Official Title: A Phase III, Randomized, Open-Label, Active-Controlled Study to Assess the Safety, Pharmacokinetics and Efficacy of Baloxavir Marboxil in Chinese Pediatric Patients 1 to < 12 Years of Age with Influenza Symptoms

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STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS AND EFFICACY OF BALOXAVIR MARBOXIL IN CHINESE PEDIATRIC PATIENTS 1 TO < 12 YEARS OF AGE WITH INFLUENZA SYMPTOMS**
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STATISTICAL ANALYSIS PLAN APPROVAL	
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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document V 3.0.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	See electronic date stamp on the last page of this document	V 2.0, 2 Feb 2024

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice a day
BMI	Body Mass Index
CRF	Case Report Form
EC_{50}	50% effective concentration
FAS	Full Analysis Set
FASi	Full Analysis Set-infected participants
IxRS	Interactive Voice/Web-Based Response System
LLoD	Lower Limit of Detection
LLoQ	Lower Limit of Quantification
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PK	pharmacokinetic
PKAS	pharmacokinetic analysis set
PT	preferred term
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SOC	system organ class
TEAEs	treatment-emergent adverse events
TTAS	time to alleviation of influenza signs and symptoms

1. INTRODUCTION

The analyses described in this Statistical Analysis Plan (SAP) will supersede those specified in Protocol YV44465 for the purposes of a regulatory filing.

The objective of this study is to evaluate the safety, pharmacokinetics, and efficacy of baloxavir marboxil in Chinese pediatric participants aged 1 to < 12 years with influenza symptoms.

There are no changes to the planned analyses described in the protocol.

1.1 TRIAL OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 1 Primary and Secondary Objectives and Corresponding Estimand

Safety (Primary) Objective	Estimand Definition
• To describe the safety of a single dose of baloxavir marboxil compared with 5 days of oseltamivir administered BID in Chinese pediatric participants	• Population: All participants aged 1 to < 12 years with influenza symptoms who received at least 1 dose of study treatment • Endpoint: – Incidence, severity, and timing of adverse events, serious adverse events, with severity determined according to NCI CTCAE v5 – Change from baseline in vital sign measurements – Change from baseline in clinical laboratory test results • Treatment: – Experiment arm: baloxavir marboxil single dose – Control arm: oseltamivir 5 days BID • Intercurrent events and handling strategies – Treatment discontinuation: treatment policy strategy – Rescue medication: treatment policy strategy • Population-level summary: No formal statistical testing will be conducted. Analyses will be descriptive. – Incidence of adverse events, serious adverse events by System Organ Class, by Preferred Term and by worst severity – Change from baseline summaries will be presented overall and by treatment with use of descriptive statistics, including means, standard deviations, medians, and ranges for continuous variables

Table 1 Primary and Secondary Objectives and Corresponding Estimand (cont.)

Efficacy (Secondary) Objective	Estimand Definition
• To describe the clinical efficacy of baloxavir marboxil compared with oseltamivir in Chinese pediatric participants	• Population: All participants aged 1 to < 12 years with influenza symptoms who received at least 1 dose of study treatment who have had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study • Endpoints: – Time to alleviation of influenza signs and symptoms, defined as the length of time taken from the start of treatment to the point at which all of the following criteria are met and remain so for at least 21.5 hours: A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms (Items 14 and 15 of the CARIFS, see Appendix 1. A "yes" response to the following question on the CARIFS: "Since the last assessment has the subject been able to return to day care/school (if applicable), or resume his or her normal daily activity in the same way as performed prior to developing the flu?" (if possible). Return to afebrile state (tympanic temperature ≤ 37.2°C). – Duration of fever (time to return to afebrile state [tympanic temperature ≤37.2°C] and remaining so for at least 21.5 hours) – Duration of symptoms (alleviation of all symptoms as defined by a score of 0 [no problem] or 1 [minor problem] and remaining so for at least 21.5 hours, for all 18 symptoms specified in the CARIFS questionnaire) – Time to return to normal health and activity based on the CARIFS questionnaire – Frequency of influenza-related complications (death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures, myositis) – Proportion of participants requiring antibiotics for influenza related complications • Treatment: – Experiment arm: baloxavir marboxil single dose – Control arm: oseltamivir 5 days BID • Intercurrent events and handling strategies – Treatment discontinuation: treatment policy strategy

Table 1 Primary and Secondary Objectives and Corresponding Estimand (cont.)

Efficacy (Secondary) Objective	Estimand Definition
	– Rescue medication: treatment policy strategy • Population-level summary: No formal statistical testing will be conducted. Analyses will be descriptive. Time to event endpoints and duration endpoints will be summarized with use of Kaplan Meier plots and median survival time for each treatment arm.
Virology (Secondary) Objective	**Estimand Definition**
• To evaluate the virological activity of baloxavir marboxil compared with oseltamivir in Chinese pediatric participants	• Population: All participants aged 1 to < 12 years with influenza symptoms who received at least 1 dose of study treatment who have had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study • Endpoints: – Time to cessation of viral shedding by virus titer and by RT-PCR with use of samples from respiratory swabs – Change from baseline in influenza virus titer and in the amount of virus RNA (RT-PCR) at each timepoint with use of samples from respiratory swabs – Proportion of participants with positive influenza virus titer and proportion of participants positive by RT-PCR at each timepoint with use of samples from respiratory swabs – Area under the curve in virus titer and in the amount of virus RNA (RT-PCR) with use of samples from respiratory swabs • Treatment: – Experiment arm: baloxavir marboxil single dose – Control arm: oseltamivir 5 days BID • Intercurrent events and handling strategies – Treatment discontinuation: treatment policy strategy – Rescue medication: treatment policy strategy • Population-level summary: Summaries will be presented overall and by treatment with use of descriptive statistics, including means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables Time to event endpoints will be summarized with use of Kaplan Meier plots and median survival time.

BID = twice a day; CARIFS = Canadian Acute Respiratory Illness and Flu Scale; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PCR = polymerase chain reaction; RT-PCR = reverse transcriptase polymerase chain reaction.

Table 2 Other Secondary Objectives and Endpoints

Pharmacokinetic (Secondary) Objective	Corresponding Endpoints
• To describe the PK of baloxavir after single-dose administration of baloxavir marboxil in Chinese pediatric participants	• Plasma concentrations of baloxavir (RO7191686, active metabolite) will be summarized by time (C_{24} and C_{72}) and body weight group (<20kg and ≥20 kg) • Population PK model derived parameters (e.g., AUC_{inf}, C_{max}, and other PK parameters as appropriate) (modeling report)
Virology (Secondary) Objective	**Corresponding Endpoints**
• To evaluate the polymorphic and treatment-emergent amino acid substitutions in the PA gene and drug susceptibility in participants with evaluable virus in Chinese pediatric participants	• Polymorphic and treatment-emergent amino acid substitutions in the PA gene • Drug susceptibility in participants with evaluable virus
Palatability (Secondary) Objective	**Corresponding Endpoint**
• To evaluate the palatability of the oral suspension	• Proportion of participants reporting each palatability and acceptability response (see Appendix 3)

AUC_{inf} = area under the concentration-time curve extrapolated to infinity; C_{24} = concentration at 24 hours postdose; C_{72} = concentration at 72 hours postdose; C_{max} = maximum observed concentration; PK = pharmacokinetic; $t_{1/2}$ = elimination half-life; T_{max} = time of maximum observed concentration.

1.2 STUDY DESIGN

This is a multicenter, randomized, open-label, active-controlled (i.e., oseltamivir) study to assess the safety, pharmacokinetics, and efficacy of baloxavir marboxil compared with oseltamivir in Chinese pediatric participants aged 1 to < 12 years with influenza symptoms within 48 hours of symptom onset.

Approximately 100 pediatric participants are planned to be enrolled. Of the overall sample size, approximately 1/3 participants who are 1 to < 5 years old and 2/3 participants who are 5 to < 12 years old are planned to be enrolled.

Participants will be screened and randomized on Day 1 and assigned in a 2:1 ratio to receive a single oral dose of baloxavir marboxil based on body weight (2 mg/kg for participants weighing < 20 kg or 40 mg for participants weighing ≥ 20 kg to < 80 kg or 80 mg for those weighing ≥ 80 kg)/[redacted] for oral suspension or oseltamivir (twice a day dose based on body weight) for 5 days. Re-screening of participants who fail to meet the inclusion and exclusion criteria will not be permitted for the same illness

episode, as the time from symptom onset to the treatment window is limited to 48 hours. Either drug will be started at the time of randomization.

The total study duration for each participant will be 29 days, consisting of a 5-day treatment period (mandatory visits on Days 1, 2, and 4) and a 24-day follow-up period (mandatory visits on Days 6, 10, and 29). For the following assessments at clinic visits: physical examinations, vital signs, adverse events, concomitant therapies, clinical laboratory tests, and nasal/throat swabs. Visits on Day 29 or early termination visits can be conducted remotely. Throughout the treatment follow-up periods, the parents/caregivers will maintain a participant diary for each participant in order to record body temperatures (tympanic assessment), influenza symptoms, and acetaminophen use.

Temperatures will be recorded as follows:

- Days 1−3: 4 times daily (morning, noon, evening, and bedtime);
- Days 4−9: twice a day (morning and evening);
- Days 10−15: once daily.

Influenza symptoms will be recorded as follows:

- Days 1−9: twice a day (morning and evening)
- Days 10−15: once a day.

1.2.1 Treatment Assignment

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from an Interactive Voice/Web-Based Response System (IxRS).

Participants will be randomly assigned in a 2:1 ratio to one of the two treatment arms: a single oral dose of baloxavir marboxil or oseltamivir. Randomization will be stratified by age group (1-<5 years old versus 5-<12 years old) and high risk factors for influenza complications (with versus without), see Appendix 2.

1.2.2 Independent Review Facility

No Independent Review Facility is planned for this study.

1.2.3 Data Monitoring

No Data Monitoring Committee is planned for this study.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested for this study.

2.2 SAMPLE SIZE DETERMINATION

No formal sample-size calculations were performed. Approximately 100 pediatric participants (67 participants in the baloxavir marboxil treatment group and 33 participants in the oseltamivir treatment group) are planned to be enrolled.

The sample size of 67 participants in the baloxavir marboxil treatment group will provide a probability of 87% to detect an adverse event with a 3% incidence rate for at least 1 participant. The given sample size provides a probability of at least 1 participant experiencing an adverse event with a true incidence rate from 1%−5% as shown in Table 3.

Table 3 Probability of Adverse Events by Incidence Rates

	True Incidence Rate of an Adverse Event				
	1%	2%	3%	4%	5%
Probability of at least 1 participant experiencing an adverse event	49%	74%	87%	94%	97%

Of the planned overall sample size, approximately 1/3 participants aged 1 to < 5 years old and 2/3 participants aged 5 to < 12 years old are planned to be enrolled.

The number of participants in this study will be monitored on an ongoing basis in order to ensure an adequate number of specific participants are enrolled (e.g., participants with high risk factors for influenza complications and participants meeting the definition of full analysis set-infected participants (FASi).

Note: Sparse Pharmacokinetic (PK) samples from at least 48 pediatric participants in the baloxavir group will be collected to ensure at least 40 pediatric participants' samples are available for analysis. The sample size is determined to reach approximately 10% of the overall pediatric population which are included in the population PK model.

3. ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 4..

Table 4 Participant Analysis Sets

Participant Analysis Set	Description
FAS	All randomized participants; participants will be included in the analyses according to the treatment to which they were assigned.
FASi	A subset of FAS participants who received at least 1 dose of study treatment and had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study; participants will be analyzed according to the treatment to which they were assigned.
SAS	All participants who received at least 1 dose of study treatment; participants will be analyzed according to the treatment that they actually received.
PKAS	All participants with evaluable PK samples from the baloxavir marboxil arm (i.e., who received baloxavir marboxil).

FAS = full analysis set; FASi = full analysis set-infected participants; PCR = polymerase chain reaction; PK = pharmacokinetic; PKAS = pharmacokinetic analysis set; SAS = safety analysis set.

4. STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

The statistical analyses of safety, pharmacokinetics and efficacy will be descriptive. The Safety Analysis Set (SAS) will be used for all analyses on primary endpoints and analyses of secondary efficacy and virology endpoints will be conducted on the FASi. The PK analysis set (PKAS) will be used for the PK analyses.

4.1.1 Visit Windows

Table 5 Acceptable Time Windows for Parameters Other Than Data from the Patient Diary

Time Point (Scheduled Time Point)	Acceptable Time Window
Pre-dose at Visit 1 (Day 1)'	Before dosing on Day 1
Post-dose at Visit 1 (Day 1)'	Between 0.5 and 4 hours after dosing (on Day 1)
Visit 2 (Day 2)	Day 2
Optional Visit 1 (Day 3)	Day 3
Visit 3 (Day 4)	Day 4
Visit 4 (Day 6)	Between Day 5 and Day 7 as follows: • if patient presents on Day 5 with no Day 4, and no Day 6 this will be classed as Visit 4. • if patient presents on Day 5 with no Day 4, and Day 6 this will be classed as Visit 3. • if patient presents on Day 5 with Day 4 and no Day 6 this will be classed as Visit 4.
Visit 5 (Day 10)	Between Day 8 and Day 12
Optional Visit2 (Day 15)	Between Day 13 and Day 22
Visit 6 (Day 29)	On or after Day 23
Withdrawal	Date of withdrawal + 14 days

* if time is missing for data collected on Visit 1 where, per the schedule of activities, this data should be collected at 'v1 screening' or 'v1 post-dose' it is defined as 'Pre-dose at Visit 1 (Day 1)' or 'Post-dose at Visit 1 (Day 1)' respectively.

Measurements collected within the acceptable time window for each scheduled assessment time point, including data obtained at the time of withdrawal, will be used for the analyses of all endpoints at each assessment time point. For all patients with multiple values within a visit window, the value obtained closest to the target time point will be used. If two measurements collected with the same time deviation exist before and after the target time point, the measurement obtained before the target time point will be adopted for analysis. The assessment time point having no measurements within the corresponding acceptable time window will be considered as missing.

For summaries of data not collected by visit, such as adverse events, medical history and concomitant medications, all data up to the study completion/discontinuation date will be included.

4.2 PRIMARY ENDPOINT(S)/ESTIMAND(S) ANALYSIS

4.2.1 Definition of Primary Estimand/Endpoints

The primary endpoint/estimand is to compare the safety of a single dose of baloxavir marboxil with 5 days of oseltamivir administered twice a day (BID), as defined in Table 1.

4.2.2 Main Analytical Approach for Primary Estimand/Endpoints

Safety will be assessed through summaries or listings of adverse events, clinical laboratory test results, and vital signs.

4.2.2.1 Adverse Events

Only treatment-emergent adverse events (AEs) will be summarized. Treatment-emergent AEs (TEAEs) are defined as those AEs with observed or imputed onset date on or after the start date of trial treatment. Only where the most extreme intensity is greater than the initial intensity (or if most extreme intensity was not missing and initial intensity was missing) will events with an onset date prior to the start of study drug considered treatment emergent. An AE with a completely missing start date was assumed to be treatment-emergent unless the AE had a complete non-imputed end date that was prior to study Day 1.

Adverse events will be coded and tabulated by system organ class (SOC) and/or preferred term (PT). In tabulations, PTs and their associated SOC will be presented in order of descending frequency summed across the treatment groups. AEs will also be tabulated by severity.

The following will also be summarized by treatment, and listings produced where required:

- All AEs
- Serious AEs (SAEs)
- AEs related to study drug
- AEs by severity
- AEs by outcome
- AEs leading to study drug discontinuation
- AEs leading to study withdrawal
- AEs leading to death
- AEs leading to a dose modification or interruption
- Most frequent AEs
- Adverse Event of Special Interest (AESIs) as follows (based on the data reported on AE form):

– Cases of potential drug-induced liver injury that include an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law

– Suspected transmission of an infectious agent by the study drug, as defined in protocol

If the overall number of AEs is low, then listings may be provided instead of the above summaries.

4.2.2.2 Deaths

Details of any deaths will be presented in the form of an individual patient listing.

4.2.2.3 Laboratory Data

For each of the hematological and biochemical test parameters, summary statistics of observed and change from baseline values at each time point will be presented by treatment group for each scheduled time point. For laboratory parameters, post-dose observations on Day 1 will be classed as baseline.

Each observed value will be classified into three categories: Normal (for values within the normal range), High (for values higher than normal) and Low (for values lower than normal). The frequency of each category will be summarized by treatment group for each scheduled time point. Additionally, a shift table will present the changes from baseline at each scheduled time point.

4.2.2.4 Vital Signs

Vital signs (pulse rate, respiratory rate, blood pressure) and change from baseline will be summarized by each scheduled time point. Baseline is defined as the last assessment prior to treatment.

4.2.2.5 Body Temperature

Body temperature is collected in the patient diary 4 times daily for Day 1 -3, twice daily for Day 4 - 9 and once daily thereafter. Summary statistics of observation and the change from baseline in body temperature will be presented by treatment group for each recorded time point. Baseline is defined as the first recorded assessment after treatment on Day 1.

4.3 SECONDARY ENDPOINTS/ESTIMANDS ANALYSES

4.3.1 Efficacy Secondary Endpoints/Estimands

The efficacy endpoints/estimands are specified in Table 1.

The CARIFS questionnaire data and body temperature are recorded by participant diary. This assessment data will be recorded for the following time periods:

Period	Time
Morning	05:00 – 10:59
Noon	11:00 – 14:59
Evening	15:00 – 18:59
Bedtime	19:00 – 23:59

In the case where the recorded time of an assessment is outside the period time window for that assessment, the actual assessment time will be used in the analysis.

Details of the analysis methods for these endpoints are listed below.

4.3.1.1 Time to Alleviation of Influenza Signs and Symptoms

Time to alleviation of influenza signs and symptoms (TTAS) in hours, will be summarized using descriptive statistics by treatment, as well as Kaplan-Meier plots.

It is defined as the length of time taken from the start of treatment to the point at which all of the following criteria are met and remain so for at least 21.5 hours:

- A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms (items 14 and 15 of the CARIFS questionnaire, see Appendix 1).
- A "yes" response to the following question on the CARIFS: "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?"
- Return to afebrile state (tympanic temperature $\leq$ 37.2 °C).

If a score of 4 ("don't know" or "not applicable") occurs at any assessment for items 14 or 15, the assessment will not be included in the calculation of the alleviation of symptoms.

Patients who do not experience endpoint prior to completion or withdrawal from study will be censored at the last observation timepoint.

Baseline is defined as the first CARIFS assessment after start of treatment on Day 1.

Patients with symptom scores $\leq$ 1 for both items 14 and 15, as well as tympanic temperature $\leq$ 37.2°C and a "yes" response to the question "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?" at baseline will be excluded from the analysis.

The number of patients with completed CARIFS as well as the number with missing CARIFS per assessment, will be presented by treatment. Additionally, the number and percentage of those with "don't know/not applicable" per question per assessment will be presented by treatment.

Supplementary Analyses

In the main analysis of the TTAS, only complete assessments (i.e., assessments that have responses for items 14 and 15 of the CARIFS questionnaire, the normal daily activity question and temperature) that do not have scores of 4 for items 14 and 15 are considered in the calculation of the TTAS. A supplementary analysis will be conducted that considers all assessments in the calculation of the TTAS, where a score of 4 for items 14 or 15 does not break the incidence of alleviation.

Another supplementary analysis will be conducted in which the following criterion will be removed from the calculation of the TTAS:

- A “yes” response to the following question on the CARIFS: “Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?”

In addition, analyses based on virus type and subtype may be conducted if there are a sufficient number of patients with each type/subtype.

4.3.1.2 Duration of Fever

Duration of fever will be summarized using descriptive statistics by treatment, as well as Kaplan-Meier plots. It is defined as the time from the start of treatment to return to afebrile state (tympanic temperature $\leq$ 37.2 °C) and remaining so for at least 21.5 hours. Patients who did not return to afebrile state will be censored at the last observation timepoint. Patients who are afebrile at baseline (tympanic temperature $\leq$ 37.2 °C) or whose body temperature is not collected will be excluded from the analysis.

4.3.1.3 Duration of Symptoms

Duration of symptoms is defined as alleviation of all symptoms as defined by a score of 0 [no problem] or 1 [minor problem] and remaining so for at least 21.5 hours, for all 18 symptoms specified in the CARIFS questionnaire.

Duration of symptoms will be summarized using descriptive statistics by treatment, as well as Kaplan-Meier plots.

If a score of 4 (“do not know” or “not applicable”) occurs at any assessment during the study for any item, with the exception of items 10, 11 and 12, the assessment will not be included in the calculation of the alleviation of symptoms. However, if a score of 4 occurs for items 10, 11 or 12, the assessment will be included, with a score of missing for these items, in which case the other non-missing items of the assessment will be used.

All patients will be included in the analysis, regardless of their symptoms at baseline.

Supplementary Analyses

In the main analysis of the duration of symptoms, only complete assessments (i.e., assessments that have responses for all 18 symptoms in the CARIFS questionnaire) that do not contain a score of 4 for any items, with the exception of items 10, 11, and 12, are considered. A supplementary analysis will be conducted that considers all assessments in the calculation of the duration of symptoms, where a score of 4 does not break the incidence of alleviation for items other than 10, 11, and 12, and a score of 4 is considered alleviation for items 10, 11, and 12.

In addition, duration of individual symptoms will be summarized using descriptive statistics by treatment. Patients who have an individual symptom score $\leq$ 1 or missing at

baseline or whose individual symptom score are all missing will be excluded from the analysis.

4.3.1.4 Time to Return to Normal Health and Activity

"Normal health and activity" is identified by a "yes" response to the following question on the CARIFS: "Since the last assessment has the patient been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?".

Time to return to normal health and activity will be summarized using descriptive statistics by treatment, as well as Kaplan-Meier plots.

Patients who do not return to normal health and activity will be censored at the last observation timepoint.

Patients in FASi will be removed from this analysis if a 'Yes' response to this item is reported at baseline.

4.3.1.5 Frequency of Influenza-Related Complications

Influenza-related complications include death, hospitalization, radiologically-confirmed pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures and myositis, as recorded by question "If this event is one of the following influenza-related complications, select from the list" on the AE CRF form.

The number of influenza-related complications, as well as the number and percentage of patients with these complications, after treatment, will be presented by treatment.

4.3.1.6 Proportion of participants requiring antibiotics for influenza related complications

The number and percentage of patients requiring antibiotics for any reason will be presented by treatment group.

4.3.2 Virology Secondary Endpoints/Estimands

The virology endpoints/estimands are specified in Table 1. Details of the analysis methods for these endpoints are listed below.

For all virology analyses, baseline is defined as the last pre-dose assessment and where no pre-dose assessment is available baseline will be defined as the first post-dose assessment on Day 1. For nasal swab influenza hemagglutinin subtype, baseline is defined as the last pre-dose assessment and where no pre-dose assessment is available, baseline will be defined as the first post-dose assessment on Days 1−3.

4.3.2.1 Time to Cessation of Viral Shedding by Virus Titer

Time to cessation of viral shedding by virus titer is defined as the time, in hours, between the initiation of study treatment and first time when the influenza virus titer was below the

lower limit of detection (LLoD). Patients whose virus titers have not reached the limit by the last observation timepoint are treated as censored at that timepoint.

Patients positive for virus titer on Day 1 will be included in the analysis.

This endpoint will be summarized using descriptive statistics by treatment, as well as Kaplan-Meier plots.

Supplementary analyses based on virus type and subtype may be conducted if there are a sufficient number of patients in each type/subtype.

4.3.2.2 Time to Cessation of Viral Shedding by RT-PCR

Time to cessation of viral shedding by RT-PCR, in hours, is defined as the time between the initiation of study treatment and the first time when the virus RNA by RT-PCR is below the LLoD (qualitative assessment). Patients whose virus RNA have not reached the limit by the last observation timepoint are treated as censored at that timepoint. For the patients with multiple virus types, this endpoint is defined as the time between the initiation of the study treatment and the first time when the virus RNA by RT-PCR qualitative result is negative for all virus types.

Patients positive for virus RNA by RT-PCR on Day 1 will be included in the analysis.

This endpoint will be summarized using descriptive statistics by treatment, as well as Kaplan-Meier plots.

Supplementary analyses based on virus type and subtype may be conducted if there are a sufficient number of patients in each type/subtype.

4.3.2.3 Change from Baseline in Influenza Virus Titer at Each Timepoint

Change from baseline in influenza virus titer (log_{10} $TCID_{50}$/mL) is defined as the change from baseline in influenza virus titer on Days 2, 4, 6, 10, 15 and 29 and will be presented by treatment. If influenza virus titer is less than the lower limit of quantification (LLoQ), the virus titer is imputed as LLoQ - 0.001 (0.749 log_{10} $TCID_{50}$/mL).

Only patients with a positive virus titer on Day 1 will be included in this analysis.

4.3.2.4 Change from Baseline in the Amount of Virus RNA (RT-PCR) at Each Timepoint

Change from baseline in the amount of virus RNA (unit: log_{10} virus particles/mL) will be presented by treatment and was defined as the change from baseline in the amount of virus RNA on Days 2, 4, 6, 10, 15 and 29.

If the amount of virus RNA is less than the LLoQ, the amount of virus RNA will be imputed as LLoQ - 0.001. If a patient is infected with multiple virus types, the sum of those amounts of virus RNA will be used for analysis.

Patients positive for virus RNA by RT-PCR on Day 1 will be included in this analysis.

LLoQ and LLoD of current assay version (v2) are as follows:

Influenza Type	LLoQ (log_{10} vp/mL)	LLoD (log_{10} vp/mL)
Influenza A	2.79	2.60
Influenza B	2.63	2.80

If there is any change of LLoQ and LLoD, they will be documented in the laboratory record.

4.3.2.5 Proportion of Patients with Positive Influenza Virus Titer at Each Timepoint

Proportion of patients positive for influenza virus titer will be presented by treatment at each visit and is defined as the percentage of patients whose influenza virus titer is not less than the LLoD (0.75 log_{10} $TCID_{50}$/mL) or is positive among those assessed for influenza virus titer on Days 2, 4, 6, 10, 15 and 29.

Patients with a positive influenza virus titer on Day 1 were included in this analysis.

4.3.2.6 Proportion of Patients Positive for Virus RNA by RT-PCR at Each Timepoint

Proportion of patients positive for virus RNA by RT-PCR will be presented by treatment at each visit and is defined as the percentage of patients with a positive qualitative result among those assessed by RT-PCR on Days 2, 4, 6, 10, 15 and 29.

Patients positive for virus RNA by RT-PCR on Day 1 will be included in this analysis.

4.3.2.7 Area Under the Curve in Virus Titer

The AUC in virus titer will be presented by treatment group and will be calculated using the trapezoidal method. AUC of change from time 0 (t_0) to time K (t_k) is given by the formula

$$\sum_{k=1}^{K} \frac{(y_k + y_{k-1})(t_k - t_{k-1})}{2}$$

where t_k (hours) represents the date of the k^{th} viral titer assessment (k = 0, ..., K) and y_k represents the log_{10} value of the k^{th} viral titer assessment ($TCID_{50}$/mL).

Twenty-four hours of time will be converted into one day. Patients with a positive virus titer on Day 1 will be included in this analysis. The lower limit will be defined as 0.75 log_{10} $TCID_{50}$/mL for flu A and flu B. If a patient is infected with multiple virus types, the sum of those virus titers will be used for analysis.

Additionally, the AUC in virus titer adjusted for baseline will be presented by treatment group and will be calculated using the trapezoidal method. AUC of change from time 0 (t_0) to time K (t_k) is given by the formula

$$\sum_{k=1}^{K} \frac{(y_k + y_{k-1} - 2y_0)(t_k - t_{k-1})}{2}$$

where t_k (hours) represents the date of the k^{th} viral titer assessment (k = 0, ..., K) and y_k represents the $\log_{10}$ value of the k^{th} viral titer assessment ($TCID_{50}$/mL).

Twenty-four hours of time will be converted into one day. Patients with a positive virus titer on Day 1 will be included in this analysis. The lower limit will be defined as 0.75 $\log_{10}$ $TCID_{50}$/mL for flu A and 0.75 $\log_{10}$ $TCID_{50}$/mL for flu B ($TCID_{50}$/mL). If a patient is infected with multiple virus types, the sum of those virus titers will be used for analysis.

4.3.2.8 Area Under the Curve in the Amount of Virus RNA (RT-PCR)

AUC in virus RNA (RT-PCR) will be presented by treatment group and is defined as AUC of change from baseline in the amount of virus RNA (RT-PCR). AUC unadjusted and adjusted for baseline will be calculated using the trapezoidal method similar to AUC in virus titer.

Patients positive for virus RNA by RT-PCR on Day 1 will be included in this analysis. If a patient is infected with multiple virus types, the sum of the amount of virus RNA will be used for analysis.

4.3.3 Other Secondary Endpoints/Estimands

The other secondary endpoints are specified in Table 2. Details of analysis methods for these endpoints are listed below.

4.3.3.1 Polymorphic and treatment-emergent amino acid substitutions in the PA gene

Sanger sequencing of the influenza PA gene will be performed to evaluate the incidence of polymorphic (pre-dose vs. reference) and treatment-emergent (post-dose vs.pre-dose) amino acid substitutions in subjects treated with baloxavir marboxil with evaluable virus. Sequencing will be performed for samples taken at baseline (pre-dose) and at the last evaluable timepoint (RNA titer ≥ 4 $\log_{10}$ vp/mL). The frequency of baseline polymorphic substitutions will be reported in percent of total sequenced baseline samples, and the frequency of treatment-emergent substitutions will be reported in percent of total paired samples (pre-dose and post-dose sequence pairs).

Supplementary analyses based on virus type and subtype may be conducted if there are a sufficient number of patients in each type/subtype.

4.3.3.2 Drug susceptibility in participants with evaluable virus

As assessments of the drug susceptibility of the influenza virus, the 50% effective concentration (EC_{50}) of baloxavir will be measured by the ViroSpot™ assay using baseline swab samples for participants who receive baloxavir marboxil. EC_{50} values will be compared with EC_{50} values of reference strains and the respective ratio (EC_{50} / EC_{50} reference) will be reported.

The following influenza virus vaccines strains from the 2024/25 Northern hemisphere season will be used as references:

- A/Wisconsin/67/2022 (H1N1) pdm09-like virus
- A/Massachusetts/18/2022 (H3N2)-like virus
- B/Austria/1359417/2021-like virus (B/Victoria/2/87 lineage)

Summary statistics may be provided by virus type and subtype if there are a sufficient number of patients in each type/subtype.

4.3.3.3 Proportion of participants reporting each palatability and acceptability response

Participants who have received baloxavir marboxil will be asked to answer a questionnaire regarding the palatability and acceptability of the study drug. Responses will be summarized by frequency and percentage.

4.4 OTHER SAFETY ANALYSES

4.4.1 Extent of Exposure

The duration of treatment exposure will be summarized with descriptive statistics by treatment group for SAS.

The duration of treatment exposure [days] in the oseltamivir group is defined as the dosing period during which a patient takes medication as follows:

(final dose date) – (initial dose date) + 1

For the baloxavir marboxil group, duration of exposure is defined as 1 day if actual baloxavir marboxil [redacted] for oral suspension are dosed.

The treatment compliance rate will be summarized with descriptive statistics by the treatment group for the SAS. In addition, the frequency and percentage of patients with compliance $<80\%$ and $\geq 80\%$ will be presented.

The treatment compliance rate [%] in the oseltamivir group is defined as: actual frequency of treatment exposure / expected frequency of treatment exposure $*$ 100.

For baloxavir marboxil group treatment compliance is defined as 100% if patients are dosed per protocol.

The total dose in milligram will be summarized with descriptive statistics by the treatment group for the SAS.

4.5 OTHER ANALYSES

4.5.1 Summaries of Conduct of Study

Enrollment, and early discontinuation from the study will be summarized by treatment arm for FAS. The reasons for study treatment not administered and early discontinuation from study will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm for FAS.

4.5.2 Summaries of Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment arm for FAS and FASi. Baseline data are the last data obtained prior to initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

The baseline summary will include the following:

- Age
- sex
- Race/ethnicity
- Weight
- Height
- Body Mass Index (BMI)
- Influenza vaccination history
- Influenza Subtype by PCR
- High risk factors for influenza complications

Medical history data, including surgery and procedures and baseline conditions, as well as previous and concomitant treatment will be summarized descriptively by treatment group for FAS.

4.5.3 Pharmacokinetic Analyses

Individual and mean plasma RO7191686 concentration versus time data will be tabulated and plotted. Individual plasma concentration at 24 and 72 hours postdose (C_{24} and C_{72}, respectively) of RO7191686 will be listed and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum), and presented by age and/or bodyweight group.

As this study uses an optimized sparse PK regimen, individual PK parameters of RO7191686 (such as AUC, C_{max},) will be determined using a population PK analysis, and reported separately (modeling report).

Additional PK analyses may be conducted as appropriate.

4.5.4 Analyses of Subgroups of Interest

Subgroup analyses of the following endpoints will be conducted:

- Safety endpoints including AE, vital signs, laboratory data and exposure
- Time to alleviation of influenza signs and symptoms
- Time to cessation of viral shedding by RT-PCR
- Time to cessation of viral shedding by virus titer
- Polymorphic and treatment-emergent amino acid substitutions in the PA gene

The subgroups to be considered include but are not limited to the following:

- Age group: 1-<5 versus 5-<12 years old

4.6 INTERIM ANALYSES

4.6.1 Planned Interim Analyses

No interim analyses are planned.

5. SUPPORTING DOCUMENTATION

Appendix 1 CANADIAN ACUTE RESPIRATORY ILLNESS AND FLU SCAL

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Item	No Problem	Minor Problem	Moderate Problem	Major Problem	Don't Know/Not Applicable
1. Poor appetite	☐	☐	☐	☐	☐
2. Not sleeping well	☐	☐	☐	☐	☐
3. Irritable, cranky, fussy	☐	☐	☐	☐	☐
4. Feels unwell	☐	☐	☐	☐	☐
5. Low energy, tired	☐	☐	☐	☐	☐
6. Not playing well	☐	☐	☐	☐	☐
7. Crying more than usual	☐	☐	☐	☐	☐
8. Needing extra care	☐	☐	☐	☐	☐
9. Clinginess	☐	☐	☐	☐	☐
10. Headache	☐	☐	☐	☐	☐
11. Sore throat	☐	☐	☐	☐	☐
12. Muscle aches or pains	☐	☐	☐	☐	☐
13. Fever	☐	☐	☐	☐	☐
14. Cough	☐	☐	☐	☐	☐
15. Nasal congestion, runny nose	☐	☐	☐	☐	☐
16. Vomiting	☐	☐	☐	☐	☐
17. Not interested in what's going on	☐	☐	☐	☐	☐
18. Unable to get out of bed	☐	☐	☐	☐	☐

Since the last assessment has the subject been able to return to day care/school (if applicable), or resume their normal daily activity in the same way as performed prior to developing the flu?

☐ Yes ☐ No

This form was filled out by:

☐ Parent

☐ Carer

☐ Other

Note: The term "Carer" in this questionnaire corresponds to the term "caregiver" used throughout the protocol.

Appendix 2 High Risk Factors for Influenza Complications

According to the definition by Centers for Disease Control and Prevention, participants in this study with the following conditions are considered to have high risk factors for influenza complications:

- Asthma
- Neurologic and neurodevelopment conditions
- Blood disorders (such as sickle cell disease)
- Chronic lung disease (such as cystic fibrosis)
- Endocrine disorders (such as diabetes mellitus)
- Heart disease (such as congenital heart disease)
- Kidney diseases
- Liver disorders
- Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)
- Body mass index of 40 or higher
- A weakened immune system due to disease or medications
- On long-term aspirin- or salicylate-containing medications
- Participants who have had a stroke

Appendix 3 Palatability and Acceptability Assessment of Study Drug

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Palatability and Acceptability Assessment of Study Drug

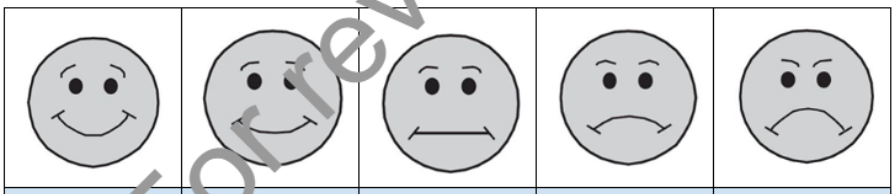
Instructions: We are interested in understanding how you or your child experienced the taste of this medicine. This questionnaire should be completed as soon as possible after the medicine has been swallowed.

Children aged 5 years or older and able to read, can complete this questionnaire by themselves

For children younger than 5 years of age or not able to read, we would like the parent/care-giver to complete this questionnaire

1. Who is completing this questionnaire?
   - ☐ Child by themselves
   - ☐ Parent/caregiver on the behalf of the child

2. How was the taste of the medicine? Please tick the face that best matches how you / the child felt about the taste. For parents/care-givers, if the child cannot communicate please base it upon the reactions of the child.



☐	☐	☐	☐	☐
Like very much	Like a little	Not sure	Dislike a little	Dislike very much

3. Would you / the child be happy to take this medicine again?

Yes	No	Not sure
☐	☐	☐

Version 1.0

6. REFERENCES

Not applicable.

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