collected after the high-fat breakfast and before dose administration.