Official Title: A Phase I, Single-Center, Open-Label, Parallel, Two Dose Level Study to Investigate the Pharmacokinetics, Safety, and Tolerability Following a Single Dose of Baloxavir Marboxil in Healthy Chinese Volunteers

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STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: YP40902

A PHASE I, SINGLE-CENTER, OPEN-LABEL, PARALLEL, TWO DOSE LEVEL STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY FOLLOWING A SINGLE DOSE OF BALOXAVIR MARBOXIL IN HEALTHY CHINESE VOLUNTEERS

AUTHORS: [redacted], [redacted], [redacted]

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.2 (Dated 06Mar2020) for Protocol YP40902.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1	17APR2019	[redacted]	Not Applicable – First Version
0.2	30MAY2019	[redacted]	1. In Section 6.5, add the scenario when 2 tests have the same testing dates (or testing times when testing time are applicable). 2. Remove the summary for 'Total'. 3. Remove the definition and summary of TEAE. Remove the imputation rule of AE partial or missing date. 4. Remove the summary of adverse event of special interest.
1.0	06JUN2019	[redacted]	Not Applicable – First Finalized Version
2.0	16AUG2019	[redacted]	Update vital sign markedly abnormal criteria.
2.1	5Nov2019	[redacted]	All subjects enrolled set are added in section 5.1
2.2	14DEC2019	[redacted]	Add section 9 for screen failure patients' analysis

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of pharmacokinetic and safety data for Protocol YP40902. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 2.0, dated 10Jan2019.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to evaluate the pharmacokinetics of baloxavir marboxil and baloxavir after a single oral dose of baloxavir marboxil.

2.2. SECONDARY OBJECTIVES

The secondary objective is to evaluate the safety and tolerability following a single oral dose of baloxavir marboxil.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

OVERALL DESIGN

Study Design

This Phase I study is an open-label, randomized, parallel-group, two dose level study in healthy Chinese participants to evaluate the PK, safety, and tolerability of baloxavir marboxil and baloxavir following a single oral administration of baloxavir marboxil.

Treatment Groups and Duration

A total of 32 healthy Chinese participants 16 in each group will be enrolled in the study.

After signing the informed consent, a screening period of up to 28 days is provided to complete the study-related assessments.

During the in-house period, on confirming all the eligibility requirements, the participants will be randomly allocated to one of the two parallel groups, 40 mg or 80 mg of study medication (baloxavir marboxil). The

participants will be admitted to the study center on Day -1 and receive study medication on morning of Day 1. Safety assessments and PK sampling will be carried out at scheduled timepoints. The study medication will be given after an overnight fast of approximately 10 hours followed by a fast of at least 4 hours postdose. Participants will receive standard meals while in the study center and can be discharged at the investigator's discretion on Day 4 after the 72-hour assessments have been completed.

The participants will visit the study center on Days 6, 8, 10, 12, and 15 for PK sampling, safety, and other assessments such as vital signs, ECG, and laboratory test etc.

Length of Study

The total duration of the study for each participant will be up to 6 weeks divided as follows:

- Screening: Up to 4 weeks
- In-house period: Day -1 to morning of Day 4
- Post-dosing and follow-up observation: Days 6, 8, 10, 12, and 15.

Participants will be admitted to the study center on Day -1 and will be discharged approximately 72 hours after the study medication administration.

End of Study

The end of the study is defined as the date when the last observation of the last participant occurs and is expected 14±1 day after the dose administration of last participant, unless the participant withdraws his/her consent or withdraws early due to any other reason.

NUMBER OF PARTICIPANTS

A total of 32 healthy Chinese participants, 16 participants in each group will be enrolled in the study. The number of participants (16 participants for each dose level) is chosen based on practical clinical judgement, the PK variability observed, anticipated drop-rate, and China's regulatory requirement. It is considered that 16 study participants in each group would provide sufficient data to characterize the PK of baloxavir and baloxavir marboxil.

SAMPLE SIZE DETERMINATION

A total of 32 Chinese participants will be enrolled in this study with 16 participants in each group of 40 mg and 80 mg baloxavir marboxil. The number of participants (16 participants for each dose level) is chosen based on practical clinical judgment, the PK variability observed (AUC and C_{max} in Caucasian and Japanese healthy participants), anticipated drop-rate, and China's regulatory requirements.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in section 1.3, Table 1 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

1. The all subjects randomized (RND) set is added to include all subjects provided informed consent for this study and are randomized to study medication.
2. The all subjects enrolled set (ENR) is added to include all subjects who provided informed consent for this study.

4. PLANNED ANALYSES

4.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC for this study.

4.2. INTERIM ANALYSIS

There are no interim analyses planned for this study.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by [redacted] Biostatistics following sponsor authorization of this statistical analysis plan, and database lock.

5. ANALYSIS SETS

5.1. ALL SUBJECTS ENROLLED SET [ENR]

The all subjects enrolled (ENR) set will contain all subjects who provide informed consent for this study.

5.2. ALL SUBJECTS RANDOMIZED SET [RND]

The all subjects randomized (RND) set will contain all subjects provide informed consent for this study and are randomized to study medication.

For analyses and displays based on RND, subjects will be classified according to randomized treatment.

5.3. SAFETY ANALYSIS SET [SAF]

The safety analysis set (SAF) will contain all subjects who received at least 1 dose of the study medication, whether prematurely withdrawn from the study or not. Subjects will be grouped by the actual dose regimen they received. All safety analyses will be based on the safety analysis set.

5.4. PK ANALYSIS POPULATION

All participants who receive study medication and who have evaluable PK data with no relevant protocol deviations with respect to the primary PK endpoint will be included in the PK analysis population.

Analyses will be carried out on the PK analysis population.

6. GENERAL CONSIDERATIONS

6.1. SUMMARY STATISTICS

For categorical variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative non-PK variables will be summarized using descriptive statistics, including n (number of subjects with non-missing observations), arithmetic mean, standard deviation (SD), 95% confidence interval (CIs) for the mean, median, minimum, and maximum values.

Summary statistics of plasma PK concentrations will include: n, arithmetic mean, SD, CV%, median, minimum and maximum.

Summary statistics for all plasma PK parameters (except for T_{max}) include: n, geometric mean, geometric CV%, arithmetic mean, SD, CV%, median, minimum, and maximum.

The PK parameter T_{max} will be summarized using n, median, minimum and maximum.

In general, data will be presented for each dose group (baloxavir marboxil 40 mg and 80 mg). An n ≥2 will be

required for calculations of descriptive statistics. If n =1, only n, minimum and maximum will be presented.

6.2. PRECISION

Safety variables (i.e., clinical laboratory values, vital signs, and ECG intervals) will be reported to the same precision as the source data. The derived variables (i.e., BMI) will be reported 1 more decimal place than the source data.

All PK concentrations will be reported and analyzed with the same precision as the source data regardless of how many significant figures or decimals the data carry. Derived PK parameters will be rounded for reporting purposes in by-subject listings. The unrounded derived PK data will be considered the source data for the calculation of descriptive statistics. For most derived PK parameters, values will be rounded to 3 significant digits, with the following exceptions:

- Parameters directly derived from source data (e.g., C_{max}) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (e.g., T_{max}) will be reported with the same precision as the actual elapsed sampling time value of the source data.

For the reporting and presentation of descriptive statistics and the results of statistical analyses, the following rules for precision will be applied.

Statistic	Precision for Reporting
Counts (n)	None
Percentages (%)	1 decimal place
Mean and difference between means (unadjusted and adjusted)	Actual data + 1 decimal place or digit
Median	Actual data + 1 decimal place or digit
SD	Actual data + 2 decimal place or digit
SE	Actual data + 2 decimal place or digit

Confidence intervals	Actual data + 1 decimal place or digit
Min	Same as actual data
Max	Same as actual data
CV%	1 decimal place
Geometric n	None
Geometric Mean	Actual data + 1 decimal place or digit
Geometric CV%	Actual data + 1 decimal place or digit
Slope	2 decimal places
Ratio between means	2 or 3 decimal places (according to endpoint)
p-values	3 decimal places *Note: Any p-value less than 0.001 will be presented as <0.001. Any p value greater than 0.999 will be presented as >0.999.*

6.3. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/ stop day of assessments and events.
Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

Study Day = (date of event – reference date).

Unless otherwise specified, In the situation where the event date is partial or missing, Study Day and any

corresponding durations will appear missing in the listings.

6.4. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered as baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

6.5. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will contribute to the best/ worst case value where required (e.g. shift table).
In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries
Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.6. WINDOWING CONVENTIONS

There will be no visit windowing for these analyses. All data will be organized and analyzed according to the scheduled times as outlined in the protocol and by the visit denoted on the Case Report Form (CRF).

6.7. STATISTICAL TESTS

No statistical tests will be performed.
Unless otherwise specified in the description of the analyses, two-sided 95% s will be used.

6.8. COMMON CALCULATIONS

- For quantitative measurements, change from baseline will be calculated as:

Test Value at Visit X – Baseline Value

- Percent change from baseline will be calculated as:
  (Test Value at Visit X – Baseline Value)/Baseline Value *100
- The time from Date of Event A to Date of Event B (days) is calculated as:
  (Date of Event B - Date of Event A + 1)/365.25.
- The time from Date of Event A to Date of Event B (months) is calculated as:
  (Date of Event B - Date of Event A + 1)/30.4375.
- The time from Date of Event A to Date of Event B (weeks) is calculated as:
  (Date of Event B - Date of Event A + 1)/7.

6.9. SOFTWARE VERSION

All derivations, statistical analyses, summaries, and listings will be generated using SAS version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina). Noncompartmental PK parameter calculations will be performed using Phoenix® WinNonlin® 8.0 or higher (Certara, L.P., Princeton, New Jersey, United States). Graphics will be prepared using the same version of SAS.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

There will be no adjustment for covariates in these analyses.

7.2. MULTICENTER STUDIES

This study will be conducted at one site. Center pooling is not applicable for use in analyses for this study.

7.3. MISSING DATA

For identification of previous or concomitant medications/non-drug treatment, no formal imputation will be performed on missing or incomplete dates. Rules presented in Appendix 2 Table 2 will be used to define if a medication/non-drug treatment is considered as a previous, concomitant or both previous and concomitant

medication/non-drug treatment.

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by [redacted] Biostatistics.

9. SCREEN FAILURE

This study will list or summarize the category and reasons in table and listings for the patients who experience screen failure. All patients who signed informed consent form (ENR) will be analyzed.

10. DISPOSITION AND WITHDRAWALS

All subjects who are randomized will be accounted for in this study.

Subject disposition and withdrawals will be presented for the RND set.

Following summaries will be produced by dose group:

- Subjects randomized
- Subjects randomized but not treated
- Subjects treated
- Subject who completed the study
- Subject who discontinued the study and reasons

11. PROTOCOL DEVIATIONS

Protocol deviation will be collected by clinical team and entered into clinical trial management system (CTMS). The major protocol deviation will be tabulated by dose group. All protocol deviations will be presented in listing including category, term, PD date, and severity for SAF. The categories of protocol deviation may include:

- Informed Consent Criteria
- Eligibility and Entry Criteria
- Concomitant Medication Criteria

- Laboratory Assessment Criteria
- Study Procedures Criteria
- Serious Adverse Event Criteria
- Visit Schedule Criteria
- IP Compliance
- Administrative Criteria
- Source Document Criteria
- Regulatory or Ethics Approvals Criteria
- Other Criteria

12. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the SAF by dose group.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent
- Sex
- Ethnicity
- Race
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Breath Alcohol Test
- Urine Cotinine Test
- Urine Drug Screen

12.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ height (m)^2
- Age (Years) = (Date of Informed Consent – Date of Birth+1)/365.25

13. MEDICAL HISTORY

Medical History information will be presented for the SAF by dose group.

All medical history from eCRF page 'Medical History' will be coded with Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 22.0 (MedDRA v22.0) or higher and will be summarized by system organ class (SOC) and preferred term (PT) for SAF. Number of subjects and percentage to the analysis set will be presented in frequency tables, ordered by primary SOC and PT in descending order of the frequency in group. For SOCs or PTs with the same frequency in group, categories will be sorted alphabetically.

14. PRIOR AND CONCOMITANT MEDICATIONS/ NON-DRUG TREATMENT

Medications will be presented for the SAF and coded using WHO Drug Dictionary Global version 01MAR2019. Medications will be presented by PT for the SAF.

Non-Drug treatments will be and coded using MedDRA v22.0 and presented by SOC and PT for the SAF.

See Appendix 2 for handling of partial dates for medications/non-drug treatments, in the case where it is not possible to define a medication/non-drug treatment as prior or concomitant, the medication/non-drug treatment will be classified as concomitant.

- 'Prior' medications/ non-drug treatments are these which started and stopped prior to the first dose of study medication.
- 'Concomitant' medication/non-drug treatments are these which:

  - started prior to, on or after the first dose of study medication
  - AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.

15. STUDY MEDICATION EXPOSURE AND COMPLIANCE

The date of study medication administration will be taken from the eCRF 'Drug Administration' form. Study medication administration will be tabulated and listed by group for SAF.

Missing or partial dates or time for study medication administration will not be imputed.

16. PHARMACOKINETIC ANALYSIS

16.1. PLASMA CONCENTRATION DATA

Individual PK blood sample collection times, derived sampling time deviations, and plasma concentrations of baloxavir marboxil and its metabolite will be listed.

Plasma concentrations for baloxavir marboxil and its major metabolite, baloxavir, will be summarized using descriptive statistics for each dose level by scheduled time, as described in Section 6.1. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics, except for the calculation of geometric mean where BLQ values will be set to ½ of the lower limit of quantitation (LLOQ). Concentrations that are missing will be omitted from the calculation of descriptive statistics.

For each analyte, figures of overlaid arithmetic mean concentration-time profiles at each dose level will be presented. Individual subject concentration-time profiles grouped by dose (all profiles presented in one plot) and by-subject plots displaying on the same graph profiles for both analytes (one plot for each subject) will also be presented. All concentration-time profiles will be depicted on linear and semi-logarithmic scales.

16.2. PLASMA PHARMACOKINETIC PARAMETERS

Single-dose PK parameters for plasma baloxavir marboxil and its major metabolite, baloxavir, will be estimated by noncompartmental methods using actual elapsed time from dose administration in the final analysis. Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters.

The following data handling conventions for concentrations apply to the PK analysis:

- Pre-dose samples that are missing or BLQ will be assigned a numerical value of zero.
- Any pre-dose concentration values that are quantifiable will be included in the PK analysis. Concentrations and the calculated PK parameters shall be listed and included in the applicable summaries and inferential statistics. Profiles with anomalous pre-dose concentration value which is not greater than 5% of C_{max} will be evaluated. The presence of anomalous pre-dose concentration value greater than 5% of C_{max} in the profile will be evaluated on a case-by-case basis to determine if exclusion is warranted by the data.

- Post-dose BLQ concentrations will be assigned a value of zero if they precede quantifiable data points in the initial portion of the profile (before C_{max}).
- A BLQ value that occurs between quantifiable data points, especially prior to C_{max} will be evaluated to determine if an assigned concentration of zero makes sense, or if reanalysis or exclusion of the data is warranted.
- Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing.
- Trailing BLQ values at the end of the collection interval (after the last quantifiable concentration) will be set to zero.
- If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantifiable values will be set to missing (blank data) and excluded from the PK analysis, unless otherwise warranted by the concentration time profile.

Handling of PK Concentration Values From Subjects Who Vomit:

- If a subject vomits at or before the 12th hour following dosing, only their PK concentration values up to the emesis event will be included in the PK concentration summary. If a subject vomits after the 12th hour following dosing, all their PK concentration values will be included in the PK concentration summary.

The molecular formula and molecular weight (MW) for each analyte are listed below:

- Baloxavir marboxil:
- Molecular Formula: $C_{27}H_{23}F_2N_3O_7S$
- Molecular Weight: 571.55 Da

- Baloxavir:
- Molecular Formula: $C_{25}H_{19}F_2N_3O_4S$
- Molecular Weight: 495.55 Da

Based on clinical PK data to date from Caucasian and Japanese subjects, baloxavir plasma concentrations have not been quantifiable in any of the collected samples. The same observation is anticipated in the current study. As such, the metabolite-to-parent exposure ratios (MRC_{max} and $MRAUC_{0\text{-}inf}$) will only be calculated if there is detectable

baloxavir plasma levels within the profile. MRC_{max} will be calculated if the profile contains 1 or more quantifiable baloxavir concentration; whereas a minimum of 4 quantifiable baloxavir concentrations are required for the calculation of $MRAUC_{0\text{-}inf}$.

The following PK parameters will be calculated for both analytes where estimable, unless otherwise indicated:

C_{max} (ng/mL)	Maximum observed plasma concentration obtained directly from the concentration versus time data.
T_{max} (h)	Time to maximum observed plasma concentration, obtained directly from the observed concentration versus time data.
$AUC_{0\text{-}inf}$ (ng·h/mL)	Area under the concentration-time curve in plasma from zero (pre-dose) extrapolated to infinite time, extrapolated to infinity by addition of the last observed quantifiable concentration divided by the elimination rate constant: $AUC_{0\text{-}last} + C_{last}/\lambda_z$.
$AUC_{0\text{-}last}$ (ng·h/mL)	Area under the concentration-time curve in plasma from zero (pre-dose) to the time of the last quantifiable concentration.
$AUC_{0\text{-}t}$ (ng·h/mL)	Area under the concentration-time curve in plasma from zero (pre-dose) to time t. Time t may be chosen as the latest common time point where evaluable concentrations are available in at least 90% of participants.
λ_z (1/h)	Apparent terminal rate constant, determined by linear regression of the terminal log-linear segment concentration-time curve.
$t_{1/2}$ (h)	Apparent terminal elimination half-life, determined as: $\ln 2/\lambda_z$.
CL/F (L/h)	Apparent systemic clearance after oral dosing, calculated for baloxavir marboxil only as follows: $Dose/AUC_{0\text{-}inf}$.
V_z/F (L)	Apparent volume of distribution following oral dosing based on the terminal phase, calculated for baloxavir marboxil only as follows: $Dose/(\lambda_z \cdot AUC_{0\text{-}inf})$.
C_{24} (ng/mL)	Observed plasma concentration at scheduled 24 hour post-dose sample.
C_{48} (ng/mL)	Observed plasma concentration at scheduled 48 hour post-dose sample.
C_{72} (ng/mL)	Observed plasma concentration at scheduled 72 hour post-dose sample.

MRC_{max}	Mole ratio of metabolite C_{max} to parent (baloxavir marboxil) C_{max}, calculated as follows: $MRC_{max}: \frac{\text{baloxavir } C_{max}}{\text{baloxavir marboxil } C_{max}} \times \frac{\text{baloxavir marboxil MW}}{\text{baloxavir MW}}$
$MRAUC_{0\text{-inf}}$	Mole ratio of metabolite $AUC_{0\text{-inf}}$ to parent (baloxavir marboxil) $AUC_{0\text{-inf}}$, calculated as follows: $MRAUC_{0\text{-inf}}: \frac{\text{baloxavir } AUC_{0-inf}}{\text{baloxavir marboxil } AUC_{0-inf}} \times \frac{\text{baloxavir marboxil MW}}{\text{baloxavir MW}}$

The following PK parameters will be calculated for diagnostic purposes and listed but will not be summarized.

$t_{1/2}$, Interval	The time interval (h) of the log-linear regression to determine λ_z
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z.
Rsq	Goodness of fit statistic for calculation of λ_z.
$\%AUC_{ex}$	Percentage of $AUC_{0\text{-inf}}$ obtained by extrapolation, calculated as $[(C_{last}/\lambda_z)/AUC_{0\text{-inf}} \times 100]$.

Areas under the curve (AUCs) will be calculated by linear up/log down trapezoidal summation, where at least 3 quantifiable post-dose concentrations are available for AUCs. If the $\%AUC_{ex}$ is >30.0% of $AUC_{0\text{-inf}}$, then the corresponding individual subject number will be flagged with an asterisk "*" in the listing; $AUC_{0\text{-inf}}$ and related parameters will not be included in the applicable summaries and inferential statistics.

For partial AUC ($AUC_{0\text{-t}}$):

- If concentration at the end of the interval is available but collection time is missing, partial AUC will be calculated using scheduled time. In this case, the partial AUC estimate will be listed only and flagged for exclusion from the summaries and inferential statistics.
- If concentration at the end of the interval is the first BLQ value, partial AUC will be calculated (i.e. represents AUC_{all}). If concentration at the end of the interval is a later consecutive BLQ value, the partial AUC will not be calculated.

Visual assessment will be used to identify the terminal log-linear segment of the concentration-time curve for λ_z calculation. A minimum of 3 data points will be used for determination. If Rsq <0.800, λ_z and related parameters will be listed only.

The nominal dose (e.g., 40 mg or 80 mg) will be used for calculation of baloxavir marboxil dose-dependent PK parameters (CL/F and V_z/F).

For each analyte, individual PK parameters will be listed and summarized by dose levels using descriptive statistics, as described in Section 6.1.

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set (SAF).
There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

17.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 22.0.
An overall summary of number of subjects within each of the categories described in the sub-section below, will be provided as specified in the templates.
Listings will include .

17.1.1. ALL AEs

Incidence of AEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and relationship to study medication.

17.1.1.1. Severity

Severity is classed as mild/ moderate/ severe (increasing severity). If a subject reports an AE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

17.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as 'not related' and 'related' (increasing severity of relationship). A 'related' AE is defined as an AE with a relationship to study medication as 'related' to study medication. AEs with a missing relationship to study medication will be regarded as 'related' to study medication. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

17.1.2. SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are those events recorded as 'Serious' on the Adverse Events page of the (e)CRF. A summary of serious AEs by SOC and PT will be prepared.

17.1.3. ADVERSE EVENTS LEADING TO DEATH

AEs leading to Death are those events which are recorded as 'Fatal' on the Adverse Events page of the (e)CRF. A summary of AEs leading to death by SOC and PT will be prepared.

17.2. DEATHS

If any subjects die during the study as recorded on the 'End of study' page of the (e)CRF with 'Death' selected, the information will be presented in a summary table and a data listing.

17.3. LABORATORY EVALUATIONS

Results from the local laboratory will be included in the reporting of this study for Hematology, Clinical Chemistry, Urinalysis, Coagulation, Thyroid Functions, Lipid Profiles. The test details can be found in Appendix 4, Table 7 of the protocol.

Presentations will use SI Units.
Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.
In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries. The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Incidence of abnormal values according to normal range criteria (for quantitative measurements)
- Shift from baseline to worst value by Investigator's Assessment

17.3.1. Laboratory Reference Ranges and Markedly Abnormal Criteria

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).

High: Above the upper limit of the laboratory reference range.

17.4. ECG Evaluations

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study. The following ECG parameters will be reported for this study:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTc Interval (msec)
- QTcF Interval (msec)
- Pulse Rate (bpm)
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (ANCS)
    - Abnormal, Clinically Significant (ACS)
    - Not Evaluable

If triplicate ECG testing is done for this study, the latest test on the same visit will be used in the summaries.

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)
- Overall Assessment by visit
- Shift from baseline to worst post-baseline by Overall Assessment

- The summary statistics for QTcF, number of subjects with value > 450, > 480 and > 500, change from baseline > 30, > 60 and > 90 will be summarized
- Listing of all ECG parameters

17.4.1. ECG Markedly Abnormal Criteria

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria for worst post-baseline result:

- Absolute values for QTcF will be classified as:

  - > 450 msec
  - > 480 msec
  - > 500 msec

- Change from Baseline for QTcF will be classified as:

  - >30 msec increase from baseline
  - >60 msec increase from baseline

17.5. Vital Signs

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (^{0}C)
- Weight (kg)

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit
- Incidence of markedly abnormal values
- Shift from baseline according to markedly abnormal criteria

17.5.1. Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria.

Variable	Unit	Low	High
Systolic Blood Pressure	mmHg	≤ 90 mmHg OR change from baseline ≤ -20 mmHg	≥ 180 mmHg OR change from baseline ≥ 20 mmHg
Diastolic Blood Pressure	mmHg	≤ 50 mmHg OR change from ≤ -15 mmHg	≥ 105 mmHg OR change from baseline ≥ 15 mmHg
Heart rate	Bpm	≤ 50 bpm OR change from baseline ≤ -15 bpm	≥ 120 bpm OR change from baseline ≥ 15 bpm
Temperature	°C	NA	≥ 38.3 °C OR change from baseline ≥ 1.1 °C

17.6. Other Safety Assessments

The Serology and pregnancy test data will only be listed.

18. REFERENCES

Protocol YP40902 baloxavir marboxil v2 Published Output-2, dated 10JAN2019

Annotated Trail Design for study YP40902 v1.0, dated 18FEB2019

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

[redacted] OUTPUT CONVENTIONS

Outputs will be presented according to the [redacted] general guidelines and template for outputs conventions.

GENERAL RULES

The following conventions will be applied for reporting descriptive statistics of all continuous data (except PK values):

- Q1, Q3, Minimum, and Maximum will have same decimal place as RAW/SDTM data for non-derived data (e.g. weight).
- Mean, and Median have the one more digit than RAW/SDTM data for non-derived data (e.g. weight).
- SD will be presented with one digit more than mean.
- Statistics on derived data (e.g. treatment exposure time in days) will be rounded to reasonable number of digits. Maximal digits should be available in ADaM datasets.

Qualitative variables will be summarized by counts and percentages. Unless otherwise stated, the calculation of proportions will be based on the number of subjects of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables, Listings and Graphs

Treatment Group	For Tables, Listings and Graphs
Baloxavir marboxil 40 mg	40 mg
Baloxavir marboxil 80 mg	80 mg

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Scr
Baseline	BL
Day 1	D1
…	…
Day 15	D 15

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized treatment group (or treatment received if it's a safety output),
- Subject ID,
- Date (where applicable).

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS/NON-DRUG TREATMENTS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of study, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of study, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of study, assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of study, assign as concomitant
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of study, assign as concomitant

START DATE	STOP DATE	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of study, assign as concomitant
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Missing	Assign as concomitant