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

NCT Number: NCT06774859

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PROTOCOL

PROTOCOL TITLE:	**A PHASE *III*, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, AND EFFICACY OF BALOXAVIR MARBOXIL IN CHINESE PEDIATRIC PATIENTS 1 TO < 12 YEARS OF AGE WITH INFLUENZA SYMPTOMS**
PROTOCOL NUMBER:	YV44465
VERSION NUMBER:	2
TEST COMPOUND:	Baloxavir marboxil (RO7191686)
STUDY PHASE:	Phase *III*
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: Not applicable EudraCT Number: Not applicable EU Trial Number: Not applicable NCT Number: Not applicable
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Version	Date Final
2	See electronic date stamp on final page of this document
1	18 October 2022

PROTOCOL AMENDMENT, VERSION 2:

RATIONALE

Protocol YV44465 has been amended to meet the [redacted]. Additionally, the amendment has included study changes from the Sponsor. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The study phase has been modified from Phase IV to Phase III as this study will investigate the safety and efficacy in Chinese children 1–<12 years old with influenza for the first time (front matters).
- The synopsis has been simplified to align with Clincial Trials Regulation and other guidelines (Section 1.1).
- The note for a post-exposure prophylaxis (PEP) study has been removed as the potential PEP design (where the participants with influenza in this study may serve as the index patients for a PEP study) is no longer planned to be related with the current study (Sections 1.1 and 2.1).
- The schedule of activities has been amended to improve the clarity, consistency, and order of footnotes (Section 1.3, Table 1).
- The information about Cobas® essays for SARS-CoV-2 and influenza A/B testing has been removed due to its non-availability in China (Section 1.3, Table 1; Sections 5.1 and 8.10.1)
- [redacted]
- The regulatory approval status for baloxavir marboxil in China has been updated (Section 2.2).
- Additional descriptions about the planned proportions of 1–<5 years old and 5–<12 years old patients have been added (Section 4.1 and 9.1.1).
- Participant's body weight at screening for oseltamivir dosage has been updated to align with the prescribing information (Section 6.1.2, Table 7).
- Two stratification factors (age group and high risk factors for influenza complications) have been added for randomization to ensure the target 2:1 allocation ratio within different groups (Section 6.3).
- Prohibited therapy has been updated to include traditional Chinese medicines with antiviral effects (Section 6.8.4).
- It has been made explicit that expedited safety reports are notified to regulatory authorities using applicable systems (Section 8.3.4).
- A statement has been added to allow for potential increase of sample size to ensure an adequate number of a specific group of patients including patients with high risk

factors for influenza complications and patients with positive result for influenza using PCR (Section 9.1.1).

- A statement has been added to enable potential subgroup analyses (Section 9.3.1).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Roche practices (Section A1–4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section A1–6).
- A list of high risk factors for influenza complications has been added to define the high risk population (Appendix 8).

Additional minor changes have been 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

PROTOCOL TITLE:	**A PHASE *III*, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, AND EFFICACY OF BALOXAVIR MARBOXIL IN CHINESE PEDIATRIC PATIENTS 1 TO < 12 YEARS OF AGE WITH INFLUENZA SYMPTOMS**
PROTOCOL NUMBER:	YV44465
VERSION NUMBER:	2
TEST COMPOUND(S):	Baloxavir marboxil (RO7191686)
SPONSOR NAME:	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 your local study monitor.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE *III*, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS AND EFFICACY OF BALOXAVIR MARBOXIL IN CHINESE PEDIATRIC PATIENTS 1 TO < 12 YEARS OF AGE WITH INFLUENZA SYMPTOMS**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: Not applicable EudraCT Number: Not applicable EU Trial Number: Not applicable NCT Number: Not applicable

STUDY RATIONALE

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

OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, pharmacokinetics, and efficacy of baloxavir marboxil in Chinese pediatric participants aged 1 to < 12 years with influenza symptoms. The table below presents the primary and secondary objectives for the study expressed with use of the estimand framework in accordance with the International Council for Harmonisation (ICH) E9(R1) statistical principles for clinical trials.

Safety (Primary) Objective	Estimand Definition
• To describe the safety of a single dose of baloxavir marboxil compared with 5 days of oseltamivir administered BID in Chinese pediatric participants	• Population: All participants aged 1 to < 12 years with influenza symptoms who received at least 1 dose of study treatment • Endpoint: – Incidence, severity, and timing of adverse events, serious adverse events, with severity determined according to NCI CTCAE v5 – Change from baseline in vital sign measurements – Change from baseline in clinical laboratory test results • Treatment: – Experiment arm: baloxavir marboxil single dose – Control arm: oseltamivir 5 days BID • Intercurrent events and handling strategies – Treatment discontinuation: treatment policy strategy – Rescue medication: treatment policy strategy

Safety (Primary) Objective	Estimand Definition
	• Population-level summary: No formal statistical *testing* will be conducted. Analyses will be descriptive. – Incidence of adverse events, serious adverse events by System Organ Class, by Preferred Term and by worst severity – Change from baseline summaries will be presented overall and by treatment with use of descriptive statistics, including means, standard deviations, medians, and ranges for continuous variables
Efficacy (Secondary) Objective	**Estimand Definition**
• To describe the clinical efficacy of baloxavir marboxil compared with oseltamivir in Chinese pediatric participants	• Population: All participants aged 1 to $<$ 12 years with influenza symptoms who received at least 1 dose of study treatment who have had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study • Endpoints: – Time to alleviation of influenza signs and symptoms, defined as the length of time taken from the start of treatment to the point at which all of the following criteria are met and remain so for at least 21.5 hours: A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms (Items 14 and 15 of the CARIFS) A "yes" response to the following question on the CARIFS: "Since the last assessment has the subject been able to return to day care/school (if applicable), or resume his or her normal daily activity in the same way as performed prior to developing the flu?" (if possible) Return to afebrile state (tympanic temperature $\leq$37.2°C) – 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 *based on the CARIFS questionnaire* – Frequency of influenza-related complications (death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures, myositis)

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

Virology (Secondary) Objective	Estimand Definition
•	• Population-level summary: Summaries will be presented overall and by treatment with use of descriptive statistics, including means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables. Time to event endpoints will be summarized with use of Kaplan Meier plots and median survival time.

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

Other Secondary Objectives and Endpoints

Pharmacokinetic (Secondary) Objective	Corresponding Endpoints
• To describe the PK of baloxavir after single-dose administration of baloxavir marboxil in Chinese pediatric participants	• Plasma concentrations of S-033447 (active metabolite) will be summarized by time (C_{24} and C_{72}) and body weight • Population PK model derived parameters (e.g., AUC_{inf}, C_{max}, T_{max}, $t_{1/2}$) (modeling report)
Virology (Secondary) Objective	**Corresponding Endpoints**
• To evaluate the polymorphic and treatment-emergent amino acid substitutions in the *PA* gene and drug susceptibility in participants with evaluable virus in Chinese pediatric participants	• Polymorphic and treatment-emergent amino acid substitutions in the *PA* gene • Drug susceptibility in participants with evaluable virus
Palatability (Secondary) Objective	**Corresponding Endpoint**
• To evaluate the palatability of the oral suspension	• Proportion of participants reporting each palatability and acceptability response

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

OVERALL DESIGN AND STUDY POPULATION

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

Several key aspects of the study design and study population are summarized below.

Phase:	*Phase III*	***Population Type:***	*Pedatric patients*
Control Method:	*Active comparator*	***Population Diagnosis or Condition:***	*Influenza*
Interventional Model:	*Parallel group*	***Population Age:***	*1–<12 years*
Test Product:	*Baloxavir marboxil (RO7191686)*	***Site Distribution:***	*Multi-site in China*
Active Comparator:	*Oseltamivir*	***Study Treatment Assignment Method:***	*Randomization and stratification*
Number of Arms:	*2*	***Number of Participants to Be Enrolled:***	*Approximately 100*

STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are baloxavir marboxil *and oseltamibir. Baloxavir marboxil is the test product.* Oseltamivir is an active control.

Participants will be screened and randomized on Day 1 and assigned in a 2:1 ratio to receive a single oral dose of baloxavir marboxil based on body weight (2 mg/kg for participants weighing <20 kg or 40 mg for participants weighing ≥ 20 kg to <80 kg or 80 mg for those weighing ≥ 80kg)/[redacted] for oral suspension reconstituted with water by site staff or oseltamivir (twice a day dose based on body weight) for 5 days.

DURATION OF PARTICIPATION

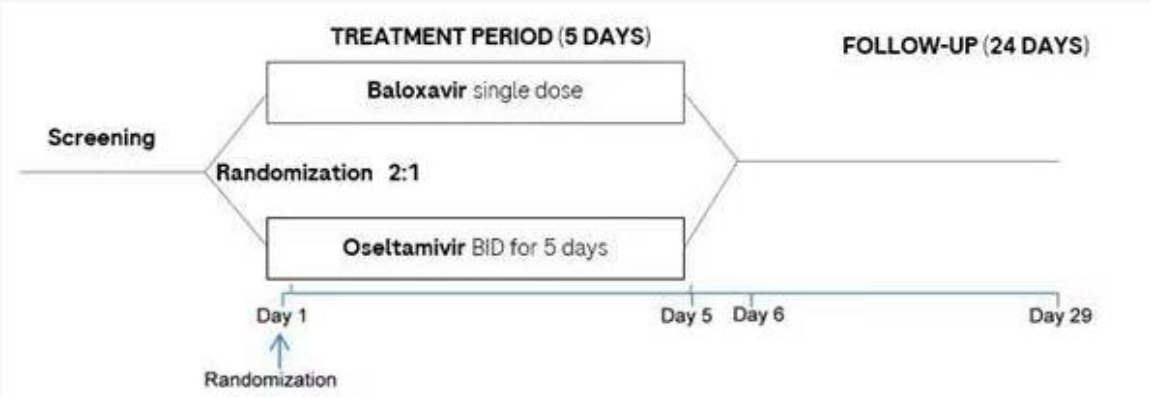
The study consists of two periods: a 5-day treatment period (mandatory visits on Days 1, 2, and 4) and a 24-day follow-up period (mandatory visits on Days 6, 10, and 29). Therefore, the total study duration for each participant will be 29 days.

COMMITTEES

Independent Committees:	*Not applicable*
Other Committees:	*Not applicable*

1.2 STUDY SCHEMA

Figure 1 Study Schema



BID = twice a day.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities

Day	Protocol Reference	Day 1 [a]		Day 2	Day 3	Day 4	Day 5	Day 6	Day 10	Day 15	Day 29/ET
Visits		Screening (Predose)	V1 (Postdose)	V2	Op V1 [b]	V3		V4	V5	Op V2 [b]	V6
Visits window (days)		0 (−1)	−1			+1		−1, +1	−2, +2	−3, +3	±3
Visit		x		x [c]	*x* [c]	x [c]		x [c]	x [c]	x [c]	x [c, d]
Informed consent	8	x									
Local influenza test	8.10.1	x									
Local SARS-Cov-2 test [e]	8.10.1	x									
Inclusion/exclusion criteria	5.1 5.2	x									
Demographics	8	x									
Medical history	*8*	*x*									
Influenza vaccination history	*8*	*x*									
Randomization	4.1	x									
Baloxavir marboxil administration	6.1.1	x									
Oseltamivir BID administration [f]	6.1.2	x		x	x	x	x				
Palatability assessment	8.11 Appendix 6		x [g]								

Table 1 Schedule of Activities (cont.)

Day		Protocol Reference	Day 1 [a]		Day 2	Day 3	Day 4	Day 5	Day 6	Day 10	Day 15	Day 29/ET
Visits			**Screening (Predose)**	**V1 (Postdose)**	**V2**	**Op V1 [b]**	**V3**		**V4**	**V5**	**Op V2 [b]**	**V6**
Visits window (days)			**0 (–1)**	**–1**			**+1**		**–1, +1**	**–2, +2**	**–3, +3**	**±3**
Visit			**x**		**x [c]**	***x*** **[c]**	**x [c]**		**x [c]**	**x [c]**	**x [c]**	**x [c, d]**
Participant diary	Body temperature [h]	4.1 8.2.2		x [i] (4 × daily)			x (2 × daily till Day 9)			x (once daily)		
	CARIFS symptoms assessment [j]	4.1 8.1.1.1 A5–1.1		x [i] (twice a day till Day 9)						x (once daily)		
Physical examination [k]		8.2.1	x		x	(x)	x		x	x	(x [l])	x
Vital signs		8.2.2	x		x	(x)	x		x	x	(x [l])	x [m]
Concomitant therapies assessment		6.8	x		*x*	(x)	x		x	*x*	(x [l])	x
Clinical laboratory tests		8.2.3		x					x		(x [l])	(x [l])
Respiratory samples (central virology test) [n]		8.10	x		x		x		x	x	*(x [l])*	(x [l])
PK samples [o]		8.4		x [p]	(x) [p]		(x) [p]		x			
Adverse event assessment [q]		8.3 Appendix 3		x	x	(x)	x		x	x	(x [l])	x

Table 1 Schedule of Activities (cont.)

BID = twice a day; CARIFS = Canadian Acute Respiratory Illness and Flu Scale; ET = Early termination; Op = optional; PCR = polymerase chain reaction; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome–coronavirus 2; V = visit.

[a] Informed consent/assent and screening in Index Patients can be performed on the day before Day 1.

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

[c] The visit may be a home visit performed by a mobile nursing professional for appropriate sites.

[d] Can be performed remotely.

[e] Participants will test for SARS-CoV-2 with point-of-care/local laboratory *methods*. Only participants testing PCR (–) *or antigen (–)* for SARS-CoV-2 will be enrolled into the study.

[f] Oseltamivir will be given orally, 12 hours apart. If the first dose is taken after 4 p.m. (16:00 hours) on Day 1, the next dose will be taken in the morning of Day 2. For these participants, the tenth dose will be taken on the morning of study Day 6. *If the first dose is taken prior to 4 pm (16:00 hours) on Day 1, the next dose should be taken in the evening of the same day (i.e., prior to midnight on the same calendar day with a minimum of 7 hours between doses). For these participants, the tenth dose will be taken in the evening of study Day 5.*

[g] The palatability questionnaire (Appendix 6) should be completed as soon as possible after swallowing the baloxavir marboxil drug solution on Day1. The questionnaire will be completed for pediatric participants receiving baloxavir marboxil only.

[h] The parent/caregiver will assess and record in the participant diary, body temperature (tympanic assessment) 4 times daily (morning, noon, evening, and bedtime) from Days 1–3; twice daily (morning and evening) on Days 4–9; once daily on Days 10–15. The results will be recorded in the participant diary.

[i] On Day 1, symptom and temperature assessments for the participant diary should only be completed and filled out for the postdose time window(s).

[j] The parent/caregiver will complete the CARIFS questionnaire twice a day (morning and evening) on Days 1−9 and then once a day on Days 10−15. The results will be recorded in the participant diary.

[k] A complete physical examination will be conducted at screening. Limited, symptom-directed physical examinations will be performed postdose. Height and body weight will be measured at screening only.

[l] Conduct assessment if the investigator determines that influenza symptoms or viral shedding are persisting or at the investigator's discretion.

[m] Vital signs will be recorded if abnormal physical examination findings or adverse events are recorded since the last visit or at the investigator's discretion on Day 29.

[n] *Respiratory samples will be collected using nasopharyngeal or nasal swabs.* At each swab timepoint, a virology test will be performed by the central laboratory.

[o] PK samples will be collected in baloxavir marboxil treated participants and sent to a central laboratory.

Table 1 Schedule of Activities (cont.)

[p] PK samples will be collected at Day 1 (1 sample between 0.5 and 2 hours postdose). Participants will be assigned to have either the Day 2 (24 hours postdose) or the Day 4 sample (72 hours postdose). Only 1 sample from Days 6–10 is required and can be collected at either Visit 4 or Visit 5.

[q] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 28 days after the first dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study drug (see Appendix 3).

Table 2 Schedule of Pharmacokinetic Samples

Visit Day	Timepoint	Sample Type
Day 1	One sample between 0.5 and 2 hours postdose	Drug PK (plasma)
Day 2 [a]	24 hours postdose	Drug PK (plasma)
Day 4 [a]	72 hours postdose	Drug PK (plasma)
Days 6–10	Only 1 sample is to be collected at visit Day 6 or Day 10	Drug PK (plasma)

PK = pharmacokinetic.

[a] Participants will be assigned to have either the Day 2 or Day 4 sample taken.

2. INTRODUCTION

2.1 STUDY RATIONALE

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

2.2 BACKGROUND

Influenza is an acute respiratory infection caused by a virus of the orthomyxoviridae family which occurs in three forms: influenza A, B, and C. Influenza virus types A and B can cause an acute febrile infection of the respiratory tract characterized by the sudden onset of fever, malaise, headaches, myalgias, and cough.

Children are relatively less immunized by natural infection with influenza virus and thus, have weak cross-protection against influenza virus, making them highly susceptible to influenza infection. In previous annual influenza epidemic seasons, the infection rate of influenza in children ranged from 20%–30% (Muli 2019); in some high epidemic seasons, the infection rate of influenza in children in specific areas could even reach about 50% (Cowling et al. 2014).

The rate of influenza vaccination varies from region to region and the accuracy of prediction of virus subtypes to include in the vaccine varies between different years. It takes a few weeks from the time of vaccination until the production of antibodies is sufficient to protect the body from infection (Centers for Disease Control and Prevention 2019).

Neuraminidase inhibitor (NAI) interferes with the release of progeny influenza virus from infected host cells, thereby halting the spread of infection and has served as a prevailing anti-flu treatment in China, both for pediatric and adult patients (aged ≥ 1 year). Oseltamivir, for instance, is an NAI dosed twice a day (BID) for 5 consecutive days for the treatment of influenza.

Xofluza™ (otherwise known as baloxavir marboxil) is a small molecule novel CAP-dependent endonuclease inhibitor, which blocks transcription of influenza viral mRNA needed for viral replication. The compound was discovered by *Shionogi Pharma Co.,Ltd.*. A single oral dose of baloxavir marboxil was shown to be efficacious in both the treatment of influenza A or B virus infection in otherwise healthy (OwH) and high risk patients (pediatric, adolescent, and adult), and post-exposure prophylaxis (PEP) settings, was well-tolerated, and reduced viral titers more rapidly than oseltamivir.

For OwH adults, the time to alleviation of symptoms (TTAS) was significantly shorter (by 26.5 hours) in the baloxavir marboxil group when compared with the placebo group (median, 53.7 hours vs. 80.2 hours), and similar to the oseltamivir group (53.5 hours vs.

53.8 hours). For high-risk patients aged 12 years or older, baloxavir marboxil significantly reduced the time to improvement of influenza symptoms (TTIIS, the primary endpoint) versus placebo (median time 73.2 hours vs. 102.3 hours; $p < 0.001$). For children aged 1 to < 12 years with an influenza infection, baloxavir marboxil was comparable with oseltamivir for reducing the duration of influenza symptoms, including fever. As demonstrated in nonclinical in vitro and in vivo studies, baloxavir marboxil is a potent antiviral with broad activity against all types and subtypes of the influenza virus, including influenza strains resistant to existing antivirals, and those with highly pathogenic and pandemic potential.

27 April 2021, the application for marketing of baloxavir marboxil tablets was approved in China for the treatment of uncomplicated influenza in patients aged 12 years and older and who have been symptomatic for no more than 48 hours and are (1) OwH or (2) are at high risk of developing influenza complications. *On 21 March 2023, the application for marketing of baloxavir marboxil tablets was approved in China for the treatment of uncomplicated influenza in otherwise healthy patients aged 5 to <12 years. On 29 Dec 2023, the application for marketing of baloxavir marboxil suspension was approved for the treatment of uncompliated influenza in otherwise healthy and high risk patients aged 5 to <12 years.*

Detailed information on baloxavir marboxil is provided in the Baloxavir marboxil Investigator's Brochure.

2.3 BENEFIT–RISK ASSESSMENT

The purpose of this study is to further evaluate the safety, pharmacokinetics, and efficacy of baloxavir marboxil in Chinese pediatric participants aged 1 to < 12 years with influenza symptoms. Baloxavir marboxil has been approved in Japan for the treatment of *adult, adolescent, and pediatric* patients *(≥10 kg)* with acute uncomplicated influenza. Since its approval in Japan, baloxavir marboxil has been approved in multiple regions worldwide, including the United States and European Union.

The clinical efficacy and safety of baloxavir marboxil versus placebo and oseltamivir were demonstrated in two pivotal Phase III trials (CAPSTONE 1 [NCT02954354] and CAPSTONE 2 [NCT02949011], respectively). In these studies, baloxavir marboxil showed significant improvements in TTAS (CAPSTONE 1) and TTIIS (CAPSTONE 2) compared with placebo, and a faster reduction in infectious viral titers compared with placebo and oseltamivir in adults and adolescents was observed. In the patients of CAPSTONE-2 who were infected with influenza B virus, the median TTIIS was significantly shorter in the baloxavir marboxil group compared with the placebo and oseltamivir group (median time 74.6 hours for baloxavir marboxil vs. 100.6 hours for placebo and 101.6 for oseltamivir, respectively).

The evidence of baloxavir marboxil dosing in pediatric patients aged 1 to < 12 years for treatment comes from the pivotal Study CP40563 (MINISTONE-2), a randomized,

double-blind, active (oseltamivir) controlled Phase III trial to evaluate the safety, pharmacokinetics, and efficacy of a single dose of baloxavir marboxil in OwH children aged 1 to < 12 years. In the study, 173 children were randomized and dosed, 115 patients to the baloxavir marboxil group and 58 patients to the oseltamivir group, median TTIIS (95% CI) was similar between groups: 138.1 hours (116.6 hours to 163.2 hours) with baloxavir marboxil versus 150.0 hours (115.0 hours to 165.7 hours) with oseltamivir. In conclusion, baloxavir marboxil was comparable with oseltamivir at reducing the duration of flu symptoms with a fair tolerance in children infected with influenza.

Additional data from three Japanese Phase III pediatric Studies 1618T0822 (T0822), 1705T0833 (T0833), and 1813T0835 (T0835) help support the evaluation of safety, resistance, and pharmacokinetics of baloxavir marboxil in pediatric patients aged 1 to < 12 years with a consistent safety profile. Baloxavir marboxil was well-tolerated and did not have any significant safety concerns in pediatric patients < 12 years of age.

A higher incidence of treatment-emergent I38X substitutions with reduced susceptibility has been observed in children compared with adolescents and adults. However, clinical benefit for patients with an I38X substitution was comparable with those treated with oseltamivir in Study CP40563 (Baker et al. 2020). To note, influenza viruses with reduced susceptibility to antivirals are transient in immunocompetent patients, are cleared by the immune system and have no impact on clinical progression or choice of therapy for future influenza infections (Holmes et al. 2021).

Taking into account the efficacy and safety profile of baloxavir marboxil in patients, especially the pediatric population, as well as the risk mitigations measures, the benefit-risk ratio is expected to be acceptable in this study. All participants will benefit from receiving an influenza antiviral (either oseltamivir, already approved in China, or baloxavir marboxil).

More details about the known and expected benefits, risks, and reasonably expected adverse events of baloxavir marboxil may be found in the Baloxavir marboxil Investigator's Brochure.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

This study will evaluate the safety, pharmacokinetics, and efficacy of baloxavir marboxil in Chinese pediatric participants aged 1 to < 12 years with influenza symptoms. Table 3 presents the primary and secondary objectives for the study expressed with use of the estimand framework in accordance with the International Council for Harmonisation (ICH) E9(R1) statistical principles for clinical trials (U.S. Food and Drug Administration [FDA] 2021). Table 4 presents the remaining objectives and corresponding endpoints.

Table 3 Primary and Secondary Objectives and Corresponding Estimand

Safety (Primary) Objective	Estimand Definition
• To describe the safety of a single dose of baloxavir marboxil compared with 5 days of oseltamivir administered BID in Chinese pediatric participants	• Population: All participants aged 1 to < 12 years with influenza symptoms who received at least 1 dose of study treatment (see Sections 5.1 and 5.2, respectively) • Endpoint: – Incidence, severity, and timing of adverse events, serious adverse events, with severity determined according to NCI CTCAE v5 – Change from baseline in vital sign measurements – Change from baseline in clinical laboratory test results • Treatment: – Experiment arm: baloxavir marboxil single dose – Control arm: oseltamivir 5 days BID • Intercurrent events and handling strategies – Treatment discontinuation: treatment policy strategy – Rescue medication: treatment policy strategy • Population-level summary: No formal statistical $testing$ will be conducted. Analyses will be descriptive. – Incidence of adverse events, serious adverse events by System Organ Class, by Preferred Term and by worst severity – Change from baseline summaries will be presented overall and by treatment with use of descriptive statistics, including means, standard deviations, medians, and ranges for continuous variables

Table 3 Primary and Secondary Objectives and Corresponding Estimand (cont.)

Efficacy (Secondary) Objective	Estimand Definition
• To describe the clinical efficacy of baloxavir marboxil compared with oseltamivir in Chinese pediatric participants	• Population: All participants aged 1 to < 12 years with influenza symptoms who received at least 1 dose of study treatment who have had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study • Endpoints: – Time to alleviation of influenza signs and symptoms, defined as the length of time taken from the start of treatment to the point at which all of the following criteria are met and remain so for at least 21.5 hours: A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms (Items 14 and 15 of the CARIFS, see Section A5–1.1). A "yes" response to the following question on the CARIFS: "Since the last assessment has the subject been able to return to day care/school (if applicable), or resume his or her normal daily activity in the same way as performed prior to developing the flu?" (if possible). Return to afebrile state (tympanic temperature ≤ 37.2°C). – Duration of fever (time to return to afebrile state [tympanic temperature ≤ 37.2°C] and remaining so for at least 21.5 hours) – Duration of symptoms (alleviation of all symptoms as defined by a score of 0 [no problem] or 1 [minor problem] and remaining so for at least 21.5 hours, for all 18 symptoms specified in the CARIFS questionnaire) – Time to return to normal health and activity *based on the CARIFS questionnaire* – Frequency of influenza-related complications (death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures, myositis) – Proportion of participants requiring antibiotics for influenza related complications • Treatment: – Experiment arm: baloxavir marboxil single dose – Control arm: oseltamivir 5 days BID • Intercurrent events and handling strategies – Treatment discontinuation: treatment policy strategy with use of appropriate summary statistics

Table 3 Primary and Secondary Objectives and Corresponding Estimand (cont.)

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

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

Table 4 Other Secondary Objectives and Endpoints

Pharmacokinetic (Secondary) Objective	Corresponding Endpoints
• To describe the PK of baloxavir after single-dose administration of baloxavir marboxil in Chinese pediatric participants	• Plasma concentrations of S-033447 (active metabolite) will be summarized by time (C_{24} and C_{72}) and body weight • Population PK model derived parameters (e.g., AUC_{inf}, C_{max}, T_{max}, $t_{1/2}$) (modeling report)
Virology (Secondary) Objective	**Corresponding Endpoints**
• To evaluate the polymorphic and treatment-emergent amino acid substitutions in the *PA* gene and drug susceptibility in participants with evaluable virus in Chinese pediatric participants	• Polymorphic and treatment-emergent amino acid substitutions in the *PA* gene • Drug susceptibility in participants with evaluable virus
Palatability (Secondary) Objective	**Corresponding Endpoint**
• To evaluate the palatability of the oral suspension	• Proportion of participants reporting each palatability and acceptability response (see Appendix 6)

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

4. STUDY DESIGN

4.1 OVERALL DESIGN

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

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

Participants will be screened and randomized on Day 1 and assigned in a 2:1 ratio to receive a single oral dose of baloxavir marboxil based on body weight (2 mg/kg for participants weighing < 20 kg or 40 mg for participants weighing ≥ 20 kg to < 80 kg or 80 mg for those weighing ≥ 80 kg))/[redacted] for oral suspension or oseltamivir (twice a

day dose based on body weight) for 5 days. Re-screening of participants who fail to meet the inclusion and exclusion criteria will not be permitted for the same illness episode, as the time from symptom onset to the treatment window is limited to 48 hours. Either drug will be started at the time of randomization.

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

Temperatures will be recorded as follows.

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

Influenza symptoms will be recorded as follows.

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

A study schema is provided in Section 1.2 (see Figure 1). A schedule of activities and a sample collection schedule are provided in Section 1.3 (see Table 1 and Table 2).

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

The safety and efficacy of baloxavir marboxil has been investigated in pediatric, adolescent, and adult patient populations. The single dose of baloxavir marboxil was well-tolerated and demonstrated comparable efficacy with oseltamivir in children aged 1 to $<$12 years with influenza infection. Given the unmet need and burden of influenza in young children in China, who have a higher risk of contracting the influenza virus and developing severe complications in the epidemic influenza seasons, this study is justified to confirm the safety, pharmacokinetics, and efficacy of baloxavir marboxil in Chinese pediatric participants aged 1 to $<$12 years.

4.2.2 Rationale for Control Group

It may not be considered ethical to withhold active treatment from children with influenza symptoms given the potential severity of the disease, so a placebo control group has not been included. Oseltamivir is a well-established and well-characterized antiviral agent

effective against influenza in patients aged 2 weeks or older and is currently the standard of care for influenza treatment.

While the main objectives for this study are to assess the safety of baloxavir marboxil, pharmacokinetics and efficacy data will be collected as secondary endpoints. Use of oseltamivir in this study will allow a descriptive evaluation of secondary efficacy and virological endpoints, as well as serve as a comparator of adverse events.

The dose of oseltamivir to be used in this study is the approved dose for children in the treatment of influenza, which is based on body weight. The standard duration of treatment in healthy children is 5 days of BID dosing, which will be assessed in this study.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

In this study, baloxavir marboxil will be administered based on the participants' body weight recorded at screening (i.e., 2 mg/kg for participants weighing <20 kg or 40 mg for participants weighing ≥ 20 kg) to obtain a similar exposure of the metabolite S-033447 to that resulting from the administration of 40 mg or 80 mg baloxavir marboxil (based on body weight) to adults in Phase III studies.

Proposed pediatric doses in this study were determined according to the modeling and simulation of S-033447 pharmacokinetics in the pediatric population. A baloxavir marboxil population PK model was developed with use of data from pediatric, adolescent and adult patients (Population Pharmacokinetics Report No. 1099597), by using PK data obtained in the Phase III studies involving pediatric patients (global Study CP40563 and Japan Studies 1618T0822 and 1705T0833), and adults and adolescents (Studies T0821, T0831, T0832). The proposed doses are expected to lead to a similar S-033447 exposure in the Asian pediatric population compared with Asian adults.

Simulation of Asian and non-Asian pediatric drug exposure was performed for 200 patients (2400 patients in total) for every 5-kg body weight for 6.7 kg- to greater than 30 kg pediatric patients, and the proposed dosing regimens were evaluated with respect to the ability to match adult drug exposure in terms of area under the concentration–time curve (AUC), maximum observed concentration (C_{max}), concentration at 24 hours postdose (C_{24}), and 72 hours postdose (C_{72}). The proposed dose and body weight cutoff for flat dosing were based on a comparison of the simulated drug exposures 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 ≥ 80 kg), those obtained in the pediatric Phase III study (1618T0822), and those obtained in the Phase I study (1527T0816) through corrected QT interval (QTc) for patients receiving 80 mg baloxavir marboxil. Simulations showed that optimal exposure in Asian and non-Asian pediatric patients matching to adult patients of both respective ethnicity groups, in terms of both total (AUC) and sustained (C_{72}) drug exposure, was achieved with 2 mg/kg in children weighing <20 kg and flat dosing of 40 mg in children

weighing ≥20 kg. The proposed pediatric doses have been further evaluated in the Study CP40563, which demonstrated a matching exposure between Caucasian pediatrics and adults. A similar dose regimen (2 mg/kg for body weight <10 kg and 20 mg for body weight between 10 and 20 kg) has also been evaluated in the Study T0835, which demonstrated a matching exposure between Japanese pediatric patients and adults.

The safety and efficacy of baloxavir marboxil in pediatric and adult patients with influenza virus infection have been demonstrated in previous studies and in the market. In this study, baloxavir marboxil will be administered as [redacted] for oral suspension. Bioequivalence of the suspension and the 20-mg tablet (which was tested in clinical studies) was confirmed in a previous study.

For details of the formulation and handling of baloxavir marboxil, see the pharmacy manual.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last scheduled procedure shown in the schedule of activities (see Section 1.3).

The end of this study is defined as the date when the last participant, last visit occurs or the date at which the last data point required for statistical analysis or follow-up is received from the last participant, whichever occurs later. The total length of the study, from screening of the first participant to the end of the study, is expected to be approximately 24 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.

4.5 DURATION OF PARTICIPATION

The study consists of two periods: a 5-day treatment period (mandatory visits on Days 1, 2, and 4) and a 24-day follow-up period (mandatory visits on Days 6, 10, and 29). Therefore, the total study duration for each participant will be 29 days.

5. STUDY POPULATION

Approximately 100 Chinese pediatric participants aged 1 to <12 years with influenza symptoms are planned for enrollment in this study. Pharmacokinetic (PK) samples will be collected for baloxavir marboxil treated pediatric participants according to the schedule of activities *until approximately 48 pediatric participants' samples are collected to ensure at least 40 pediatric participants' samples are available for analysis*.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Potential participants are eligible to be included in the study only if all of the following criteria apply:

- Signed Informed Consent Form (ICF)

  A parent or authorized adult will be required to sign the ICF on behalf of the pediatric participant. The informed consent/assent of voluntary participation should be obtained in accordance with local requirements.
- Signed Assent Form when appropriate, as determined by participants' age and individual site and country standards
- Age 1 to <12 years at the time of signing ICF
- A participant who has a diagnosis of influenza virus infection and meets all the following conditions.
  - Fever $\geq 38°C$ (tympanic temperature) at screening

    AND
  - At least one of the respiratory symptoms of influenza virus infection (e.g., cough and nasal discharge/nasal congestion)

    AND
  - A rapid influenza diagnostic test (RIDT) or polymerase chain reaction (PCR) shows positive for influenza A/B, e.g., point-of-care/local laboratory results with use of nasal aspirate, throat swab, or nasal drip/droplet (or other appropriate sample)

    Results from local testing as part of standard of care are acceptable if samples are collected within 24 hours of screening and recorded in the participants' medical records.
- The time interval between the onset of symptoms and screening is ≤ 48 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 participant, parent, or caregiver)
- A participant who will be able to take baloxavir marboxil [redacted] for oral suspension or oseltamivir capsule for oral suspension/oral in the opinion of the investigator/sub-investigator
- A participant whose parent/guardian is willing and able to adhere to the study requirements in the opinion of the investigator/sub-investigator
- A participant who is able to adhere to the study requirements appropriately for the level of understanding

- PCR (–) or antigen test (–) for severe acute respiratory virus-coronavirus 2 (SARS-CoV-2) *using* point-of-care/local laboratory *test* with nasal aspirate, throat swab, or nasal drip/droplet (or other appropriate sample)

  Results from local testing as part of standard of care are acceptable if samples are collected within 24 hours of screening and recorded in the participants' medical records.

5.2 EXCLUSION CRITERIA

Potential participants are excluded from the study if any of the following criteria apply.

- A participant having severe influenza virus infection symptoms requiring inpatient treatment
- *Evidence of* severe renal impairment (equivalent to CLCr <30 mL/min or estimated glomerular filtration rate <30 mL/min/1.73 m^2), vascular, neurologic, or metabolic disease (e.g., diabetes, thyroid disorders, adrenal disease), uncontrolled hepatitis, cirrhosis, or pulmonary disease (e.g. uncontrolled bronchial asthma)
- Received systemic corticosteroid or immunosuppressive therapy
- Primary immunodeficiency syndrome
- History of organ transplantation
- HIV infection
- Immunization with a live/attenuated influenza vaccine in 2 weeks prior to randomization
- Previous malignancy within the last 5 years or has an active cancer at any site
- Previous encephalitis/encephalopathy, uncontrolled epilepsy with antiepileptic drugs, or influenza virus infection-associated abnormal behavior within the last 2 years
- Complications by an infection requiring systemic antibiotic drug, antifungal and/or antiviral drug at screening
- Use of prohibited concomitant drugs while in the study in the opinion of the investigator
- A participant who received any medications with anti-flu effect such as baloxavir, peramivir, oseltamivir, zanamivir, favipiravir, arbidol, amantadine or traditional Chinese anti-influenza medicines within 30 days before screening
- Known allergy and/or clinically problematic intolerance to baloxavir, oseltamivir and/or acetaminophen
- Diagnosed with or suspected SARS-CoV-2 infection, or close contacts of diagnosed or suspected SARS-CoV-2 infected participants
- Severe underlying disease or condition potentially affecting study evaluation in the opinion of the investigator/sub-investigator
- A participant who received an investigational or unapproved drug product within 30 days or $5\times$ the half-life before screening, whichever is longer

- Females participants who have commenced menarche (i.e., child-bearing potential)

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

Baloxavir marboxil co-administration with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc) should be avoided. Therefore, study medication should not be co-administered with any of the aforementioned foods, liquids, or medications.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

This study has no contraception requirements.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) cannot be re-screened for the same illness episode, as the time from flu symptom onset to treatment window is limited to 48 hours. The investigator will maintain a record of reasons for screen failure (see Section 8).

6. STUDY TREATMENT, OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN, AND CONCOMITANT THERAPY

The investigational medicinal product (IMP) for this study is baloxavir marboxil. Oseltamivir (also an IMP) will be administered as an active control.

6.1 STUDY TREATMENT ADMINISTERED

Table 5 provides a description of assigned study treatments for this study.

Table 5 Study Treatment Description

	Baloxavir marboxil	Oseltamivir
Use	Experimental	Active comparator
Drug form	[redacted] for oral suspension	Capsules/oral suspension
Unit dose strength(s)	2 mg/mL	75 mg/capsule
Dosage level(s)	2 mg/kg, 40 mg or 80 mg single dose	30 mg, 45 mg, 60 mg, 75 mg BID
Formulation(s)	Refer to Pharmacy Manual	Refer to Pharmacy Manual

Packaging	50-mL glass bottle	Blister packs containing 10 capsules, 1 packs per box
Labeling	Per local requirements	Per local requirements
Route of administration	Oral suspension	Oral/oral suspension
Source	Sponsor	Sponsor

The treatment regimens are summarized in Section 4.1.

Guidelines for treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 3.

6.1.1 Baloxavir marboxil

Baloxavir marboxil will be supplied by the Sponsor as white to light yellow [redacted] for oral suspension in 50-mL glass bottles. Baloxavir marboxil will be administered orally as a single dose on Day 1, only. The [redacted] for oral suspension will be reconstituted with water to provide a fixed dose based on the body weight of the child (2 mg/kg for participants weighing <20 kg, or 40 mg for participants weighing ≥ 20 kg to <80 kg, and 80 mg for those weighing ≥ 80 kg). For information on the formulation, packaging, and handling of baloxavir marboxil, see the pharmacy manual (see Table 5).

Table 6 Baloxavir Marboxil Administration by Treatment Group

Participant's Body Weight at Screening	Dose, Formulation
<20 kg	2 mg/kg, oral suspension
≥ 20 kg to <80 kg	40 mg (20 mL), oral suspension
≥ 80 kg	80 mg (40 mL), oral suspension

6.1.2 Oseltamivir

Oseltamivir will be supplied by the Sponsor as a capsule/oral suspension and administered orally BID (morning and evening) for 5 days. Participants can take the capsule directly. If participants can't take the capsule, they can take the oral suspension prepared by the capsule. The powder for suspension will be reconstituted with water, to provide a fixed dose based on the body weight of the child. The first does of oseltamivir will be administered on Day 1 at the site by the investigator/study nurse and the investigator/study nurse will give training on the oseltamivir administration to the parents/guardians. Participants can take the oseltamivir on the second dose on Day 1 and Day 2 to Day 5 at home.

Oseltamivir will be given orally 12 hours apart. If the first dose is taken after 4 p.m. (16:00 hours) on Day 1, the next dose will be taken in the morning of Day 2. For these participants, the tenth dose will be taken on the morning of Day 6. If the first dose is taken prior to 4 p.m. (16:00 hours) on Day 1, the next dose should be taken in the evening of the same day (i.e., prior to midnight on the same calendar day with a minimum of 7 hours between doses). For these participants, the tenth dose will be taken in the evening of Day 5.

For information on the formulation and handling of oseltamivir, see the pharmacy manual and the local prescribing information for oseltamivir (see Table 7).

Table 7 Oseltamivir Administration by Treatment Group

Participant's Body Weight at Screening	Dose. Formulation
≤ 15 kg	30 mg BID, oral suspension
>15 kg to ≤ 23 kg	45 mg BID, oral suspension
>23 kg to ≤ 40 kg	60 mg BID, oral suspension
>40 kg	75 mg BID, oral/oral suspension

BID = twice a day.

6.1.3 Rescue Medication

If influenza symptoms, such as fever and headache, are so severe, in the opinion of the participant/caregiver, that the participant needs rescue therapy between Days 1 and 29, the use of acetaminophen at a dose appropriate to the age and weight of the child will be permitted. If acetaminophen is used, the participant/parent/caregiver will record the use in the participant diary, and the investigator will record the date, time, and dose at the next visit.

Acetaminophen will not be provided by the Sponsor.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel e.g., pharmacist or mobile nurse) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, with use of an interactive voice or Web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

Investigational medicinal products 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 with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs 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 IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log. Caregivers will be reminded to return remaining medicine with packaging and/or empty bottles to the study site.

Refer to the pharmacy manual and/or the Baloxavir marboxil Investigator's Brochure or local prescribing information for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT

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

Participants will be randomly assigned in a 2:1 ratio to one of the two treatment arms: a single oral dose of baloxavir marboxil or oseltamivir. *Randomization will be stratified by age group (1–<5 years old versus 5–<12 years old) and high risk factors for influenza complications (with versus without, see Appendix 8 for the definition of high risk factors).*

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision.

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Appendix 3.

6.5 DOSE MODIFICATION

Baloxavir marboxil is administered as a single-dose treatment, so no dose modification or treatment discontinuation is possible. Modification of the oseltamivir dose is not permitted; however, participants who received oseltamivir can discontinue treatment if adverse events are considered to be related to oseltamivir.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not have any plans to provide baloxavir marboxil or oseltamivir or any other study treatments to participants 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 website:

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

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities for a period per the investigator's judgement.
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).

6.8 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 participant 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 must be reported to the investigator and recorded on the Concomitant Medications eCRF along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

6.8.1 Permitted Therapy

Acetaminophen is permitted between Days 1–29 for severe influenza symptoms at a dose appropriate to the weight and age of the child. See Section 6.1.3 for further details.

6.8.2 Cautionary Therapy

Baloxavir marboxil co-administration with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc) should be avoided.

6.8.3 Herbal Therapies

Concomitant use of herbal therapies (including Chinese traditional medications) during this study is strongly discouraged because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown.

6.8.4 Prohibited Therapy

The use of the following drugs and over-the-counter drugs will be prohibited from the time of signing the informed consent until completion of study assessments on Day 15 (or until completion of assessments at study withdrawal). The concomitant use of topical skin preparations like a compress is allowed.

- Antipyretics/analgesics other than acetaminophen
- Corticosteroids in oral, injection, or *nasal* formulation

  Only systemic (oral, injection, rectal or enema) and nasal formulations will be prohibited. The concomitant use of inhaled corticosteroids is allowed, and any changes in dose and mode of administration should be recorded.
- Immunosuppressive agents
- Antibiotics and antifungals

  Unless bacterial or fungal infection is suspected after study drug administration.
- *Other* systemic antivirals *except for study drugs, including traditional Chinese medicines with antiviral effects*
- Influenza vaccines
- Other investigational drugs

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study for additional assessments. The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Participants must permanently discontinue study treatment if any of the following criteria are met:

- Study termination or site closure
- Participant withdrawal of consent
- Any medical condition that the investigator or Sponsor determines may jeopardize the participant'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 participant
- If the participant or any other household members/close contact is diagnosed with the SARS-CoV-2 infection by a healthcare professional/institution, and Chinese public health guidance at the time prevents the participant participating in mandatory study visits the participant will be discontinued from the study, with cessation of clinic and/or home visits. Following discontinuation from the study and if not already assessed that day, an early discontinuation visit should be conducted remotely (e.g., via telephone). Collection of a respiratory sample will not be required (see Section 5.4).

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Participants who discontinue study treatment prematurely will not be replaced. Participants will return to the clinic for a treatment completion or treatment discontinuation visit on Day 29 (±3 days) (see Appendix 1 for additional details). See the schedule of activities (see Section 1.3) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3). See the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) 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.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Written ICFs and assent forms, where appropriate, for participation in the study must be obtained before performing any study-related procedures (including screening

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

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a detailed record of all participants screened, to document eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., diagnostic test for influenza and/or SARS–CoV-2) within 24 hours of screening may be utilized for inclusion into the study provided the procedures meet the protocol specified criteria and are performed within the timeframe defined in the schedule of activities.

Medical history, including clinically significant diseases, surgeries, cancer history, and reproductive status in female participants will be recorded at baseline. In addition, all medications used by the participant within 2 weeks prior to initiation of study treatment will be recorded. Demographic data, including age, sex, and parent/caregiver will be recorded. 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.

Physical examinations will be performed at screening and other specified visits. Limited, symptom-directed physical examinations will be performed at specified post-baseline visits and as clinically indicated. Vital signs, including measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, as well as tympanic temperature should be recorded.

At applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the participant's home or another suitable location to improve access and convenience for participants participating in the study. The Sponsor will select a health-care company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable

regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a participant and the participant gives written informed consent to participate in MN visits, the MN network will communicate with the participant and the participant's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Section 1.3) will specify the assessments that may be performed by an MN professional.

8.1 EFFICACY ASSESSMENTS

8.1.1 Clinical Outcome Assessments

8.1.1.1 Canadian Acute Respiratory Illness and Flu Scale

The Canadian Acute Respiratory Illness and Flu Scale (CARIFS) will be used to document the treatment outcome of baloxavir marboxil (Jacobs et al. 2000).

The CARIFS is a widely accepted parental questionnaire and is composed of 18 questions, each with a 4-point ordinal scale to measure the duration of illness. The questionnaire covers three domains: symptoms (e.g., cough), function (e.g., play), and parental impact (e.g., clinginess) and the CARIFS is calculated as the sum of the items. Data handling conventions are defined and described in the Statistical Analysis Plan (SAP).

The questionnaire will be completed in its entirety by the parent or caregiver at specified timepoints during the study (see Section A5–1.1). To ensure instrument validity and that data standards met health authority requirements, the questionnaire should be administered and performed before the parent/caregiver or participant received any information on disease status. The first questionnaire will be completed on Day 1 after treatment administration.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination, performed at screening, will include, at a minimum, assessments of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated. Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from abnormalities identified at screening should be recorded in participant notes. New or worsened clinically significant abnormalities i.e., beyond expected variation or normal age-related changes should be recorded as adverse events on the Adverse Event eCRF. Limited physical examinations may be performed by an MN professional.

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention). After initiation of study treatment, any new or worsened clinically significant abnormalities i.e., beyond expected variation or normal age-related changes should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Vital Signs

Tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (three consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention). After initiation of study treatment, any new or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. Vital sign measurement may be performed by an MN professional.

8.2.3 Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event Case Report Form (CRF, see Appendix 3).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days of the first dose of study treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Sample collection may be performed by an MN professional.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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 (see Appendix 3). All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 28 days after the first dose of study treatment (Day 1) at the timepoints specified in the schedule of activities (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements *for expedited* safety reporting to regulatory authority *(which includes the use of applicable systems, such as EudraVigilance)*, Institutional Review Boards (IRBs) or Ethics Committees (ECs), and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Baloxavir marboxil	Baloxavir marboxil Investigator's Brochure
Oseltamivir	Oseltamivir U.S. Prescribing Information

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 investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Baloxavir marboxil Investigator's Brochure/U.S. Prescribing Information and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 3.

8.3.6 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.7 Adverse Events of Special Interest

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 the investigator becomes aware of the event; see Section A3–5 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 A3–7.6)
- Suspected transmission of an infectious agent by a study treatment, 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 participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

8.3.8 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study participants access to Medical Monitors is available 24 hours per day, 7 days per week. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

Plasma samples for each timepoint will be collected for measurement of plasma concentrations of S-033447 as specified in the schedule of activities (see Section 1.3 [Table 2]).

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the course of the study on the basis of newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Sample collection may be performed by an MN professional.

Samples will be used to evaluate the pharmacokinetics of S-033447. Samples collected for analyses of S-033447 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on plasma samples. Participant confidentiality will be maintained. At visits during which plasma samples for the determination of S-033447 will be taken, one sample of sufficient volume can be used.

Pharmacokinetic samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

8.5 PHARMACODYNAMICS

Pharmacodynamic biomarker assessments will not be performed in this study.

8.6 GENETICS

Genetic biomarker assessments will not be performed in this study.

8.7 BIOMARKER ASSESSMENTS

Biomarker assessments will not be performed in this study.

8.8 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will not be performed in this study.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

Health economics and medical resource utilization assessments will not be performed in this study.

8.10 VIROLOGY ASSESSMENTS

8.10.1 Respiratory Sampling

Respiratory samples will be collected at the timepoints indicated in the schedule of activities (see Table 1).

At screening, 2 samples will be collected (1 for local and 1 for central laboratory analysis) by the investigator or site staff.

For local analysis, RIDT or PCR will be used to confirm the participant is positive for influenza A/B, e.g., point-of-care/local laboratory results with use of nasal aspirate, throat swab, or nasal drip/droplet (or other appropriate sample).

Respiratory samples sent to the central labs for virology testing will be *collected using nasal swabs or nasopharyngeal swabs, and* analyzed by reverse transcriptase-polymerase chain reaction [RT-PCR], 50% of the tissue culture infectious dose ($TCID_{50}$), phenotyping, and genotyping.

Detailed instructions for collecting respiratory samples are provided in the laboratory manual and must be followed.

8.10.1.1 Samples Collected at Screening

Two samples will be collected (1 for local and 1 for central laboratory analysis) *for influenza tests* by the investigator or site staff. A respiratory sample for local analysis is not needed if the medical record documents show influenza A/B positive and SARS-CoV-2 negative test results based on respiratory samples collected within 24 hours prior to signed ICF (as part of standard of care).

8.10.1.2 Samples Collected Post-Randomization

One sample is collected for central laboratory analysis according to the schedule of activities (Section 1.3).

Furthermore, the investigator may at any time collect a sample for local analysis of SARS-CoV-2 if the investigator suspects co-infection. If a participant has a positive SARS-CoV-2 result based on a local analysis, all swabbing will stop and they should be discontinued (see Section 7.1).

Sample collection may be performed by an MN professional.

8.10.2 Polymorphic and Treatment-emergent Amino Acid Substitutions in the *PA* Gene

Sanger sequencing of the influenza PA gene will be performed to evaluate the incidence of polymorphic (baseline vs. reference) and treatment-emergent (post-baseline vs. baseline) amino acid substitutions in baloxavir-treated subjects with evaluable virus.

8.10.3 Drug Susceptibility

Drug susceptibility of the influenza virus, the 50% effective concentration (EC_{50}) will be evaluated by ViroSpot™ assay for participants who receive baloxavir marboxil.
For participants who received oseltamivir, drug susceptibility will be measured with the NA-Star assay.

8.11 PALATABILITY AND ACCEPTABILITY ASSESSMENT OF STUDY DRUG QUESTIONNAIRE

A palatability questionnaire (Appendix 6) will be completed immediately following dosing with baloxavir marboxil to determine the perceived acceptability of baloxavir marboxil for each participant.

A two-question palatability and acceptability questionnaire will be used to record palatability and acceptability. The questionnaire will be completed by the participant on their own or by a parent/guardian depending on the child's ability to read and/or understand the questions. If the child is unable to understand the questions being asked the parent/guardian will complete the questionnaire on the child's behalf to determine perceived acceptability. If the child cannot communicate the parent should base the response on the child's reaction to the medication.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested for this study.

9.1.1 Sample Size Determination

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

The sample size of 67 participants in the baloxavir marboxil treatment group will provide a probability of 87% to detect an adverse event with a 3% incidence rate for at least 1 participant. The given sample size provides a probability of at least 1 participant experiencing an adverse event with a true incidence rate from 1%–5% as shown in Table 8.

Table 8 Probability of Adverse Events by Incidence Rates

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

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

The number of participants in this study will be monitored on an ongoing basis in order to ensure an adequate number of specific participants are enrolled (e.g., participants with high risk factors for influenza complications [see Appendix 8 for definition] and participants meeting the definition of full analysis set-infected participants (FASi).

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

9.2 ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 9.

Table 9 Participant Analysis Sets

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

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

9.3 STATISTICAL ANALYSES

The Statistical Analysis Plan will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary endpoints.

9.3.1 General Considerations

Treatment assignments will be unblinded to the Sponsor after the data have been cleaned and verified and the database has been locked after the last participant, last visit, in the primary treatment period.

The statistical analyses of safety, pharmacokinetics and efficacy will be descriptive. The Safety Analysis Set (SAS) will be used for all analyses on primary endpoint and analyses of secondary efficacy and virology endpoints will be conducted on the FASi. The PK analysis set (PKAS) will be used for the PK analyses. *Additional subgroup analyses may be performed, and details will be specified in the SAP.*

9.3.2 Estimation Methods for the Primary Estimand/Endpoint

The primary objective for this study is to compare the safety of a single dose of baloxavir marboxil with 5 days of oseltamivir administered BID. All participants exposed to study treatment will be used for safety analyses. Participants will be analyzed according to the treatment they actually received.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs.

Study treatment exposure (such as treatment duration, total dose received) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment–emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade. Changes in vital signs will be summarized.

9.3.3 Estimation Methods for the Efficacy (Secondary) Estimands/Endpoints

The statistical analyses of efficacy endpoints are descriptive. All participants who received at least one dose of study treatment and who have had a laboratory

confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study will be used for all efficacy analyses (FASi).

The data will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Time-to-event endpoints and duration endpoints will be summarized with use of Kaplan-Meier plots and summaries of the median survival time. Summaries will be presented by treatment group.

Full details of all tables, listings, graphs, and descriptive analyses will be provided in the SAP, which will be finalized prior to unblinding.

9.3.3.1 Time to Alleviation of Influenza Signs and Symptoms

Time to alleviation of influenza signs and symptoms in hours, will be summarized with use of descriptive statistics by treatment, as well as Kaplan-Meier plots. It is defined as the length of time taken from the start of treatment to the point at which all of the following criteria are met and remain so for at least 21.5 hours:

- A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms (items 14 and 15 of the CARIFS questionnaire – see Section A5–1.1)
- A "yes" response to the following question on the CARIFS: "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?"
- Return to afebrile state (tympanic temperature $\leq$37.2°C)

9.3.4 Estimation Method for Virology (Secondary) Endpoints

The FASi set will be used for all virology analyses.

9.3.4.1 Time to Cessation of Viral Shedding by Virus Titer

Time to cessation of viral shedding by virus titer is defined as the time, in hours, between the initiation of any study treatment and first time when the influenza virus titer is below the limit of detection. Participants whose virus titers have not reached the limit by the last observation timepoint will be treated as censored at that timepoint. One day is converted into 24 hours.

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

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

9.3.4.2 Time to Cessation of Viral Shedding by RT-PCR

Time to cessation of viral shedding by RT-PCR, in hours, is defined as the time between the initiation of any study treatment and first time when the virus RNA by RT-PCR qualitative result is negative (no cycle threshold [Ct]- value detectable). Participants who do not have a negative result by the last observation time point will be treated as

censored at that time point. For the participants with multiple virus types, this endpoint is defined as the time between the initiation of the study treatment and first time when the virus RNA by RT-PCR is below the limit of detection for all virus types. One day is converted into 24 hours.

Participants with a positive virus RNA on Day 1 will be included in this analysis.

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

9.3.4.3 Change from Baseline in Influenza Virus Titer at Each Timepoint

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

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

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

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

If the amount of virus RNA is less than the lower limit of quantification, the amount of virus RNA will be imputed as 2.18 for influenza A and 2.93 for influenza B (log_{10} virus particles/mL). If a participant is infected with multiple virus types, the sum of those amounts of virus RNA will be used for analysis.

Participants with a positive by RT-PCR on Day 1 will be included in this analysis.

9.3.4.5 Proportion of Participants with Positive Influenza Virus Titer at Each Timepoint

The proportion of participants positive for an influenza virus titer will be presented by treatment at each visit and is defined as the percentage of participants whose influenza virus titer is not less than the lower limit of quantification (0.75 $log_{10}TCID_{50}$/mL) or positive among those assessed for influenza virus titer on Days 2, 4, 6, and 10.

Participants with a positive influenza virus titer on Day 1 will be included in this analysis.

9.3.4.6 Proportion of Participants Positive by RT-PCR at Each Timepoint

Proportion of participants positive by RT-PCR will be presented by treatment at each visit is defined as the percentage of participants with detectable virus RNA (2.05 for

influenza A and 2.83 for influenza B $\log_{10}$ virus particles/mL) among those assessed by RT-PCR on Days 2, 4, 6, and 10.

Participants with a positive result by RT-PCR on Day 1 will be included in this analysis.

9.3.5 Other Analyses

9.3.5.1 Summaries of Conduct of Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

9.3.5.2 Summaries of Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age, sex, parent/caregiver or self-reported race/ethnicity) will be summarized by treatment arm. Baseline data are the last data obtained prior to initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

9.3.5.3 Pharmacokinetic Analyses

Individual and mean plasma S-033447 concentration versus time data will be tabulated and plotted. As this study uses an optimized sparse PK regimen, individual PK parameters of S-033447 (AUC, C_{max}, time to maximum concentration, and terminal half-life) will not be determined with use of model-independent methods. However, individual drug concentrations determined plasma concentration 24 and 72 hours postdose (C_{24} and C_{72}, respectively) of S-033447 will be listed and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum).

Additional PK analyses will be conducted as appropriate.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

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A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) or Ethics Committee (EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- 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
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Clinical Trials Directive (2001/20/EC) or *Clinical Trials* Regulation 536/2014 (*EEA* sites only), and all other applicable local regulations

A1–2 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 study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If the ICF is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or the participant's legally authorized representative must re-consent by signing the most current version of the ICF or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each ICF must be provided to the participant or the participant's legally authorized representative.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the ICF.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 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 20 sites globally will participate to enroll approximately 100 participants. Enrollment will occur through an interactive voice or Web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8 and Appendix 2. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

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/*or* other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be provided upon request. 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/

A1–7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on electronic Case Report Forms (CRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–8 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results.
In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site 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.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant 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.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells) • Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, BUN or urea, creatinine, total protein, albumin, phosphate, total and direct bilirubin, ALP, ALT, and AST

Investigators must document their review of each laboratory safety report.

Appendix 3
Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a participant or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 [NCI] Common Terminology Criteria for Adverse Events [CTCAE]; see Section A3–3.2); 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 electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3–5 for reporting instructions).

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the electronic Caser Report Form (eCRF).

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 grading scale. The investigator will use the grading scale in Table A3-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table A3-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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 (v 5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Examples of instrumental activities of daily living include 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 participants 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 A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes 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

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 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.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial 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 the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 28 days after the first dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware 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 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 the investigator becomes aware 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 more than 28 days after the first dose of study treatment are provided in Section A3–6.

A3–6 REPORTING 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 first dose of study treatment), if the event is believed to be related to prior exposure to study 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 Adverse Event /Special Situations Form, using the fax number or email address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and 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 of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

For adverse events, 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.

A3–7.2 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.

A3–7.3 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant 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 the investigator becomes aware that the event became serious; see Section A3–5 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 participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.4 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected.
A laboratory value abnormality that is not associated with the underlying disease 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., dose 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 A3–7.3 for details on recording persistent adverse events).

A3–7.5 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected.
A vital sign abnormality that is not associated with the underlying disease 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., dose 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 (e.g., 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 A3–7.3 for details on recording persistent adverse events).

A3–7.6 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 A3–7.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.7 DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5). 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 solely 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 A3–6.

A3–7.8 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").

A3–7.9 LACK OF EFFICACY OR WORSENING OF INFLUENZA

Medical occurrences or symptoms of deterioration that are anticipated as part of influenza should not be recorded as adverse events. However, deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. 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").

A3–7.10 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 A3–2), 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 participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment

became necessary because of the expected normal progression of the condition

- The participant has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

A3–7.11 CASES OF OVERDOSE, MEDICATION ERROR, DRUG ABUSE, OR DRUG MISUSE

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (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
- Intentional overdose: intentional 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.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm}
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

In cases where drug is to be self-administered by the participant, drug misuse could involve the drug being administered to someone other than the participant.

Special situations and adverse events associated with special situations are to be reported separately on the Adverse Event eCRF, as outlined in the sections below.

A3–7.11.1 Reporting Special Situations

All special situations associated with baloxavir marboxil and oseltamivir, 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.

- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.}
- 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.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the participant: Enter the drug name and "participant supplied drug to third party" as the event term. Check the "Drug misuse" box.

A3–7.11.2 Reporting Adverse Events Associated with Special Situations

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 the investigator becomes aware of the event; see Section A3–5). For baloxavir marboxil and oseltamivir, adverse events associated with special situations should be recorded as described below for each situation:

- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.

- 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.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose (special situation) and one entry to report the adverse event (headache).
The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

Appendix 4
Safety Plan: Management of Identified and Potential Risks

There are currently no identified or potential risks associated with baloxavir marboxil; therefore, this appendix is not applicable.

Appendix 5
Clinical Outcome Assessment Instruments

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A5–1 CLINICAL OUTCOME ASSESMENT INSTRUMENTS

Participant-reported outcomes (PRO) and observer-reported outcomes (ObsRO) instruments will be self-administered (as appropriate) at the clinic at specified timepoints during the study (see schedule of activities in Section 1.3) and/or at home on a daily basis (please see the schedule of activities in Section 1.3 for frequency). At the clinic, instruments will be administered before the participant or observer receives any information on disease status, prior to the performance of non-PRO/ObsRO assessments. The first questionnaire will be completed on Day 1 after treatment administration.

Participant-reported outcomes and ObsRO instruments, translated into the local language as appropriate, will be completed through paper diaries.

Participants and observers should be given the following instructions for completing PRO and ObsRO instruments at home:

- Participants and observers should complete the instruments in a quiet area with minimal distractions and disruptions.
- Participants and observers should answer questions to the best of their ability; there are no right or wrong answers.
- Participants and observers should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

A5–1.1 CANADIAN ACUTE RESPIRATORY ILLNESS AND FLU SCALE

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

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

Since the last assessment has the subject been able to return to day care/school (if applicable), or resume their normal daily activity in the same way as performed prior to developing the flu? ☐ Yes ☐ No

This form was filled out by:

☐ Parent

☐ Carer

☐ Other

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

Appendix 6
Palatability and Acceptability Assessment of Study Drug

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

Palatability and Acceptability Assessment of Study Drug

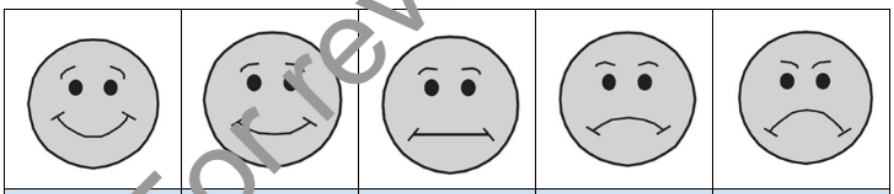
Instructions: We are interested in understanding how you or your child experienced the taste of this medicine. This questionnaire should be completed as soon as possible after the medicine has been swallowed.

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

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

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

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



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

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

Yes	No	Not sure
☐	☐	☐

Version 1.0

Appendix 7
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

1. Stop the study treatment administration, if possible.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by participant status and as directed by the physician in charge.
6. Continue to observe the participant and document observations.

Appendix 8
High Risk Factors for Influenza Complications

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

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

REFERENCE

Centers for Disease Control and Prevention. People at higher risk of flu complications [resource on the Internet]. [updated: 25 August 2023; cited: 15 January 2024]. Available from: https://www.cdc.gov/flu/highrisk/index.htm.

Appendix 9 Abbreviations

Abbreviation or Term	Definition
AUC	area under the concentration–time curve
BID	twice a day
C_{24}	concentration 24 hours postdose
C_{72}	concentration 72 hours postdose
CARIFS	Canadian Acute Respiratory Illness and Flu Scale
C_{max}	maximum observed concentration
CRF	Case Report Form
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
FASi	full analysis set-infected participants
FDA	U.S. Food and Drug Administration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IP	Index Patient
IRB	Institutional Review Board
IxRS	interactive voice or Web-based response system
MN	mobile nursing
NAI	neuraminidase inhibitor
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OwH	otherwise healthy
PCR	polymerase chain reaction
PK	pharmacokinetic
POC	proof-of-concept
RIDT	rapid influenza diagnostic test
RT-PCR	reverse transcriptase polymerase chain reaction
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory virus–coronavirus 2
TCID	50% of the tissue culture infectious dose
TTAS	time to alleviation of symptoms
TTIIS	time to improvement of influenza symptoms
ULN	upper limit of normal

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