Official Title: A Multicenter, Single-Arm, Open-Label Study to Assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Pediatric Patients From Birth To <1 Year With Influenza-Like Symptoms

NCT Number: NCT03653364

Document Date: Protocol Version 6: 27-April-2022

PROTOCOL

TITLE:	**A MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, AND EFFICACY OF BALOXAVIR MARBOXIL IN OTHERWISE HEALTHY PEDIATRIC PATIENTS FROM BIRTH TO <1 YEAR WITH INFLUENZA-LIKE SYMPTOMS**
PROTOCOL NUMBER:	CP40559
VERSION NUMBER:	*6*
IND NUMBER:	126653
EUDRACT NUMBER:	2018-002154-70
NCT NUMBER	*NCT03653364*
TEST PRODUCT:	Baloxavir marboxil (RO7191686)
MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL:	See electronic *signature and* date stamp *on the final page of the document*

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
6	*See electronic date stamp on the final page of this document*	[redacted]	[redacted]	[redacted]
4	1 June 2020	*Thailand*	*5*	*8 Jun 2021*
2	25 May 2019	South Africa	3	7 May 2020
1	2 July 2018	—	—	—

PROTOCOL AMENDMENT VERSION 6
RATIONALE

Protocol CP40559 has been amended to remove the requirement for fever at screening and to reflect a reduction in the minimum number of patients required in Cohort III. Changes to the protocol, along with a rationale for each change, are summarized below:

- Background on influenza has been updated to include additional symptoms in adults and children (Section 1.1).
- Background on baloxavir marboxil has been updated to indicate the completion of two pediatric studies and to include the approval date for baloxavir marboxil in European Union (Section 1.2).
- A rapid antigen test has been added as an option to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at prescreening to facilitate enrollment of eligible patients at sites where rapid testing is available (Section 3.1, Section 4.1, Section 4.1.1, and Section 4.5.1).
- The minimum number of patients recruited into cohort III has been reduced to 3 patients as this was judged to be sufficient to assess PK in this age group. (Section 3.1).
- A palatability assessment has been added to list of assessments to be conducted at clinic visits because it was previously omitted (Section 1.3).
- The requirement for fever at screening has been removed. Given the requirement for rapid antigen testing for influenza at screening, this change will allow enrollment of patients who have symptomatic influenza with a fever of $<$38 °C at screening (Section 4.1.1).
- The window for pre-screening testing for influenza and SARS-CoV-2 has been increased from 24 hours to 48 hours. This change will facilitate enrollment of patients at sites where rapid testing is unavailable (Section 4.1.1 and Appendix 1).
- Clarification has been added to allow influenza and SARS-CoV-2 test results undertaken as standard of care (and within 48 hours of study screening) to be used for eligibility assessment, without the need to retest (Section 4.1.1, 4.5.1 and Appendix 1)
- Negative SARS-CoV-2 results from either a polymerase chain reaction or rapid antigen test can now be used to confirm study eligibility (Section 4.1.1 and Appendix 1).
- Clarification has been added that a patient hospitalized for observation, monitoring or precautionary supportive care may be acceptable for enrollment in the study, provided they fulfill all other eligibility criteria (Section 4.1.1).
- Clarification has been added that parents/caregivers will measure the patient temperature as indicated in the schedule of activities and record the temperature measurement in the patient eDiary (Section 4.5.4).

- Clarification has been added that tympanic temperature measurements taken by parents/caregivers and recorded in the patient eDiary will be used to evaluate the safety endpoints (Section 6.5)
- The text has been amended to clarify that optional interim analyses may be conducted if appropriate.

Additional minor changes were made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, AND EFFICACY OF BALOXAVIR MARBOXIL IN OTHERWISE HEALTHY PEDIATRIC PATIENTS FROM BIRTH TO <1 YEAR WITH INFLUENZA-LIKE SYMPTOMS**
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MEDICAL MONITOR:	[redacted] *M.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the CRO.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, AND EFFICACY OF BALOXAVIR MARBOXIL IN OTHERWISE HEALTHY PEDIATRIC PATIENTS FROM BIRTH TO <1 YEAR WITH INFLUENZA-LIKE SYMPTOMS**
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TEST PRODUCT:	Baloxavir marboxil (RO7191686)
PHASE:	Phase III
INDICATION:	Influenza
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, pharmacokinetics, and efficacy of baloxavir marboxil in otherwise healthy patients from birth to < 1 year of age with influenza-like symptoms. Specific objectives and corresponding endpoints for the study are outlined below.

Safety (Primary) Objective	**Corresponding Endpoint**
• To evaluate the safety of a single dose of baloxavir marboxil	• Incidence, severity, and timing of adverse events, serious adverse events, vital sign measurements, and clinical laboratory tests
Pharmacokinetic Objective	**Corresponding Endpoints**
• To evaluate the PK of baloxavir marboxil after single-dose administration	• Plasma concentrations of baloxavir marboxil (pro-drug) and S-033447 (active metabolite) will be summarized by time (C_{24} and C_{72}) and cohort • Population PK model derived PK parameters (e.g., AUC_{inf}, C_{max}, T_{max}, $t_{1/2}$ (modelling report)
Efficacy (Secondary) Objectives	**Key Corresponding (Secondary) Endpoint**
• To evaluate the efficacy of baloxavir marboxil	• 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 remaining 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) – 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?" – First return to afebrile state (tympanic temperature $\leq$37.2°C)

Efficacy (Secondary) Objectives (cont.)	Corresponding Endpoint (cont.)
• To evaluate the efficacy of baloxavir marboxil	• Duration of fever (time to return to afebrile state [tympanic temperature $\leq$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 • Frequency of influenza-related complications (death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures, myositis) • Proportion of patients requiring antibiotics
Secondary Virology Objective	**Corresponding Endpoints**
• To evaluate the virological activity of baloxavir marboxil	• Time to cessation of viral shedding by virus titer and by *reverse transcription-polymerase chain reaction* (RT-PCR) • Change from baseline in influenza virus titer and in the amount of virus RNA (RT-PCR) at each time point • Proportion of patients with positive influenza virus titer and proportion of patients positive by RT-PCR at each time point • Area under the curve in virus titer and in the amount of virus RNA (RT-PCR)
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the polymorphic and treatment-emergent amino acid substitutions and drug susceptibility in patients with evaluable virus	• Polymorphic and treatment-emergent amino acid substitutions in the PA, PB1, and PB2 genes • Drug susceptibility in patients with evaluable virus
Exploratory Palatability Objective	**Corresponding Endpoints**
• To evaluate the palatability of the oral suspension in the pediatric population	• Proportion of patients within each response category for Question 1 of the palatability assessment • Proportion of patients with issues with the administration of the full dose

AUC_{inf} = area under the concentration–time curve from Time 0 to infinity; C_{24} = plasma concentration 24 hours postdose (acceptable time window 20 to 28 hours); C_{72} = plasma concentration 72 hours postdose; CARIFS = Canadian Acute Respiratory Illness and Flu Scale; C_{max} = maximum plasma concentration; PA = polymerase acidic protein; PK = pharmacokinetic; RT-PCR = reverse transcriptase-polymerase chain reaction; $t_{1/2}$ = half-life; T_{max} = time to maximum plasma concentration.

STUDY DESIGN

DESCRIPTION OF STUDY

This is a multicenter, single-arm, open-label study to assess the safety, pharmacokinetics, and efficacy of baloxavir marboxil in otherwise healthy pediatric patients from birth to < 1 year with influenza-like symptoms.

Potential patients will be prescreened using an influenza test (rapid influenza diagnostic test [RIDT] or polymerase chain reaction [PCR]) and a coronavirus disease 2019 (COVID-19) test (*approved rapid antigen test [RAT] or PCR*). This is to ensure that patients with a high probability of having influenza infection are enrolled and to minimize the likelihood of enrolling a COVID-19 patient in the study. Patients will be screened on Day 1 and assigned to one of three cohorts, based upon their age, to receive a single oral dose of baloxavir marboxil based on body weight and age. Re-screening of patients who fail to meet the inclusion and exclusion criteria will not be permitted, as the time from symptom onset to treatment window is limited to 96 hours.

The study consists of two periods: a 1-day treatment period (screening and study drug administration on Day 1) and a 28-day safety follow-up period (mandatory visits on Days 2, 4, 6, 10, and 29). Therefore, the total study duration for each patient will be 29 days.

The following assessments will be conducted at clinic visits: physical examination, vital signs, adverse events, concomitant therapies, clinical laboratory tests, nasal/throat swabs *and palatability assessment*.

Throughout the treatment and safety follow-up periods, the parents/caregivers will maintain a patient diary for each patient in order to record body temperatures (tympanic assessment), influenza symptoms, and acetaminophen use. Temperatures will be recorded four times daily (morning, noon, evening, and bedtime) on Days 1 to 3; twice daily (morning and evening) on Days 4 to 9; and once daily on Days 10 to 15. Influenza symptoms will be recorded twice daily (morning and evening) on Days 1 to 9 and once daily on Days 10 to 15.

This study will be conducted at sites in the United States and globally.

To facilitate early and close monitoring of safety parameters over time, an Internal Monitoring Committee (IMC) will review aggregate safety data on an ongoing basis as defined in the IMC charter. If there is any concern noted in the safety parameters, the Sponsor may suspend or discontinue the entire study, as appropriate.

NUMBER OF PATIENTS

This study is designed to enroll approximately 30 otherwise healthy male and female pediatric patients with influenza-like symptoms. Patients will be recruited in parallel to the following three cohorts:

- **Cohort I**: $\geq$3 months to $<$12 months old (minimum 8 patients)
- **Cohort II**: $\geq$4 weeks to $<$3 months old (minimum 4 patients)
- **Cohort III**: birth to $<$4 weeks old (minimum *3* patients)

TARGET POPULATION

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Written informed consent for study participation obtained from patient's parents or legal guardian
- Age from birth to $<$1 year at screening
- Parent/guardian willing and able to comply with study requirements, in the investigator's judgment
- Patients with a diagnosis of influenza virus infection confirmed by the presence of all of the following:

– *In the investigator's judgement there is a clinical suspicion of influenza*

– At least one respiratory symptom (either cough or coryza)

– Positive prescreening influenza test (RIDT or PCR) performed within *48* hours of screening

Results from local testing as part of standard of care are acceptable if samples are collected within 48 hours of screening and recorded in the patients' medical records.

- Patients with a negative prescreening COVID-19 test (*RAT or* PCR) *performed within 48 hours of screening*

Results from local testing as part of standard of care are acceptable if samples are collected within 48 hours of screening and recorded in the patients' medical records.

- The time interval between the onset of symptoms and screening is ≤ 96 hours (the onset of symptoms is defined as the time when body temperature first exceeded 37.5°C if known, or the time when the first symptom was noticed by the parent or caregiver)

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Hospitalized for complications of influenza or significant comorbidities

  Patients hospitalized for observation, monitoring or precautionary supportive care may still be acceptable for enrollment provided all eligibility criteria are met.
- Concurrent infections requiring systemic antiviral therapy at screening
- Require, in the opinion of the investigator, any of the prohibited medication during the study
- Preterm neonates (born at < 37 weeks gestation)
- Weigh < 2.5 kg at screening

  Only children > 4.5 kg will be eligible to take part in countries that have volume limits for blood draws set at 1% of the total blood volume (maximum over 24-hour period) and 3% of the total blood volume (maximum over 30-day period).
- Previous treatment with peramivir, laninamivir, oseltamivir, zanamivir, or amantadine within 2 weeks prior to screening
- Immunization with a live/attenuated influenza vaccine during the 2 weeks prior to screening
- Concomitant treatment with steroids or other immuno-suppressant therapy
- Known HIV infection or other immunosuppressive disorder
- Uncontrolled renal, vascular, neurologic or metabolic disease (e.g., diabetes, thyroid disorders, adrenal disease), hepatitis, cirrhosis or pulmonary disease, or patients with known chronic renal failure
- Active cancer at any site
- History of organ transplant
- Known hypersensitivity to study drug (i.e., baloxavir marboxil) or the drug product excipients
- Known hypersensitivity to acetaminophen
- Participation in a clinical trial with an investigational drug within 4 weeks or five half-lives of exposure to an investigational drug prior to screening, whichever is longer

END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur 29 days after the last patient has been enrolled.

LENGTH OF STUDY

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 9 months. Given the seasonal variability of incidence and severity of influenza, the total length of the study may be extended to complete enrollment.

In addition, the Sponsor may decide to terminate the study at any time.

INVESTIGATIONAL MEDICINAL PRODUCTS

TEST PRODUCT (INVESTIGATIONAL DRUG)

The investigational medicinal product (IMP) for this study is baloxavir marboxil.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

Not applicable.

STATISTICAL METHODS

PRIMARY ANALYSIS

The safety evaluable population will be used for all analyses.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to National Cancer Institute Common Terminology Criteria of Adverse Events, Version 5.0 (NCI CTCAE v5.0).

The safety of baloxavir marboxil will be evaluated from adverse events, vital sign measurements, and clinical laboratory tests. Safety parameters will be summarized or listed for the safety population.

DETERMINATION OF SAMPLE SIZE

No formal sample-size calculations have been performed. Approximately 30 pediatric patients will be enrolled in order to estimate the pharmacokinetic (PK) parameters and maturation factor which is incorporated in the population PK model with a probability of $>90\%$.

INTERIM ANALYSES

An interim PK analysis is planned for this study. The PK samples, up to and including those collected at Visit 4/5 of first 6 patients dosed, will be batched for an early shipment. This will enable a timely review of the systemic plasma concentrations, in particular the concentrations at 24 hours and 72 hours after dosing. This is in order to verify, in a timely manner, that exposures at the proposed doses are in reasonable agreement with the corresponding values seen in adults. The estimated turnaround time between last sample collected and data review is estimated to be approximately 2 to 3 weeks and recruitment will continue during this time. Data review will be performed by members of the Sponsor study team.

No other interim analyses are planned in this study. However, given there is no formal statistical hypothesis testing in this study, the Sponsor may choose to conduct *optional* interim analyses *as appropriate*. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AUC	area under the concentration–time curve
AUC_{inf}	area under the concentration–time curve from Time 0 to infinity
BID	twice daily
C_{24}	plasma concentration 24 hours postdose (acceptable time window: 20 to 28 hours)
C_{72}	plasma concentration 72 hours postdose
C_{max}	maximum plasma concentration
CARIFS	Canadian Acute Respiratory Illness and Flu Scale
CL/F	apparent clearance
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
E.U.	European Union
FDA	Food and Drug Administration
HA	hemagglutinin complex
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ITT	intent-to-treat
ITTi	intent-to-treat influenza-infected
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit
M2	matrix-2
NA	neuraminidase
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NONMEM	non-linear mixed-effects model
OwH	*otherwise healthy*
PCR	polymerase chain reaction
PK	pharmacokinetic
PKEP	pharmacokinetic-evaluable patient

Abbreviation	Definition
PRO	patient-reported outcome
QTc	corrected QT interval
RAT	*rapid antigen test*
RIDT	rapid influenza diagnostic test
RT-PCR	reverse transcription-polymerase chain reaction
$TCID_{50}$	50% tissue culture infectious dose
Vc/F	apparent volume of distribution for the central compartment
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON INFLUENZA

Influenza is an acute respiratory infectious disease caused by a virus of the orthomyxovirus family. Two forms are known to infect humans: influenza A and B. These viruses cause an acute febrile infection of the respiratory tract after an incubation period of 1 to 4 days, characterized by the sudden onset of fever, cough, fatigue, headache, and myalgia. *Some may experience vomiting and diarrhea, although this is more common in children than adults, and others may be infected with influenza and have respiratory symptoms in the absence of fever (CDC 2011).* Annual influenza epidemics are thought to result in between 3 to 5 million cases of severe illness and between 250,000 and 500,000 deaths every year around the world (WHO 2018).

Although the condition is usually self-limiting in healthy adults, it can be associated with substantial morbidity and occasional mortality in children, the elderly, and the immunocompromised (Paules and Subbarao 2017). Children play a central role in the dissemination of influenza in the community by virtue of their relative serosusceptibility and consequently higher illness attack rates. In addition to the acute illness, young children are at particular risk of secondary bacterial infections. Children develop more severe disease compared with adults, with higher hospitalization rates particularly in children aged <5 years (Rotrosen and Neuzil 2017).

The influenza viruses have a segmented, negative-sense, single-stranded, lipid-encapsulated RNA genome; they range between 80 and 100 nm in size. Subtypes are defined according to glycoproteins present in the viral lipid coat. The hemagglutinin complex (HA) is the major surface protein of the virus. The neuraminidase (NA) proteins are the second major surface proteins in the virion and play a role in enhancing virus penetration of the mucus layer around the target cell and in the release of virus from the cell surface. The matrix-2 (M2) protein triggers the disintegration of the virion during virus entry into the cell and may also be involved in protecting the HA prior to the assembly of new virus particles.

The following anti-influenza virus drugs are currently available in various countries: the M2 ion-channel inhibitors (i.e., amantadine and rimantadine) (CDC 2011), a RNA-polymerase inhibitor (i.e., favipiravir), and the NA inhibitors (i.e., oseltamivir, zanamivir, peramivir, and laninamivir). Many cases of seasonal influenza infection are resistant to amantadine and rimantadine, hence their use in clinical practice is limited. NA inhibitors are the mainstay of treatment for influenza infections, but their oral formulations need to be administered for 5 days, potentially resulting in poor patient compliance and convenience. In addition, inhalation formulations can only be used in patients who are able to inhale the drug. These factors contribute to an unmet medical need for anti-viral influenza drugs that can be easily administered and dosed within a single day.

Influenza viruses are known to mutate during the course of replication and can mutate into a strain resistant to existing anti-viral influenza drugs or into a strain to which most people are not immune. The latter may result in a pandemic. To protect against these situations, the development of an anti-viral influenza drug with a novel mechanism of action is warranted.

1.2 BACKGROUND ON BALOXAVIR MARBOXIL

Baloxavir marboxil is a compound discovered by Shionogi & Co., Ltd. that exerts antiviral effects against influenza. Baloxavir marboxil (also referred to as S-033188, Shionogi Compound Identification Number) is a prodrug that is converted to an active form (S-033447) in the blood, liver, and small intestine through a metabolic process called hydrolysis.

Baloxavir marboxil acts on cap-dependent endonuclease, an enzyme specific to influenza viruses, and inhibits viral cap-snatching, thereby suppressing the growth of influenza viruses.

Detailed profiles of baloxavir marboxil and its active form, S-033447, derived from non-clinical and Phase I studies, are provided in the Baloxavir Marboxil Investigator's Brochure. To date, one Phase II study, two Phase III studies in adults and adolescents (one in otherwise healthy *[OwH]* individuals and one in patients at high risk of complications), and two Phase III *Japanese* studies in *otherwise healthy* pediatric patients have been completed. Two additional Phase III pediatric studies *have been completed*, Study T0835 in Japan, which examine*d* higher doses of baloxavir than earlier studies in the Japanese pediatric population, and Study CP40563, which *investigated baloxavir marboxil in* otherwise healthy pediatric patients 1 to < 12 years of age with influenza in the global setting.

Baloxavir marboxil was first approved in Japan for the treatment of influenza A or B virus infection in OwH patients on 26 February 2018, including pediatric patients weighing > 10 kg. In the United States *(on 24 October 2018) and European Union (7 January 2021),* baloxavir marboxil was approved for the treatment of acute uncomplicated influenza in patients ≥ 12 years of age who have been symptomatic for no more than 48 hours. Regulatory filings in other global regions are completed, ongoing, or planned to gain market authorization for the use of baloxavir for the treatment of influenza.

1.2.1 Post-Marketing Safety Data

Hypersensitivity reactions have been observed in the post-marketing setting which include reports of anaphylaxis/anaphylactic reactions and less severe forms of hypersensitivity reactions including angioedema and urticaria. Refer to Section 6 of the Baloxavir Marboxil Investigator's Brochure for further details on post-marketing safety information.

1.2.2 Phase II Proof-of-Concept and Dose-Finding Study (Study 1518T0821)

In this Phase II study, the efficacy and safety of baloxavir marboxil in patients with influenza virus infection were investigated. A single dose of 10, 20, or 40 mg baloxavir marboxil or placebo was administered to 400 patients with influenza virus infection (100 patients per dose group).

The median times to alleviation of influenza symptoms in the 10-mg, 20-mg, and 40-mg groups were 54.2, 51.0, and 49.5 hours, respectively, compared with 77.7 hours in the placebo group. Of the secondary endpoints, the median times to resolution of fever in the 10-mg, 20-mg, and 40-mg groups were 33.4, 31.6, and 28.9 hours, respectively, compared with 45.3 hours in the placebo group.

All of the baloxavir marboxil groups showed a significantly greater reduction compared with the placebo group in the proportion of patients with positive influenza virus titer, change in influenza virus titer, and change in amount of influenza virus on Days 2 and 3 using the predefined secondary analysis methods.

No deaths or serious adverse events were reported in any of the groups. Adverse events were reported in 27 of 100 patients (34 events) in the 10-mg group, 23 of 100 patients (29 events) in the 20-mg group, and 26 of 100 patients (29 events) in the 40-mg group compared with 29 of 100 patients (40 events) in the placebo group. Most adverse events were mild. No statistically significant difference was found in the incidence between any of the three dose groups and the placebo group.

1.2.3 Phase III Double-Blind Study in Otherwise Healthy Patients (Study 1601T0831)

In this Phase III double-blind study in otherwise healthy adults and adolescents 12 to 64 years of age with influenza, the efficacy and safety of baloxavir marboxil were investigated. The dose studied was 40 mg for patients weighing <80 kg and 80 mg for patients weighing ≥ 80 kg.

Patients in the 20 to 64 years of age stratum received a single dose of 40 or 80 mg of baloxavir marboxil (based on the patient's body weight), repeated dose of 75 mg oseltamivir twice daily (BID) for 5 days, or placebo. In addition, patients in the 12 to 19 years of age stratum received a single dose of 40 mg or 80 mg baloxavir marboxil (based on the patient's body weight) or placebo. A total of 1,432 patients received the study drug: 610 in the baloxavir marboxil group, 309 in the placebo group, and 513 in the oseltamivir group.

The median time to alleviation of symptoms was 53.7 hours in the baloxavir marboxil group compared with 80.2 hours in the placebo group. The difference in the median time was -26.5 hours between the baloxavir marboxil group and the placebo group. The baloxavir marboxil group showed a significantly greater reduction in the time to

alleviation of symptoms compared with the placebo group (two-sided p-value <0.0001). In the adult stratum of patients, the median time to alleviation of symptoms was 53.5 hours in the baloxavir marboxil group compared with 53.8 hours in the oseltamivir group; no significant difference was found.

Of the secondary endpoints, significant decreases in both virus titer and the amount of virus RNA were found in the baloxavir marboxil group compared with the placebo group. The virus titer in the baloxavir marboxil group was reduced rapidly, and the mean virus titer on Day 2 was less than -3 $\log_{10}$ (50% tissue culture infectious dose [$TCID_{50}$/mL]) of that in the placebo group. The mean change from baseline in the influenza virus titer was significantly greater in the baloxavir marboxil group than in the placebo group from Days 2 through 5.

The median time to cessation of viral shedding determined by virus titer was 24 hours in the baloxavir marboxil group compared with 96 hours in the placebo group. The difference in the time to cessation of virus shedding was 72 hours between the groups ($p<0.0001$). A significant difference in the median time to cessation of viral shedding of 48 hours ($p<0.0001$) was found also in comparison between the baloxavir marboxil group (24 hours) and the oseltamivir group (72 hours). In addition, baloxavir marboxil rapidly and significantly reduced the proportion of patients with positive influenza virus titer from Days 2 through 5 compared with that in the placebo group. Also, when compared with the oseltamivir group, the proportion of patients with positive influenza virus titer decreased significantly in the baloxavir marboxil group.

Beneficial effects of baloxavir marboxil on fever were also demonstrated. The proportion of patients who had fever was reduced more rapidly in the baloxavir marboxil group than in the placebo group following the study drug administration. The median time to resolution of fever was shortened by 17.5 hours in the baloxavir marboxil group compared with the placebo group.

No deaths were reported in any groups. Two serious adverse events (viral meningitis and incarcerated inguinal hernia) were reported in 2 of 610 patients (0.3%) in the baloxavir marboxil group. The events resolved and were considered not related to study drug. Nine adverse events leading to withdrawal of study drug were reported: 3 events in 2 of 610 patients (0.3%) in the baloxavir marboxil group, 4 events in 1 of 309 patients (0.3%) in the placebo group, and 2 events in 2 of 513 patients (0.4%) in the oseltamivir group.

All of the adverse events leading to withdrawal of study drug in the baloxavir marboxil group were considered not related to the study drug. Adverse events were reported in 126 of 610 patients (20.7%, 172 events) in the baloxavir marboxil group, 76 of 309 patients (24.6%, 118 events) in the placebo group, and 127 of 513 patients (24.8%, 179 events) in the oseltamivir group. No statistically significant difference was found in the incidence between the baloxavir marboxil group and the placebo group (the Fisher's

exact test, two-sided p-value = 0.1781) or between the baloxavir marboxil group and the oseltamivir group (p = 0.1146).

Except for bronchitis in the placebo group, there were no common adverse events (incidence ≥ 5%) in any of the treatment groups. The relatively common adverse events (incidence ≥ 2%) in any of the groups were bronchitis, sinusitis, diarrhea, and nausea; however, each incidence of the adverse event in the baloxavir marboxil group was lower than or equal to that in the placebo group. In all three groups, the majority of the adverse events was categorized as Grade 1 or 2 and resolved.

1.2.4 Phase III, Open-Label Study in Otherwise Healthy Pediatric Patients (Study 1618T0822)

In this Phase III, open-label study in otherwise healthy pediatric patients, the efficacy of a single dose of baloxavir marboxil in patents aged 6 months to < 12 years was investigated. This study was conducted in Japan. A total of 107 patients were enrolled: 2, 31, 66, and 8 patients received a single 5-, 10-, 20-, and 40-mg dose of baloxavir marboxil, respectively. The doses administered in this study were 5, 10, 20, and 40 mg for patients who weighed 5 to < 10 kg, 10 to < 20 kg, 20 to < 40 kg, and ≥ 40 kg, respectively.

The median time to alleviation of influenza illness (time to alleviation of cough, nasal discharge/nasal congestion and fever) was 44.6 hours. Of the secondary endpoints, the median time to resolution of fever was 21.4 hours. In the virological endpoints, the mean change from baseline in the virus titer was -4.20 $\log_{10}$ ($TCID_{50}$/mL) and the mean change from baseline in the amount of viral RNA was -1.75 $\log_{10}$ (virus particles/mL) on Day 2.

No deaths, serious adverse events, or discontinuations due to adverse events were reported in the study. Adverse events were reported in 37 of 107 patients (34.6%, 49 events). All adverse events were classified as Grade 1 or 2. Most of the adverse events resolved except for 3 adverse events in 3 patients: 1 event each of dental caries, dry skin, and ligament sprain (these were judged by the investigator to not require further follow-up).

Adverse events occurring at an incidence of at least 5% was vomiting in 8 patients (7.5%, 8 events). All the cases of vomiting were classified as Grade 1, resolved, and considered not related to the study drug.

Baloxavir marboxil was considered generally safe when administered to pediatric patients with influenza at a single oral dose between 5 mg and 40 mg based on the patient's body weight.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Influenza virus infection predisposes to secondary bacterial infection, which may progress in severity leading to poor prognosis, particularly in children. Other serious complications can also develop, including cardiac and neurological complications.

Although NA inhibitors, such as oseltamivir, zanamivir, and peramivir, can be used for the treatment of pediatric patients at present, more convenient and potent anti-influenza virus drugs without restriction of use are needed for the following reasons: 1) zanamivir is not licensed for treatment of influenza in very young children due to difficulty with inhalation in this group (< 5 or 7 years of age, depending on country), 2) peramivir needs to be intravenously administered, and 3) oseltamivir requires BID dosing orally for 5 days.

The efficacy of currently marketed antivirals against preventing complications in pediatric patients has not been demonstrated. Baloxavir marboxil appears to have greater antiviral efficacy compared with currently available antivirals, offering the potential to treat influenza in the pediatric population more effectively.

A new antiviral drug against influenza is needed with a novel mode of action to overcome potential resistance to existing antivirals or offer a different resistance profile.

The results of the clinical studies outlined above have proven the efficacy and safety of baloxavir marboxil in the treatment of influenza virus infections for adult and adolescent patients. Although limited clinical data is available in children, especially in children aged < 1 year of age (one open-label Phase III study in children in Japan), a further study of children within this age group is justified to confirm the safety, pharmacokinetics, and efficacy of baloxavir marboxil in the pediatric population.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, pharmacokinetics, and efficacy of baloxavir marboxil in otherwise healthy patients from birth to < 1 year of age with influenza-like symptoms. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Safety (Primary) Objective	Corresponding Endpoint
• To evaluate the safety of a single dose of baloxavir marboxil	• Incidence, severity, and timing of adverse events, serious adverse events, vital sign measurements, and clinical laboratory tests
Pharmacokinetic Objective	**Corresponding Endpoints**
• To evaluate the PK of baloxavir marboxil after single-dose administration	• Plasma concentrations of baloxavir marboxil (pro-drug) and S-033447 (active metabolite) will be summarized by time (C_{24} and C_{72}) and cohort • Population PK model derived PK parameters (e.g., AUC_{inf}, C_{max}, T_{max}, $t_{1/2}$ (modelling report)
Efficacy (Secondary) Objective	**Key Corresponding (Secondary) Endpoint**
• To evaluate the efficacy of baloxavir marboxil	• 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 remaining 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) – 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?” – First return to afebrile state (tympanic temperature $\leq$37.2°C)

Table 1 Objectives and Corresponding Endpoints (cont.)

Efficacy (Secondary) Objective	Corresponding Endpoints
• To evaluate the efficacy of baloxavir marboxil	• 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 • Frequency of influenza-related complications (death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures, myositis) • Proportion of patients requiring antibiotics
Secondary Virology Objective	**Corresponding Endpoints**
• To evaluate the virological activity of baloxavir marboxil	• Time to cessation of viral shedding by virus titer and by *reverse transcription-polymerase chain reaction* (RT-PCR) • Change from baseline in influenza virus titer and in the amount of virus RNA (RT-PCR) at each time point • Proportion of patients with positive influenza virus titer and proportion of patients positive by RT-PCR at each time point • Area under the curve in virus titer and in the amount of virus RNA (RT-PCR)
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the polymorphic and treatment-emergent amino acid substitutions and drug susceptibility in patients with evaluable virus	• Polymorphic and treatment-emergent amino acid substitutions in the PA, PB1, and PB2 genes • Drug susceptibility in patients with evaluable virus
Exploratory Palatability Objective	**Corresponding Endpoints**
• To evaluate the palatability of the oral suspension in the pediatric population	• Proportion of patients within each response category for Question 1 of the palatability assessment • Proportion of patients with issues with the administration of the full dose

AUC_{inf} = area under the concentration–time curve from Time 0 to infinity; C_{24} = plasma concentration 24 hours postdose (acceptable time window 20 to 28 hours); C_{72} = plasma concentration 72 hours postdose; CARIFS = Canadian Acute Respiratory Illness and Flu Scale; C_{max} = maximum plasma concentration; PA = polymerase acidic protein; PK = pharmacokinetic; RT-PCR = reverse transcriptase-polymerase chain reaction; $t_{1/2}$ = half-life; T_{max} = time to maximum plasma concentration.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a multicenter, single-arm, open-label study to assess the safety, pharmacokinetics, and efficacy of baloxavir marboxil in otherwise healthy pediatric patients from birth to < 1 year with influenza-like symptoms.

This study is designed to enroll approximately 30 otherwise healthy male and female pediatric patients with influenza symptoms presenting within 96 hours of symptom onset.

Potential patients will be prescreened using an influenza test (*Rapid Influenza Diagnostic Test* [RIDT] or *Polymerase Chain Reaction* [PCR]) and a COVID-19 test (*Rapid Antigen Test* [*RAT*] *or* PCR). This is to ensure that patients with a high probability of having influenza infection are enrolled and to minimize the likelihood of enrolling a patient with COVID-19 in the study. Patients will be screened on Day 1 and assigned to receive a single oral dose of baloxavir marboxil according to body weight and age, as defined below.

Patients will be recruited in parallel to the following three cohorts:

- **Cohort I**: ≥ 3 months to < 12 months old (minimum 8 patients): 2 mg/kg
- **Cohort II**: ≥ 4 weeks to < 3 months old (minimum 4 patients): 1 mg/kg
- **Cohort III**: birth to < 4 weeks old (minimum *3* patients): 1 mg/kg

Patients will be screened on Day 1 and assigned to one of these three cohorts based upon their age (see Figure 1). Re-screening of patients who fail to meet the inclusion and exclusion criteria will not be permitted, as the time from symptom onset to treatment window is limited to 96 hours.

The study consists of two periods: a 1-day treatment period (screening and study drug administration on Day 1) and a 28-day safety follow-up period (mandatory visits on Days 2, 4, 6, 10, and 29). Therefore, the total study duration for each patient will be 29 days.

The following assessments will be conducted at clinic visits: physical examination, vital signs, adverse events, concomitant therapies, clinical laboratory tests, nasal/throat swabs *and palatability assessment*. Please see Appendix 1 for details concerning the timing of these assessments. In addition, pharmacokinetic (PK) samples will be collected at the timepoints indicated in Appendix 2.

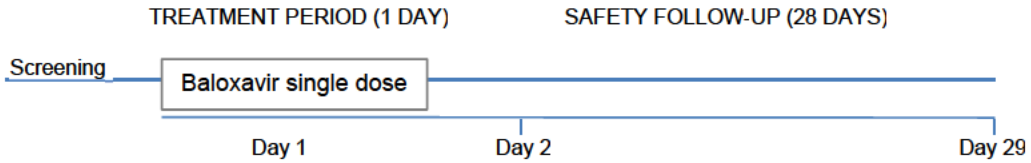
Throughout the treatment and safety follow-up periods, the parents/caregivers will maintain a patient diary

for each patient in order to record body temperatures (tympanic assessment), influenza symptoms, and acetaminophen use. Temperatures will be recorded four times daily

(morning, noon, evening, and bedtime) on Days 1 to 3; BID (morning and evening) on Days 4 to 9; and once daily on Days 10 to 15. Influenza symptoms will be recorded BID (morning and evening) on Days 1 to 9 and once daily on Days 10 to 15.

Figure 1 presents an overview of the study design.

Figure 1 Study Schema



Baloxavir = baloxavir marboxil.
Note: The baloxavir marboxil dose will be based on the body weight and age of the child.

This study will be conducted at sites in the United States and globally.

To facilitate early and close monitoring of safety parameters over time, an Internal Monitoring Committee (IMC) will review aggregate safety data on an ongoing basis as defined in the IMC charter. If there is any concern noted in the safety parameters, the Sponsor may suspend or discontinue the entire study, as appropriate.

A schedule of activities is provided in Appendix 1.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur 29 days after the last patient has been enrolled.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 9 months. Given the seasonal variability of incidence and severity of influenza, the total length of the study may be extended to complete enrollment.

In addition, the Sponsor may decide to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Baloxavir Marboxil Dose and Schedule

The safety and efficacy of baloxavir marboxil in adult and pediatric patients with influenza virus infection have been demonstrated in previous studies using baloxavir marboxil 20-mg tablets.

In this study, baloxavir marboxil will be administered as granules for suspension. Bioequivalence of the suspension and the 20-mg tablet (which was previously tested in clinical studies) was confirmed in a separate bioequivalence study.

Proposed pediatric doses in this study were determined according to the modeling and simulation of S-033447 pharmacokinetics in a pediatric population. Population PK analysis had been performed in pediatric populations by using PK data obtained in the Phase III study involving pediatric patients in Japan (1618T0822) to develop a population PK model for pediatrics.

Simulation of Caucasian pediatric drug exposure was performed for 1,000 patients (26,000 patients in total) for each age in months for $<$2-year old infants. In addition, various dosing regimens were evaluated with respect to their ability to match adult drug exposure in terms of area under the plasma concentration–time curve (AUC), maximum plasma concentration (C_{max}), and plasma concentration at 24 hours after dosing (C_{24}; acceptable time window: 20 to 28 hours), and 72 hours after dosing (C_{72}). The optimal dose selected was based on a comparison of the simulated drug exposure with those obtained in the Phase III study (1601T0831) for patients receiving 40 mg baloxavir marboxil (body weight $<$80 kg) and patients receiving 80 mg baloxavir marboxil (body weight $\geq$80 kg), those obtained in the pediatric Phase III study (1618T0822), and those obtained in the Phase I thorough corrected QT interval (QTc) study (1527T0816) for patients receiving 80 mg baloxavir marboxil. Simulations showed that optimal exposure matching to adults in terms of both total (AUC) and sustained (C_{72}) drug exposure was achieved with 2 mg/kg in infants of 3 months and older and 1 mg/kg in younger infants (4 weeks–3 months) as well as for newborns (0–4 weeks).

In this study, baloxavir marboxil will be administered according to the infant's body weight and age recorded at screening (i.e., 2 mg/kg $\geq$3 months, 1 mg/kg $<$3 months) to obtain similar exposure of S-033447 to that resulting from the administration of 40 mg or 80 mg baloxavir marboxil (based on the patient's body weight) to adults in the Phase III and Japanese pediatric Phase III studies. For information on the formulation and handling of baloxavir marboxil, see the pharmacy manual.

3.3.2 Rationale for Patient Population and Study Design

The safety and efficacy of baloxavir marboxil has been investigated in adult and adolescent populations in the United States and Japan. Two open-label studies have also been conducted in children in Japan. Given the burden of influenza in young children, particularly $<$5 years of age, this study in children is justified to confirm the safety and pharmacokinetics of baloxavir marboxil in this population.

Given the difficulties of recruiting very young children ($<$1 year) into clinical trials and the challenge of repeated sample requirements (including blood draws for PK analysis and nasal swabs for virology assays), an open-label design was selected. The rationale is that this study design enables a smaller sample size and also minimizes unnecessary

discomfort in those children who could otherwise be assigned to a placebo or active-control group in a double-blind study.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 30 pediatric patients with influenza-like symptoms are planned for enrollment in this study. Potential patients will be prescreened using an influenza test (RIDT or PCR) and a COVID-19 test (*RAT or* PCR). This is to ensure that patients with a high probability of having influenza infection are enrolled and to minimize the likelihood of enrolling a patient with COVID-19 in the study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Written informed consent for study participation obtained from patient's parents or legal guardian
- Age from birth to <1 year at screening
- Parent/guardian willing and able to comply with study requirements, in the investigator's judgment
- Patients with a diagnosis of influenza virus infection confirmed by the presence of **all** of the following:

– *In the investigator's judgement there is a clinical suspicion of influenza*

– At least one respiratory symptom (either cough or coryza)

– Positive prescreening influenza test (RIDT or PCR) performed within *48 hours of screening*

> *Results from local testing as part of standard of care are acceptable if samples are collected within 48 hours of screening and recorded in the patients' medical records.*

- Patients with a negative prescreening COVID-19 test (*RAT or* PCR) *within 48 hours of screening*

> *Results from local testing as part of standard of care are acceptable if samples are collected within 48 hours of screening and recorded in the patients' medical records.*

- The time interval between the onset of symptoms and screening is ≤ 96 hours (the onset of symptoms is defined as the time when body temperature first exceeded 37.5°C if known, or the time when the first symptom was noticed by the parent or caregiver)

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Hospitalized for complications of influenza or significant comorbidities

Patients hospitalized for observation, monitoring or precautionary supportive care may still be acceptable for enrollment provided all eligibility criteria are met.

- Concurrent infections requiring systemic antiviral therapy at screening
- Require, in the opinion of the investigator, any of the prohibited medication during the study
- Preterm neonates (born at $<$37 weeks gestation)
- Weigh $<$2.5 kg at screening

  Only children $>$ 4.5 kg will be eligible to take part in countries that have volume limits for blood draws set at 1% of the total blood volume (maximum over 24-hour period) and 3% of the total blood volume (maximum over 30-day period).

- Previous treatment with peramivir, laninamivir, oseltamivir, zanamivir, or amantadine within 2 weeks prior to screening
- Immunization with a live/attenuated influenza vaccine during the 2 weeks prior to screening
- Concomitant treatment with steroids or other immuno-suppressant therapy
- Known HIV infection or other immunosuppressive disorder
- Uncontrolled renal, vascular, neurologic or metabolic disease (e.g., diabetes, thyroid disorders, adrenal disease), hepatitis, cirrhosis, or pulmonary disease or patients with known chronic renal failure
- Active cancer at any site
- History of organ transplant
- Known hypersensitivity to study drug (i.e., baloxavir marboxil) or the drug product excipients
- Known hypersensitivity to acetaminophen
- Participation in a clinical trial within 4 weeks or 5 half-lives of exposure to an investigational drug prior to screening, whichever is longer

4.2 METHOD OF TREATMENT ASSIGNMENT

Since this is an open-label study, the Sponsor and its agents, the study site personnel, and the patients' parents/caregivers will be aware of the treatment administered in this study.

All patients will receive the same open-label treatment with the dose determined by both body weight and age (see Section 3.3.1), thus a method for assigning treatment is not warranted.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is baloxavir marboxil.

4.3.1 Study Treatment Formulation, Packaging, and Handling

Baloxavir marboxil will be supplied by the Sponsor as white to light yellow granules for oral suspension in 50-mL glass bottles. For information on the formulation and handling of baloxavir marboxil, see the pharmacy manual.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

4.3.2.1 Baloxavir Marboxil

Baloxavir marboxil is provided as granules for oral suspension; it will be administered orally as a single dose on Day 1, only. The granules for oral suspension will be reconstituted with water to provide a fixed dose depending on both the body weight and age of the child (2 mg/kg $\geq$ 3 months, 1 mg/kg $<$ 3 months).

4.3.2.2 Overdose or Incorrect Administration

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.11.

4.3.3 Rescue Medication

If influenza symptoms, such as fever and headache, are so severe, in the opinion of the patient/caregiver, that the patient needs rescue therapy between Day 1 and Day 29, the use of acetaminophen at a dose appropriate to the body weight and age of the child will be permitted only for the relief of fever or pain. If acetaminophen is used, the parent/caregiver will record the use in the patient diary, and the investigator will record the date, time, and dose at the next visit. Acetaminophen will not be provided by the Sponsor.

4.3.4 Investigational Medicinal Product Accountability

The IMP required for completion of this study (baloxavir marboxil) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of the IMP supplied by the Sponsor, using the interactive voice or web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMP will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMP must be agreed to by the Sponsor. The site must obtain written

authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMP received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.5 Continued Access to Baloxavir Marboxil

Currently, the Sponsor does not have any plans to provide the Roche IMP (baloxavir marboxil) or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing baloxavir marboxil in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 2 weeks prior to the initiation of study drug, to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Acetaminophen is permitted between Day 1 and Day 29 for severe influenza symptoms at a dose appropriate to the body weight and age of the child. See Section 4.3.3 for further details.

4.4.2 Cautionary Therapy

4.4.2.1 Herbal Therapies

Concomitant use of herbal therapies during this study is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown.

4.4.2.2 Polyvalent Cation–Containing Products

Polyvalent cation–containing products may decrease plasma concentrations of baloxavir. Thus, polyvalent cation-containing oral laxatives or oral antacids and oral supplements containing iron, zinc, selenium, calcium, or magnesium should not be taken with baloxavir marboxil.

4.4.3 Prohibited Therapy

The use of the following drugs and over-the-counter drugs with equivalent efficacy are prohibited from Day 1, after administration of study drug, until study completion or early termination:

- Systemic antiviral drugs
- Antipyretics/analgesics except acetaminophen
- Corticosteroids in injection, oral, or inhalation formulation
- Immunosuppressants

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety throughout the study.

4.5.1 Informed Consent Forms and Screening Log

Potential patients will be prescreened using an influenza test (RIDT or PCR) and a COVID-19 test (*RAT or* PCR). This is to ensure that patients with a high probability of having influenza infection are enrolled and to minimize the likelihood of enrolling a patient with COVID-19 in the study. A separate informed consent procedure will be implemented for this prescreening step. *If sites perform influenza (RIDT or PCR) and/or COVID-19 tests (RAT or PCR) as part of standard of care assessment, test results recorded in the patient medical record can be used for eligibility assessment, if samples were collected within 48 hours of screening.*

Written informed consent for participation in the study must be obtained from the child's parent/caregiver or legal guardian before performing any study-related procedures (including screening evaluations).

Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, and cancer history (including prior cancer therapies and procedures), will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within

2 weeks prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and parent/caregiver-reported race/ethnicity.

Influenza vaccination history for the 12 months before screening will be recorded, including the type of vaccine (e.g., live, inactivated) and date administered, if known.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Limited, symptom-directed physical examinations may be performed by a mobile nursing professional.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure as well as tympanic temperature.

Temperature will also be measured and recorded by parents/caregivers in patients eDiary (Section 4.5.6).

4.5.5 Laboratory and Other Biological Samples

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, chloride, bicarbonate, BUN or urea, creatinine, total protein, albumin, total and direct bilirubin, alkaline phosphatase, ALT, AST
- Plasma samples for PK analysis

- Nasopharyngeal swabs for virology tests (i.e., reverse transcriptase-polymerase chain reaction [RT-PCR], $TCID_{50}$, viral phenotyping and genotyping) and for non-influenza respiratory pathogen coinfections panel (only at the screening visit)

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exception:

- Plasma samples collected for PK analysis may be needed for PK assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.6 Patient-Reported and Investigator-Reported Outcomes

The Canadian Acute Respiratory Illness and Flu Scale (CARIFS) will be used to document the treatment benefit of baloxavir marboxil.

CARIFS is a reliable parental questionnaire and is composed of 18 questions, each with a 4-point Likert response. The questionnaire covers three domains: symptoms (e.g., cough), function (e.g., play), and parental impact (e.g., clinginess). The CARIFS is calculated as the sum of the items and measures duration of illness. Data handling conventions will be defined and described in the statistical analysis plan.

The questionnaire will be completed in its entirety by the parent or caregiver at specified time points during the study (see Appendix 1). To ensure instrument validity and that data standards meet health authority requirements, the questionnaire will be self-administered before the parent or caregiver receives any information on disease status, prior to the performance of non–patient-reported outcome (PRO) assessments, and prior to the administration of study treatment, unless otherwise specified *(see Appendix 1)*.

Parent/caregivers will use an electronic device to capture PRO data. The electronic device and/or instructions for completing the questionnaires electronically will be provided by site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

In addition, a 4-question palatability assessment (performed by the investigator or delegate) will be used to determine the perceived acceptability of baloxavir marboxil for each patient and issues that occur with regard to dosing (see Appendix 4). Palatability plays a role in patient acceptability of a drug especially in the pediatric population and is likely to have a significant impact on a patient's adherence, especially when the medicinal product has to be given as multiple doses either daily or over a number of days. This is largely determined by the characteristics of the medicinal product and the user, and compliance rates in children can range widely with factors attributed to formulation and palatability. There will be no formal statistical analysis performed for this endpoint.

Parent or Caregiver Reported Temperature

The parents or caregivers will measure the patient's temperature using tympanic thermometers provided. The temperature will be measured at specific time points during the study and will be recorded in the patient's electronic diary (Appendix 1)

The electronic device and/or instructions for recording the temperature electronically will be provided by site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment completion or treatment discontinuation visit on Day 29 (±3) days (see Appendix 1 for additional details).

4.6.2 Patient Discontinuation from Study

Patients' parents/caregivers have the right to voluntarily withdraw the patient from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient's parent/caregiver withdrawal of consent

- Study termination or site closure
- Patient's parent/caregiver non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on each patient who was withdrawn from the study by the parent/caregiver. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a parent/caregiver requests that the patient be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who are withdrawn from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with baloxavir marboxil in completed and ongoing studies. There are no anticipated important safety risks for baloxavir marboxil. Please refer to the Baloxavir Marboxil Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients potentially at higher risk for serious influenza and toxicities. Patients will undergo safety monitoring during the

study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Internal Monitoring Committee

An IMC will review the clinical study data at regular intervals as defined in the IMC charter. Should a safety concern be identified, the entire study may be suspended or discontinued, as appropriate.

5.1.2 Management of Patients Who Experience Adverse Events

Baloxavir marboxil is administered as a single-dose treatment, so no dose modification or treatment discontinuation is possible.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.8 and Section 5.3.5.9 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.6)

- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4, Section 5.5, and Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the parent/caregiver or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28-days after the last dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE Toxicity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 3):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 3 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of influenza.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of influenza, "influenza progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

The IMC will monitor the frequency of deaths from all causes.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of Influenza

Medical occurrences or symptoms of deterioration that are anticipated as part of influenza, such as fluctuation in symptoms, should only be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of influenza on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of influenza").

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event

5.3.5.11 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded

separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria *or qualifies as an adverse event of special interest*, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For baloxavir marboxil, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with baloxavir marboxil, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list

of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board/Ethic Committee (IRB/EC).

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed on the Roche Medical Emergency List), and track all calls.
The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/*Special Situations Form* provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur >28 days after the last dose of study treatment are provided in Section 5.6.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

5.5.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report

these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/*Special Situations Form* using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Baloxavir Marboxil Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An IMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities in countries where the study is being conducted, within adverse event/serious adverse event reporting timelines upon the sponsor being informed by the IMC.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary objective of this study is to evaluate the safety of baloxavir marboxil in pediatric patients from birth to <1 year with influenza-like symptoms. Therefore, and as it is a single group study, there will be no formal statistical hypothesis testing. The statistical analyses of safety, pharmacokinetics, and efficacy will be descriptive.

Full details of all planned tables, listings, graphs, and descriptive analyses will be provided in a Statistical Analysis Plan, which will be finalized prior to the end of the study.

6.1 ANALYSIS POPULATIONS

The main analysis populations are defined below.

6.1.1 Randomized Population

Not applicable.

6.1.2 Per Protocol Population

Not applicable.

6.1.3 Intent-to-Treat Patient Population

The intent-to-treat (ITT) population comprises all patients who received at least one dose of treatment regardless of whether they have any follow-up assessments. If there is any doubt whether a patient was treated, that patient will be assumed to have been treated for the purpose of analysis.

6.1.4 Intent-to-Treat Influenza-Infected Patient Population

The intent-to-treat influenza-infected (ITTi) population is a subset of ITT patients who have had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study. The ITTi population is the primary efficacy population, unless specified otherwise.

Decisions on patient exclusion from the ITTi population will be made prior to database closure. Excluded patients will be documented, together with the reason for exclusion.

6.1.5 Pharmacokinetic Evaluable Population

The pharmacokinetic-evaluable patient (PKEP) population comprises all patients in the ITT population who have at least one postdose drug concentration measurement at a scheduled visit timepoint. Patients may be excluded from the PKEP population if they significantly violate the inclusion or exclusion criteria or deviate significantly from the protocol, or if data are unavailable or incomplete (which may influence the PK analysis).

Decisions on patient exclusion from the PKEP population will be made prior to database closure by the clinical pharmacologist. Excluded patients will be documented, together with the reason for exclusion.

6.1.6 Safety Population

The safety-evaluable patient population will be the same as the ITT population (i.e., patients who have received any portion of a single dose) regardless of whether or not they had any follow-up visits.

6.2 DETERMINATION OF SAMPLE SIZE

No formal sample-size calculations have been performed.

A total of approximately 30 pediatric patients will be enrolled in order to estimate the PK parameters and maturation factor which is incorporated in the population PK model with a probability of $>90\%$.

The number of patients in the ITTi population will be monitored on an ongoing basis in order to ensure that an adequate number of influenza-infected patients are recruited.

Additional patients may be recruited if the ITTi population is considerably smaller than expected.

The number of patients in the ITTi population entering the study with ≤48 hours since symptom onset will also be monitored. Additional patients may be recruited if considerably fewer patients than expected enter the study with ≤48 hours since symptom onset.

6.3 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.4 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, and vaccination status) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

6.5 SAFETY ANALYSES

The safety evaluable population will be used for all analyses.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0.

The safety of baloxavir marboxil will be evaluated from adverse events, vital sign measurements *(including parent/caregiver recorded temperature)* and clinical laboratory tests. Safety parameters will be summarized or listed for the safety population.

6.6 PHARMACOKINETIC ANALYSES

The PKEP population (see Section 6.1.5) will be used for all analyses.

For patients with blood samples collected, individual plasma baloxavir marboxil and S-033447 concentrations will be tabulated by patient and by timepoint. Individual and mean (if appropriate) plasma baloxavir marboxil and S-033447 concentrations versus time data will be plotted by age group.

As this study uses an optimized sparse PK regimen, individual PK parameters of baloxavir marboxil and S-033447 (AUC, C_{max}, time to maximum concentration, and terminal half-life) will not be determined using model-independent methods. However, individual drug concentrations determined plasma concentration 24 and 72 hours after dosing (C_{24} and C_{72}, respectively) of S-033447 will be listed and summarized (mean,

standard deviation, coefficient of variation, median, minimum, and maximum) by age group.

In addition, a non-linear mixed-effects model (NONMEM, Version 7.3 or higher) will be used to analyze the PK data. The population typical PK parameters (e.g., apparent clearance [CL/F], apparent volume of distribution for the central compartment [Vc/F]) and their covariates will be estimated. Individual PK metrics, such as area under the concentration–time curve from Time 0 to infinity (AUC_{inf}), C_{24}, C_{72} and C_{max}, will be calculated using post hoc Bayesian estimation for each patient, and plotted against significant covariates identified (e.g., body weight, age). The derived individual values will be plotted against body weight and age. PK parameters will be tabulated and summarized (i.e., by mean, standard deviation, coefficient of variation, median, and minimum and maximum) by age group. PK exposure and response (e.g., virus titers) relationships will be explored. Population PK results may be reported in a dedicated modelling and simulation report.

Additional PK analyses will be conducted as appropriate.

Pediatric exposure matching to adults will use C_{24} (observed as well as Bayesian post hoc) as a primary PK parameter. Key secondary PK metrics, such as C_{72} and AUC_{inf} (derived as Bayesian post hoc), will assess whether exposure is sustained similarly as in adults, and to explore whether or not viral rebound, if any, may be associated with lower C_{72} values. For completeness, C_{max} will be calculated as secondary PK parameter.

6.7 EFFICACY ANALYSES

The ITTi population will be used for efficacy analyses.

The statistical analyses of efficacy endpoints will be descriptive: Kaplan-Meier plots and summary statistics for time-to-event endpoints, proportions for categorical variables and means, standard deviations, medians, and ranges for continuous variables.

Full details of all planned tables, listings, graphs, and descriptive analyses will be provided in a Statistical Analysis Plan, which will be finalized prior to the end of the study.

6.8 INTERIM ANALYSES

An interim PK analysis is planned for this study. PK samples, up to and including those collected at Visit 4/5 of first 6 patients dosed, will be batched for an early shipment. This will enable a timely review of the systemic plasma concentrations, in particular the concentration at 24 hours and 72 hours after dosing (C_{24} and C_{72}, respectively) (Appendix 1 and Appendix 2). This is in order to verify, in a timely manner, that exposures at the proposed doses are in reasonable agreement with the corresponding values seen in adults. The estimated turnaround time between last sample collected

and data review is estimated to be approximately 2 to 3 weeks, and recruitment will continue during this time. Data review will be performed by members of the Sponsor study team.

No other interim analyses are planned in this study. However, given there is no formal statistical hypothesis testing in this study, the Sponsor may choose to conduct *optional* interim analyses *as appropriate*. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will primarily be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details). In exceptional circumstances, PRO data might be collected on paper questionnaires. In the event PROs are completed on paper, the questionnaires will be maintained by the parent/caregiver and delivered to the site at the next regularly scheduled visit.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

An electronic device will be used to capture PRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server maintained by the electronic PRO vendor. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly on the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for

Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each parent/caregiver the objectives, methods, and potential risks associated with each optional procedure. Parents/caregivers will be told that they are free to refuse participation and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a parent's/caregiver's agreement to participate in optional procedures. Parents/caregivers who decline participation will not provide a separate signature.

The Consent Forms must be signed and dated by the parent/caregiver or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the parent/caregiver to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Parents/caregivers must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the parent/caregiver or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include parent/caregiver authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for parent/caregiver authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the parent/caregiver, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the parent/caregiver, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or parents/caregivers unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC

policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 25 sites in the United States and globally will participate to enroll approximately 30 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests and PK analyses), as specified in Section 4.5.5.

An IMC will be employed to monitor and evaluate patient safety throughout the study.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for more details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any

country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

[CDC] Centers for Disease Control and Prevention. Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP) [resource on the Internet]. 2011 Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm.

Paules C, Subbarao K. Influenza. Lancet 2017;390:697–708.

Rotrosen ET, Neuzil KM. Influenza: a global perspective. Pediatr Clin North Am 2017;64:911–36.

WHO. WHO fact sheet 211: influenza (seasonal) [resource on the Internet]. 2018 Available from: http://www.who.int/mediacentre/factsheets/fs211/en/.

Appendix 1
Schedule of Activities

	Prescreening[a]	Treatment Period		Follow-Up Period										
Day(s)	D1	D1		D2	D3	D4	D5	D6	D7	D8	D9	D10	D15	D29 or ET
Visits	NA	V1 Screening	V1 Post-dose	V2	OpV1[b]	V3		V4				V5	OpV2[b]	V6
Visit Window (days)	-1					+1		+1				±2	±3	±3
Prescreening influenza test	x[c]													
Prescreening COVID-19 test	x[d]													
Informed consents	x	x												
Inclusion/exclusion criteria		x												
Demographics		x												
Medical history[e]		x												
Study drug administration			x											
Patient diary:														
Body temperature measurement[f]			Four times daily			Twice daily						Once daily		
Assessment of influenza symptoms[g]			Twice daily									Once daily		
Physical examination		x[h]		x[h]	(x)[h]	x[h]		x[h]				x[h]	(x[i])	x[h]
Vital signs measurement		x		x	(x)	x		x				x	(x[i])	(x[j])
Adverse events assessment			x	x	(x)	x		x				x	(x[i])	x
Concomitant therapies assessment		x		x	(x)	x		x				x	(x[i])	x

Appendix 1
Schedule of Activities (cont.)

	Prescreening	Treatment Period		Follow-Up Period										
Day(s)		D1		D2	D3	D4	D5	D6	D7	D8	D9	D10	D15	D29 or ET
Visits	NA	V1 Screening	V1 Post-dose	V2	OpV1[a]	V3		V4				V5	OpV2[b]	V6
Visit Window (days)	NA					+1		+1				±2	±3	±3
Interview for meal consumption		x	x											
Clinical laboratory tests			x					x					(x[i])	
Nasopharyngeal swabs[k]		x		x		x		x				x	(x[i])	(x[i])
Pharmacokinetic samples[l]			x	(x)[l]		(x)[l]		x[l]						
Palatability assessment[m]			x											

CARIFS = Canadian Acute Respiratory Illness and Flu Scale; COVID-19 = coronavirus disease 2019; D = Day; ET = early termination; NA = not applicable; OpV = optional visit; PK = pharmacokinetic; V = visit.

[a] *Pre-screening assessment is not required if the patient has a negative COVID-19 test result and positive influenza test performed as SOC within 48 hours of screening recorded in their medical records*

[b] OpV1 and OpV2 are optional visits to be performed at the discretion of the investigator or parent/caregiver, for example, in the event of persistent influenza symptoms.

[c] *Test is not required if the patient has a positive influenza test result performed as SOC within 48 hours of screening recorded in their medical records*

[d] *Test is not required if the patient has negative COVID-19 test results performed as SOC within 48 hours of screening recorded in their medical records.*

[e] Prior therapies will also be reviewed.

[f] The parent/caregiver will assess and record in the patient diary, body temperature (tympanic assessment) four times daily (morning, noon, evening, and bedtime) on Days 1 to 3; twice daily (morning and evening) on Days 4 to 9; once daily on Days 10 to 15. *The first temperature recorded by the parent/caregiver will be measured post-dose.*

Appendix 1
Schedule of Activities (cont.)

[g] The parent/caregiver will complete the CARIFS questionnaire twice (morning and evening) on Days 1 to 9 and then once daily on Days 10 to 15. *The first CARIFS assessment will occur post-dose.*

[h] Perform if the investigator determines that influenza symptoms are persisting or at the investigator's discretion.

[i] Record vital sign measurements if abnormal physical examination, adverse events recorded since last visit, or at investigator's discretion on Day 29.

[j] At least two nasopharyngeal swabs (one for each nostril) will be taken at each visit.

[k] *PK samples (all patients): See Appendix 2 for collection timepoints for baloxavir marboxil and S-033447 concentration samples. Patients will be assigned to have either the Day 2 or the Day 4 sample. Only one sample from Days 6 to 10 is required and can be collected at either Visit 4 or Visit 5.*

[l] *The palatability assessment should be completed by the study investigator (or delegate) who administers baloxavir marboxil to the patient.*

Appendix 2
Schedule of Pharmacokinetic Samples

Visit	Timepoint	Sample Type
Sparse PK Sampling [a]		
Visit 1 (Day 1)	One sample between 0.5 and 2 hours post-dose	Drug PK (plasma)
Visit 2 (Day 2) [b]	24 hours post-dose	Drug PK (plasma)
Visit 3 (Day 4) [b]	72 hours post-dose	Drug PK (plasma)
Visits 4 – 5 (Days 6 – 10)	Only one sample is to be collected during the follow-up period; this sample may be collected at follow-up Visit 4 or 5	Drug PK (plasma)

PK = pharmacokinetic.

[a] Samples will be used for baloxavir marboxil and S-033447 determination.

[b] Patients will be assigned to have either the Day 2 or the Day 4 sample.

Appendix 3
Canadian Acute Respiratory Illness and Flu Scale (CARIFS) Questionnaire

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, 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 4 Palatability Assessment

Palatability Assessment

1. On the basis of the reaction/facial expression of your patient, do you think that the medication has a:
   a) very pleasant taste
   b) slightly pleasant taste
   c) neutral taste or no reaction of patients to taste
   d) slightly unpleasant taste
   e) very unpleasant taste
2. Did you have any problems administering the full dose to the patient?
   a) Yes
   b) No
3. If you answered “yes” for Question 2, what is the main reason for this problem?

4. Other comments or problems encountered administering the drug:

Signature Page for: System identifier:RIM-CLIN-438675
Protocol - CP40559 - XOFLUZA - v6 - Global/Core - Published

Approval Task	[redacted] Company Signatory 27-Apr-2022 15:08:34 GMT+0000