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

NCT Number: NCT03959332

Document Date: Protocol Version 2: 10-January-2019

PROTOCOL

TITLE:	**A PHASE I, SINGLE-CENTER, OPEN-LABEL, PARALLEL, TWO DOSE LEVEL STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY FOLLOWING A SINGLE DOSE OF BALOXAVIR MARBOXIL IN HEALTHY CHINESE VOLUNTEERS**
PROTOCOL NUMBER:	YP40902
VERSION:	2
TEST PRODUCT:	Baloxavir marboxil (RO7191686)
SPONSOR:	F. Hoffmann-La Roche Ltd and Shionogi & Co., Ltd
DATE FINAL:	06 December 2018
DATE AMENDED:	Version 1: 07 August 2018 *Version 2: See electronic date stamp below*

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	10-Jan-2019 15:03:20

PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE I, SINGLE-CENTER, OPEN-LABEL, PARALLEL, TWO DOSE LEVEL STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY FOLLOWING A SINGLE DOSE OF BALOXAVIR MARBOXIL IN HEALTHY CHINESE VOLUNTEERS**
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I agree to conduct the study in accordanc[redacted]ol.

[redacted]

Principal Investigator's Name (print)

[redacted]

Principal Investigator's Signature

Jan 17, 2019

Date

Please keep the signed original form in your study files and return a copy to your local Study Monitor.

PROTOCOL AMENDMENT – SUMMARY OF CHANGES

Amendment 1:

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rational for the amendment

This amendment includes changes in protocol sections to clarify clinical operation methods and to give clearer instructions to study centers in accordance with local clinical practice.

List of Main Changes in the Amendment:

- Table 1 and Table 1 footnote in Section 1.3: Add drug screen action on Day -1 visit in the table; move weight assessment from Day 1 to Day -1; remove hematology, urinalysis, clinical chemistry test on Day 1; remove HBcAg, HbcAb related tests and contents, add serological test for *syphilis* in the footnote 'l'; remove blood samples for pharmacogenomic testing; update information of ECG testing in the footnote 'f' from "Triplicate 12-lead ECG will be performed at specified timepoints" to "Triplicate 12-lead ECG *can* be performed at specified timepoints if deemed necessary by investigator", also add text "*Timepoints for ECG evaluation from Day 1 are provided in Table 2*".
- Table 2 in Section 1.3: Remove weight, ECG, laboratory tests at pre-dose from administration on Day 1 during the in-house period; remove blood samples for pharmacogenomic testing.
- Section 1.1 and 4.1: Add "*PK sampling*" to the assessments of participants who will visit the study center on Days 6, 8, 10,12, and 15.
- Synopsis and Sections 5.1: Update "body mass index is ≥18.5 to 26 kg/m^2" to "body mass index is ≥18.5 to <26 kg/m^2" in the inclusion criteria.
- Synopsis and Sections 5.2: Revise "average diastolic blood pressure (40-90 mmHg)" to "average diastolic blood pressure (*60*-90 mmHg)" in the exclusion criteria.
- Sections 8.2.3: Add information "*Triplicate 12-lead ECG can be performed at specified timepoints if deemed necessary by investigator*".

- Sections 8.7: Remove all pharmacogenomics information in the section and replace with “Pharmacogenomics assessments are not performed in this study”.
- Table 7 in Appendix 4: Remove HBcAb test and add serological test for syphilis.

In addition, minor formatting updates and corrections have been made. Such changes are not listed in this amendment.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AUC_{0-inf}	area under the concentration-time curve from Time 0 to infinity
AUC_{0-last}	area under the concentration-time curve from Time 0 to last measurable concentration
AUC_{0-t}	area under the plasma concentration-time curve between Time 0 and the time t
BUN	blood urea nitrogen
CEN	cap-dependent endonuclease
CL/F	apparent clearance
C_{max}	maximum plasma concentration
eCRF	electronic Case Report Form
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
NA	neuraminidase
OTC	over-the-counter
PK	pharmacokinetic
SoA	Schedule of Activities
T_{max}	time to maximum plasma concentration
$T_{1/2}$	terminal elimination half-life
ULN	upper limit of normal
Vz/F	apparent volume of distribution based on the terminal phase

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE I, SINGLE-CENTER, OPEN-LABEL, PARALLEL, TWO DOSE LEVEL STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY FOLLOWING A SINGLE DOSE OF BALOXAVIR MARBOXIL IN HEALTHY CHINESE VOLUNTEERS**
SHORT TITLE:	**THE PK, SAFETY, AND TOLERABILITY OF BALOXAVIR MARBOXIL IN HEALTHY CHINESE VOLUNTEERS**
PROTOCOL NUMBER:	YP40902
VERSION:	2
TEST PRODUCT:	Baloxavir marboxil (R07191686)
PHASE:	I

RATIONALE

The purpose of the study is to evaluate the pharmacokinetics (PK), safety, and tolerability after a single oral dose of baloxavir marboxil (40 mg or 80 mg) in healthy Chinese participants. As this is a Phase I study in healthy participants, no therapeutic benefit is anticipated for these study participants.

OBJECTIVES AND ENDPOINTS

The specific objectives and corresponding endpoints/parameters for the study are outlined below.

Objectives	Endpoints/Parameters
Primary	
• To evaluate the pharmacokinetics of baloxavir marboxil and baloxavir after a single oral dose of baloxavir marboxil	• Maximum plasma concentration (C_{max}) • Time to maximum plasma concentration (T_{max}) • Area under the plasma concentration-time curve ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{0\text{-t}}$) • Terminal elimination half-life ($t_{1/2}$) • Apparent total oral clearance (CL/F) • Apparent volume of distribution based on the terminal phase (Vz/F) • Plasma concentration at 24 hours (C24), 48 hours (C48), and 72 hours (C72)
Secondary	
• To evaluate the safety and tolerability following a single oral dose of baloxavir marboxil	• Incidence, severity, and frequency of adverse events, serious adverse events, vital signs measurements, and clinical laboratory tests.

OVERALL DESIGN

Study Design

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

Treatment Groups and Duration

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

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

During the in-house period, on confirming all the eligibility requirements, the participants will be randomly allocated to one of the two parallel groups, 40 mg or 80 mg of study drug (baloxavir marboxil). The participants will be admitted to the study center on Day -1 and receive study drug on morning of Day 1. Safety assessments and PK sampling will be carried out at scheduled timepoints. The study drug will be given after an overnight fast of approximately 10 hours followed by a fast of at least 4 hours postdose. Participants will receive standard meals while in the study center and can be discharged at the investigator's discretion on Day 4 after the 72-hour assessments have been completed.

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

Length of Study

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

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

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

End of Study

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

Data Monitoring Committee

No Data Monitoring Committee is involved in the study.

PARTICIPANT POPULATION

The study population will consist of healthy Chinese participants.

Inclusion Criteria

Participants must meet the following criteria for study entry:

- Healthy male or female Chinese participants, aged 20-59 years inclusive at the time of screening. The female participants should be of non-childbearing potential.
- Chinese participants must have Chinese parents and grandparents, all of whom were born in China.
- Healthy status as defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, viral serology, and urinalysis.
- Participants whose body weight is ≥50 to <80 kg and body mass index is ≥18.5 to <26 kg/m^2.
- Able to participate and willing to provide written informed consent and to comply with the study restrictions.
- Female participants must be either surgically sterile (by means of hysterectomy and/or bilateral oophorectomy) or postmenopausal for at least 1 year (defined as amenorrhea ≥12 consecutive months without another cause, and confirmed by follicle-stimulating hormone level > 35 mIU/mL).

Exclusion Criteria

Participants who meet any of the following criteria will be excluded at study entry:

- Participants who are considered ineligible for this study by the Principal Investigator or subinvestigator due to current or history of significant metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, urological, endocrine, neurological, or psychiatric disorders with clinical manifestations.
- Participants with the following laboratory abnormalities at screening and on Day -1:
  total bilirubin >1.5 × upper limit of normal (ULN)
  AST >1.5 × ULN
  ALT >1.5 × ULN
  estimated glomerular filtration rate <60 mL/min/1.73 m^2 by using Cockcroft-Gualt formula.
- QTc interval > 450 ms (with Fridericia's correction)
- Participants with vital signs values outside of the reference range for average systolic blood pressure (90-140 mmHg), average diastolic blood pressure (*60*-90 mmHg), or average pulse rate (40-90 beats/minute).
- Participants with a history of stomach, vagus nerve, or intestinal surgery (except for appendectomy).
- Participants who have a history of allergic symptoms including food allergy (Note: Non-active allergic rhinitis will be allowed).

- Participants who require chronic drug therapy or those who have used drugs (e.g., prescription or over-the-counter drugs, herbal and dietary supplements, and vitamins) within 3 days prior to screening or within 14 days prior to Day -1.
- Participants who have used alcohol-containing, caffeine-containing, grapefruit containing, or St. John's wort-containing products within 72 hours prior to Day -1.
- Participants who have used tobacco- or nicotine-containing products within 24 weeks prior to screening.
- Participants who have a history of abuse of drugs and/or alcohol.
- Participants who have a positive urine cotinine, drug, and alcohol screen at screening and Day -1.
- Participants who are positive for serological test for syphilis (*Treponema pallidum*), hepatitis B surface antigen, hepatitis C virus antibody, or HIV antigen/antibody at screening.
- Participants who have donated >400 mL of blood within 12 weeks or >200 mL of blood within 4 weeks prior to screening, or have donated any amount of blood between screening and Day -1.
- Participants who have been exposed to an investigational drug within 90 days prior to the initial screening visit.
- Participants who have received baloxavir marboxil previously.
- Participants who are considered inappropriate for the study by the Principal Investigator or subinvestigator.

NUMBER OF PARTICIPANTS

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

CONCOMITANT MEDICATIONS

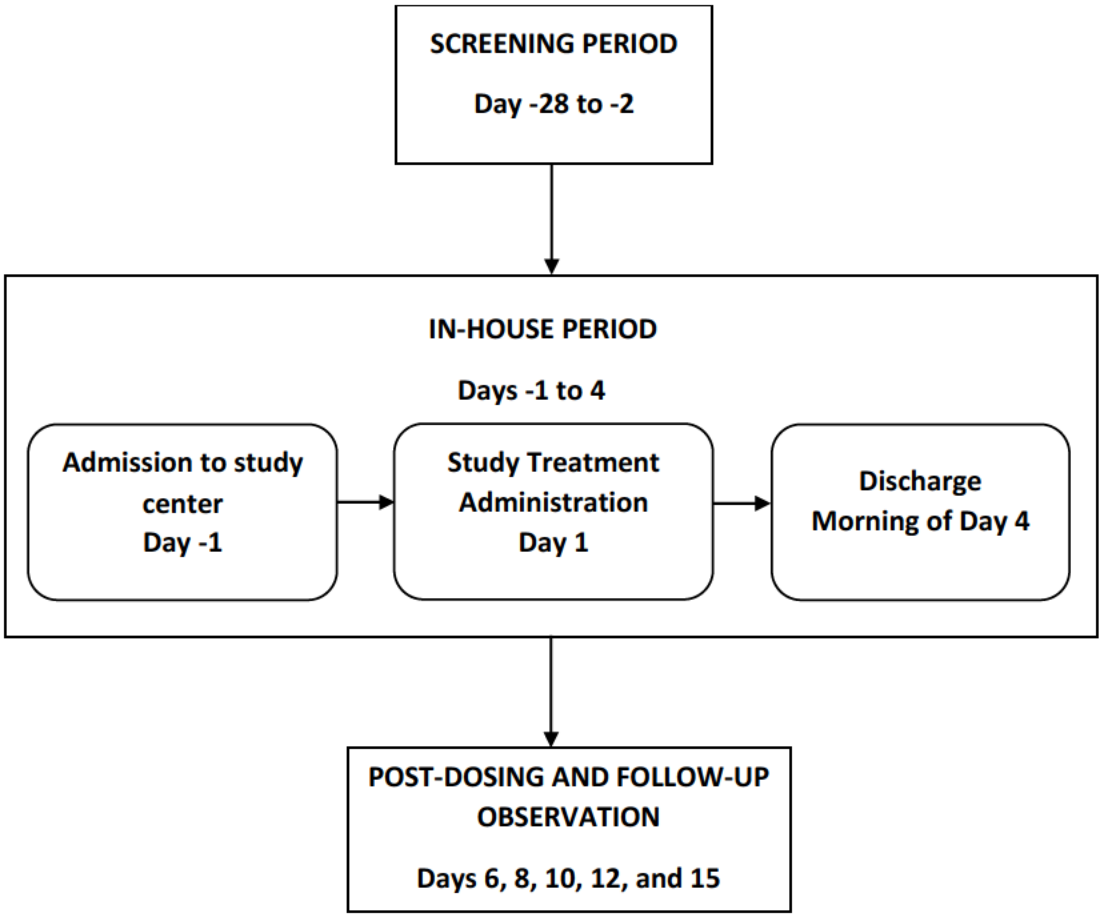
The use of drugs (e.g., prescription or over-the-counter (OTC) drugs, herbal and dietary supplements, vitamins) is prohibited for 14 days prior to admission (Day -1).

The use of drugs (e.g., prescription or OTC drugs, herbal and dietary supplements, vitamins) and procedures without any medication is prohibited from admission (Day -1) until completion of the post-dosing observation period (Day 15) (or early termination if this occurs).

1.2 SCHEMATIC OF STUDY DESIGN

An overview of the study design is provided in Figure 1.

Figure 1 Overview of Study Design



1.3 SCHEDULE OF ACTIVITIES

The Schedule of the Activities is provided in Table 1.

Table 1 Schedule of Activities

Cycle/Visit/Week	Screening	In-House					Post-Dosing and Follow-up Observation				
Day	**Day -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 6**	**Day 8**	**Day 10**	**Day 12**	**Day 15**
Time Relative (h)			**0**	**24**	**48**	**72**	**120**	**168**	**216**	**264**	**336**
Visit Window (h)				**± 2**	**± 2**	**± 2**	**± 2**	**± 24**	**± 24**	**± 24**	**± 24**
Assessments											
Informed consent [a]	x										
Demographic data	x										
Medical history	x										
Height	x										
Weight	x	x				x	x				
Drug Screen [b]	x	x									
Randomization [c]			x								
Drug Administration			x								
Physical Examination [d]	x	x	x	x	x	x	x	x	x	x	x
Vital Signs [e]	x	x	x	x	x	x	x	x	x	x	x
ECG [f]	x	x	x	x	x	x	x				
Hematology [g]	x	x		x	x	x	x		x		x
Urinalysis [h]	x	x		x	x	x	x		x		x
Clinical Chemistry [i]	x	x		x	x	x	x		x		x
Coagulation test, Thyroid and Lipid profile [j]	x	x					x				
Pregnancy test [k]	x	x									x
Serology test [l]	x										
PK Blood Samples [m]			x	x	x	x	x	x	x	x	x
Admission		x									
Discharge						x					
Ambulatory visit							x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x
Adverse events [n]	x	x	x	x	x	x	x	x	x	x	x

eCRF = electronic Case Report Form; GGT = gamma-glutamyl transferase, h = hours; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; PK = pharmacokinetic and TSH = thyroid stimulating hormone.

[a] Written informed consent for participants in the study must be obtained before performing any study-specific screening tests or evaluations.

[b] Breath alcohol, urine cotinine, and urine drug screen of (amphetamines, barbiturates, cocaine, opiates, methadone, cannabinoids, and benzodiazepines) will be evaluated.

[c] Participants will be randomized to 40 mg or 80 mg baloxavir marboxil in a 1:1 ratio.

[d] Complete physical examination will be conducted at screening and brief physical examination will be done at other visits.

[e] Vital signs include body temperature, pulse rate, blood pressure, and respiratory rate. Blood pressure and pulse rate should be measured at least 5 minutes after the participant rests in a supine position and on the same arm. Assessment of vital signs should be done prior to blood collection.

[f] Triplicate 12-lead ECG *can* be performed at specified timepoints if deemed necessary by investigator. At each timepoint at which triplicate ECGs are required, three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. Electrocardiogram should be performed prior to any scheduled vital sign measurements and blood draws. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. *Timepoints for ECG evaluation from Day 1 are provided in Table 2*.

[g] Hematology test parameters include leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[h] Urinalysis include pH, glucose, protein, and blood (leukocyte). If there is a clinically significant positive result (confirmed by a positive repeated sample), urine sample will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy and culture.

[i] Clinical chemistry test parameters include sodium, potassium, chloride, bicarbonate, glucose (fasting), urea, creatinine, total protein, serum albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, and LDH.

[j] Lipid profile includes total cholesterol and triglycerides; thyroid profile includes Free T4 and TSH; coagulation tests include INR, aPTT, and PT.

[k] Blood pregnancy test will be performed at screening and urine pregnancy test will be performed at subsequent visits. If urine pregnancy test is positive it will be confirmed by blood pregnancy test. If the blood pregnancy test is positive, then the participant must be withdrawn from the study.

[l] Serology tests for HIV, HBsAg, HCV and syphilis (*Treponema pallidum*) antibody will be performed.

[m] Timepoints for PK samples are provided in Table 2.

[n] Adverse events reported from the time of signing consent up to 14 days after the last dose should be documented and recorded in the eCRFs. Any concomitant medication should also be recorded.

Table 2 Detailed Table of Activities

Period	Day	Time from administration (h)	Randomization	Drug Administration	Physical Examination	Weight	Vital Signs	ECG	Laboratory Tests	PK Blood Samples
In-House	Day 1	Pre-dose	x		x		x			x
		0		x						
		0.5								x
		1			x					x
		2					x	x		x
		3								x
		4			x		x	x		x
		5								x
		6								x
		8								x
		12			x		x	x		x
	Day 2	24			x		x	x	x	x
		36								x
	Day 3	48			x		x	x	x	x
	Day 4	72			x	x	x	x	x	x
Post-Dosing and Follow-up Observation	Day 6	120			x	x	x	x	x	x
	Day 8	168			x		x			x
	Day 10	216			x		x		x	x
	Day 12	264			x		x			x
	Day 15	312			x		x		x	x

ECG =electrocardiogram; h = hours; PK = pharmacokinetics.

2. INTRODUCTION

Baloxavir marboxil (Xofluza™; baloxavir) is an oral cap-dependent endonuclease (CEN) inhibitor that has been developed by Roche and Shionogi. The drug blocks influenza virus proliferation by inhibiting the initiation of messenger RNA synthesis.

Influenza virus infection is an acute respiratory infection caused by the influenza virus, which is transmitted primarily through airborne droplets. It is characterized by a sudden onset of clinical symptoms such as fever, chills, headache, muscle pains, and loss of appetite, which start 1 to 4 days after infection; the fever can reach 38ºC to 40ºC within 24 hours of the onset (Monto et al. 2000; Fields et al. 2007). Other symptoms include cough, sore throat, and nasal congestion; cough is very frequent and tends to be persistent (Uchida et al. 2006). These characteristics make influenza virus infection a potentially severe disease, which should be distinguished from the common cold syndrome (Investigator Brochure, 2018).

Influenza viruses are significant human respiratory pathogens that cause both seasonal, endemic infections and periodic, unpredictable pandemics (Jeffery K. Taubenberger and David M. Morens. 2008). Despite significant advancement in vaccine and virus research, influenza continues to be a major public health concern. Each year in the United States, influenza viruses are responsible for seasonal epidemics resulting in over 200,000 hospitalizations and 30,000–50,000 deaths (Vemula et al. 2016). In China, annual influenza-associated excess mortality was 18.0 and 11.3 deaths per 100,000 population in northern and southern cities, respectively. Although China is experiencing a substantial disease burden of influenza, influenza vaccine coverage rate was only around 2.0% in 2016. A large majority of the Chinese population are not protected by influenza vaccine (Liu et al. 2017). Till date, the following anti-influenza virus drugs have been approved (with geographic variability): M2 channel inhibitors, amantadine hydrochloride and rimantadine hydrochloride; neuraminidase (NA) inhibitors, oseltamivir phosphate, zanamivir hydrate, peramivirhydrate, and laninamivir octanoate hydrate; an RNA polymerase inhibitor, favipiravir. The U.S. Centers for Disease Control and Prevention have advised that the use of amantadine hydrochloride and rimantadine hydrochloride be restricted for the treatment of influenza virus infection (CDC HEALTH ALERT, 2006).

The NA inhibitors are mainly prescribed for influenza virus infection; however, they have the following limitations: NA inhibitors should be administered within 48 hours of onset; oral NA inhibitors need to be administered for 5 days, eliciting concerns for compliance with the regimen; use of the inhaler drug is limited by the age of patients who are able to inhale the drug; and sufficient evidence is lacking regarding the inhibitory effects on exacerbations of influenza such as secondary infections and for therapeutic efficacy in patients with severe influenza. Therefore, more convenient and potent anti-influenza

virus drugs without limit of use are awaited. In addition, influenza viruses are well-known to undergo genomic mutations during replications, which could result in pandemics of mutated viruses to which many people are not immune or which could make the viruses resistant to the currently available anti-influenza virus drugs. To prepare for these possibilities, the development of new anti-influenza virus drugs with novel mechanisms of action is anticipated (Investigator Brochure, 2018).

In February 2018, baloxavir marboxil received its first global approval in Japan for the treatment of influenza A or B virus infections. The Phase III development for this drug is underway in the US, EU, and other countries for this indication (Heo 2018).

To date 11 Phase I studies, one Phase II study, and two Phase III studies have been completed and one Phase III study is ongoing. A total of 1346 participants have been exposed to at least 1 dose of baloxavir marboxil in the completed studies (Investigator Brochure, 2018).

This Phase I clinical study in healthy Chinese participants is designed to evaluate the pharmacokinetics (PK), safety, and tolerability of baloxavir and baloxavir marboxil following a single oral dose of baloxavir marboxil.

2.1 STUDY RATIONALE

The objective of the study is to evaluate the PK, safety, and tolerability after a single oral dose of baloxavir marboxil (40 mg or 80 mg) in healthy Chinese participants. This is a Phase I study in healthy participants, no therapeutic benefit is anticipated for these study participants.

The rationale for the study design is provided in Section 4.2.

2.2 BACKGROUND

Baloxavir marboxil is an anti-influenza virus drug with a novel mechanism of action. Baloxavir marboxil selectively inhibits CEN activity necessary for replication of influenza viruses. A broad spectrum of activity against seasonal influenza viruses and alleviating effects on the influenza symptoms were shown in nonclinical efficacy studies and the clinical studies in patients with influenza including the Phase II proof of concept and dose finding study, the Phase III double-blind study in otherwise healthy patients, and the Phase III open-label study in otherwise healthy pediatric patients.

The novel mechanism of action of baloxavir marboxil is anticipated to be effective against influenza virus strains resistant to currently marketed drugs.

After oral administration, baloxavir marboxil is extensively converted to its active metabolite, baloxavir, predominantly by arylacetamide deacetylase in the gastrointestinal lumen, intestinal epithelium, and liver. In the dose range studied (6 mg to 80 mg), the

maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of baloxavir increased generally in a dose-proportional manner. Following a single oral administration of baloxavir marboxil, the time to the maximum plasma concentration (T_{max}) of baloxavir was reached at 4 hours, and the elimination half-life was 79.1 hours. Although the absolute bioavailability of baloxavir marboxil/baloxavir has not been established, the absorption of the drug was estimated to be good based on the total recovery of 80.1% of the administered radioactivity in feces and more than 60% was recovered post 48 hours after dosing in the ^{14}C mass balance study. A food-effect study involving administration of baloxavir marboxil to healthy volunteers under fasted state and with a meal (approximately 400 to 500 kcal including 150 kcal from fat) indicated that the C_{max} and AUC of baloxavir were decreased by 48% and 36%, respectively, under fed conditions. The T_{max} was unchanged in the presence of food. Baloxavir showed serum protein-binding of 92.9% to 93.9%. The drug has multiple elimination pathways including UGT1A3 (the major pathway), and CYP3A4 (the minor pathway). In addition, the drug has an intestinal/biliary secretion, and a renal excretion (in urine, 3.3% of the administered dose was excreted as baloxavir). In vitro and in vivo human studies have shown that there is no clinically relevant effect of baloxavir marboxil and baloxavir on other co-administered medicines. There were no clinically relevant effects of other drugs (probenecid, itraconazole, oseltamivir phosphate) on the C_{max} and AUC of baloxavir.

A population PK analysis revealed that body weight and race were significant covariates on the PK of baloxavir. Based on the population modeling, the dose of baloxavir marboxil was proposed to be 40 mg for patients weighing < 80 kg and 80 mg for patients weighing ≥ 80 kg and investigated in the Phase III studies.

The PK/PD analysis using Phase II and Phase III data showed that at the proposed therapeutic doses, the responses of baloxavir using the virus titers change from the baseline were at the plateau, i.e., around the maximum effect.

Safety analysis of all studies indicated that baloxavir marboxil was well-tolerated with only mild to moderate and reversible adverse events. The overall safety profile was typical of the underlying influenza disease (e.g., diarrhea as the most common adverse event). As a result, no adverse drug reactions have been identified in association with baloxavir marboxil, either dose or exposure (Investigator Brochure, 2018).

In summary, based on the linear PK, good bioavailability and multiple elimination pathways as well as the flat PD and wide therapeutic window, the ethnic sensitivity of baloxavir marboxil is likely to be low. Although the exposure between Japanese and Caucasian is slightly different (the mechanism is unknown), the proposed dose (40 mg for body weight <80 kg and 80 mg for body weight ≥80 kg) was efficacious and safe in both Japanese and Caucasian patients documented in the Phase III studies. The Sponsor proposes to conduct a single-center, open-label, two parallel arms study. The

objective of the study is to evaluate the PK, safety, and tolerability of baloxavir marboxil following a single dose of oral administration to healthy Chinese participants. Participants will be randomized into two parallel groups (n=16 each), 40 mg or 80 mg under fasting. The PK data in Chinese adults will be compared with the Japanese and Caucasian PK data. Given that the disease course of influenza is the same across ethnic groups, the Sponsor believes that providing satisfactory PK data in this study will be sufficient to support the use of baloxavir marboxil to treat influenza in Chinese participants.

A detailed description of the chemistry, pharmacology, efficacy, and safety of baloxavir marboxil is provided in the Investigator's Brochure (IB).

2.3 BENEFIT/RISK ASSESSMENT

Potential benefit

This study is to be conducted in healthy Chinese participants who are not expected to gain any individual benefit from participation in this study. The risk to healthy participants, however, is justified based on safety knowledge gained from the previous clinical studies conducted to justify clinical studies in Chinese patients with influenza virus infection.

The data collected from this study is expected to guide informed dose selection in patients from China with influenza virus infection, by bridging the safety and efficacy data from global Phase III studies.

Potential risk

The results of safety of baloxavir marboxil were obtained from the 11 Phase I studies, one Phase II study, and two Phase III studies. No significant safety concerns were identified and therefore, baloxavir marboxil was considered generally safe when administered to healthy participants, patients with hepatic and renal impairment, and adult patients with influenza virus infection at a single oral dose up to 80 mg, regardless of body weight (Investigator Brochure, 2018).

Studies conducted in rats showed no adverse effects on fetal viability, intrauterine growth, or external, visceral, and skeletal morphology of live fetuses. The potential risk of baloxavir marboxil in pregnant women is unknown. Women of childbearing potential, pregnant, and breastfeeding women will not be eligible in this study.

As a risk mitigation strategy, after careful selection of the participants (meeting eligibility requirements), close monitoring of standard safety parameters (physical examination, ECGs, vital signs, laboratory assessments, pregnancy test, concomitant medication review, and adverse events) will be conducted during the in-house period and up to the follow-up visit occurring 14 days after the administration of baloxavir marboxil. The participants will be under observation in the study center for 72 hours post-study drug administration to monitor possible drug-related reaction. In addition, reactions related to

insertion of indwelling cannula (if used by the study center) will be monitored during the study center stay.

More detailed information about the risk-to-benefit profile of baloxavir marboxil is provided in the IB.

This study will be performed in compliance with the protocol, International Council for Harmonisation, Good Clinical Practice, and applicable regulatory requirements.

3. OBJECTIVES AND ENDPOINTS

This study will evaluate the PK, safety, and tolerability following a single oral dose of baloxavir marboxil in healthy Chinese participants. The objectives and corresponding endpoints/parameters are provided in Table 3.

Table 3 Objectives and Endpoints

Objectives	Endpoints/Parameters
Primary	
• To evaluate the pharmacokinetics (PK) of baloxavir marboxil and baloxavir after a single oral dose of baloxavir marboxil	• Maximum plasma concentration (C_{max}) • Time to maximum plasma concentration (T_{max}) • Area under the plasma concentration-time curve ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{0\text{-t}}$) • Terminal elimination half-life ($t_{1/2}$) • Apparent total oral clearance (CL/F) • Apparent volume of distribution based on the terminal phase (Vz/F) • Plasma concentration at 24 hours (C24), 48 hours (C48), 72 hours (C72)
Secondary	
• To evaluate the safety and tolerability following a single oral dose of baloxavir marboxil	• Incidence, severity, and frequency of adverse events, serious adverse events, vital signs measurements and clinical laboratory tests.

4. STUDY DESIGN

4.1 OVERALL DESIGN

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

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

An overview of the study design is provided in Section 1.2.

Screening:
After signing the informed consent, the participant will be screened for eligibility through medical history and other assessments as indicated in the Schedule of Activities (SoA) (Section 1.3). A screening period of up to 28 days is provided to complete the study-related assessments.

In-house Period:
On confirming all the eligibility requirements, the participants will be randomly allocated to one of the two parallel groups, 40 mg or 80 mg of study drug (baloxavir marboxil).

Participants will be admitted to the study center on Day -1. On the morning of Day 1, participants will receive a single 40 mg or 80 mg oral dose of the study drug. The study drug will be administered after an overnight fast of approximately 10 hours. No breakfast will be served in the morning of Day 1. A standard lunch will be provided 4 hours after study drug administration. Safety assessments and PK sampling will be done at scheduled timepoints. See SoA in Section 1.3. Participants will receive standard meals while in the study center and can be discharged at the investigator's discretion on Day 4 after the 72-hour assessments have been completed.

Post-Dosing and Follow-up Observation: Participants will visit the study center on Day 6 for post-dosing assessments and *PK sampling*. The participants will visit the study center on Days 8, 10, 12, and 15 for *PK sampling*, the safety and other assessments as specified in SoA.

4.1.1 Length of the Study

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

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

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

4.1.2 Stopping Rules Criteria

Study Stopping Criteria:

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to the participants.
- Participant enrollment is unsatisfactory

The Sponsor will notify the investigator, Ethics Committee, and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

Individual Participant Stopping Criteria

The investigator has the right to withdraw a participant from the study at any time. In addition, participants have the right to voluntarily withdraw from the study at any time for any reason. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Participant withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study.
- Investigator or Sponsor determines it is in the best interest of the participant.

Every effort should be made to obtain information on participants who withdraw from the study. The primary reason for withdrawal from the study should be documented in the electronic Case Report Form (eCRF).

Participants who withdrawn from the study prematurely will be asked to return to the study center to undergo the assessments specified in the follow-up visit (see Section 1.3). Participants will not be followed for any reason after consent has been withdrawn.

Participants who withdraw or are withdrawn from the study will not be replaced.

The Sponsor reserves the right to discontinue the study for safety or administrative reasons at any time while ensuring that early termination does not compromise participant's safety or well-being. If, in the opinion of the Principal Investigator, clinical observations suggest it may be unsafe to continue, the Principal Investigator may terminate the study after consultation with the Sponsor.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The data collected from this study is expected to guide informed dose selection in patients from China with influenza virus infection, by bridging the safety and efficacy data from global Phase II and Phase III studies.

4.2.1 Rationale for Study Population

The nonclinical and clinical studies of baloxavir marboxil show that there are no significant safety concerns and the study drug is considered generally safe to be administered to healthy participants as well as patients with influenza virus infection. However, the study drug has not been evaluated in clinical studies in the Chinese population. Hence healthy Chinese participants will be enrolled to determine the PK, safety, and tolerability of baloxavir marboxil following a single oral dose of 40 mg or 80 mg.

4.3 DOSE JUSTIFICATION

To evaluate the pharmacokinetics in Chinese healthy participants, the two Phase III doses 40 mg and 80 mg have been selected for this study. This is considered to be adequate to assess the PK of baloxavir marboxil in a Chinese healthy population and to compare the results with those from Caucasian and Japanese populations.

In the Phase I single ascending dose and multiple ascending dose placebo-controlled study conducted in Japan, baloxavir marboxil was administered to 40 healthy male adult subjects. A total of 6 adverse events were reported in 6 of the 40 randomized subjects and no serious adverse events were reported. Single oral doses of baloxavir marboxil up to 80 mg were found to be safe and well tolerated in healthy adult subjects.

In another Phase I study conducted in Japan to evaluate the relative bioavailability and food effect, 20 mg of baloxavir marboxil formulated as either a tablet or suspension was administered to 29 healthy subjects (14 subjects in the bioavailability part and 25 subjects in the food effect part of the study). In the bioavailability part of the study, 2 of 14 subjects experienced treatment-emergent adverse events of nasopharyngitis and blood uric acid increased. In the food effect part of the study, 10 of 15 subjects experienced at least 1 treatment-emergent adverse events (ALT increased occurred in more than 3 subjects) with a total of 15 treatment-emergent adverse events reported overall and no deaths, serious treatment-emergent adverse events or discontinuation due to treatment-emergent adverse events were reported in this study. In the Phase I drug-drug interaction study with CYP3A4 substrate conducted in the United States, a single dose of 5 mg of midazolam was administered alone or in combination with a single dose of 40 mg of baloxavir marboxil to 12 healthy adult subjects. Three adverse events were reported in 2 of the 12 subjects and no deaths or serious adverse events were noted. In the Phase I drug-drug interaction study in the United States, a single dose of 20 mg of baloxavir marboxil was administered alone or in combination with repeated dose of 200 mg of itraconazole to 12 healthy adult subjects.
Ten treatment-emergent adverse events were reported in 6 of 12 enrolled subjects. Among them, 3 treatment-emergent adverse events were reported when baloxavir marboxil was administered alone and 6 occurred when baloxavir marboxil was co-administered with itraconazole and no deaths or serious adverse events were observed.

In the Phase II proof of concept and dose finding study a single dose of 10, 20, or 40 mg of baloxavir marboxil was administered to 100 Japanese patients with influenza virus infection for each dose. Treatment-related adverse events were reported in 9 of 100 patients (12 events) in the 10 mg group, 7 of 100 patients (8 events) in the 20 mg group, and 6 of 100 patients (7 events) in the 40 mg group compared with 10 of 100 patients (14 events) in the placebo group. No deaths or serious adverse events were reported in any of the groups. No significant safety concerns were identified and therefore, baloxavir marboxil was considered generally safe when administered to the patients with influenza virus infection at a single oral dose up to 40 mg.

In the Phase III double-blind study in otherwise healthy patients in the 20 to 64 years of age stratum received a single dose of 40 or 80 mg (depending on the patient's weight) of baloxavir marboxil, repeated dose of 75 mg oseltamivir twice daily for 5 days or placebo, and patients in the 12 to 19 years of age stratum received a single dose of 40 or 80 mg (depending on the patient's weight) of baloxavir marboxil or placebo. Globally, a total of 1432 patients received the study drug: 610 in the baloxavir marboxil group, 309 in the placebo group, and 513 in the oseltamivir group. Two serious adverse events not related to the study drug were reported in the baloxavir marboxil group. No deaths were reported in all the three groups. Treatment-related adverse events were reported in 27 of 610 patients (4.4%, 37 events) in the baloxavir marboxil group, 12 of 309 patients (3.9%, 19 events) in the placebo group, and 43 of 513 patients (8.4%, 53 events) in the oseltamivir group. In all the three groups, majority of the adverse event were categorized as Grade 1 or 2 and their outcome were resolved or resolving.

As described above, no significant safety concerns were identified when compared with placebo or oseltamivir, therefore, baloxavir marboxil is considered generally safe when administered to patients with influenza at a single oral dose of either 40 or 80 mg depending on the patient's weight.

Further details are provided in the IB.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all assessments and visits of the study including the follow-up visit on Day 15.

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

5. STUDY POPULATION

Healthy Chinese participants in the age of 20-59 years, whose parents and grandparents were born in China and who do not have any evidence of active or chronic disease will be enrolled in this study.

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

5.1 INCLUSION CRITERIA

Participants must meet the following criteria for study entry:

- Healthy male or female Chinese participants, aged 20-59 years (inclusive) at the time of screening. The female participants should be of non-child bearing potential.
- Chinese participants must have Chinese parents and grandparents, all of whom were born in China.
- Healthy status as defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, viral serology, and urinalysis.
- Participants whose body weight is ≥50 to <80 kg and body mass index is ≥18.5 to <26 kg/m^2.
- Able to participate and willing to provide written informed consent and to comply with the study restrictions.
- Female participants must be either surgically sterile (by means of hysterectomy and/or bilateral oophorectomy) or postmenopausal for at least 1 year (defined as amenorrhea ≥ 12 consecutive months without another cause, and confirmed by follicle-stimulating hormone level > 35 mIU/mL).

5.2 EXCLUSION CRITERIA

Participants who meet any of the following criteria will be excluded at study entry:

- Participants who are considered ineligible for this study by the Principal Investigator or subinvestigator due to current or history of significant metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, urological, endocrine, neurological, or psychiatric disorders with clinical manifestations.
- Participants with the following laboratory abnormalities at screening and on Day -1:

  total bilirubin > 1.5 × upper limit of normal (ULN)

AST > 1.5 × ULN

ALT > 1.5 × ULN

estimated glomerular filtration rate <60 mL/min/1.73 m^2 using Cockcroft-Gualt formula

- QTc interval >450 ms (with Fridericia's correction)
- Participants with vital signs outside of the reference range for average systolic blood pressure (90-140 mmHg), average diastolic blood pressure (*60*-90 mmHg), or average pulse rate (40-90 beats/minute).
- Participants with a history of stomach, vagus nerve, or intestinal surgery (except for appendectomy).
- Participants who have a history of allergic symptoms including food allergy (Note: Non-active allergic rhinitis will be allowed).
- Participants who require chronic drug therapy or those who have used drugs (e.g., prescription or OTC drugs, herbal and dietary supplements, and vitamins) within 3 days prior to screening or within 14 days prior to Day -1.
- Participants who have used alcohol-containing, caffeine-containing, grapefruit containing, or St. John's wort-containing products within 72 hours prior to Day -1.
- Participants who have used tobacco- or nicotine-containing products within 24 weeks prior to screening.
- Participants who have a history of abuse of drugs and/or alcohol.
- Participants who have a positive urine cotinine, drug, and alcohol screen at screening and Day -1.
- Participants who are positive for serological test for syphilis (*Treponema pallidum*), hepatitis B surface antigen, hepatitis C virus antibody, or HIV antigen/antibody at screening.
- Participants who have donated > 400 mL of blood within 12 weeks or > 200 mL of blood within 4 weeks prior to screening, or have donated any amount of blood between screening and Day -1.
- Participants who have been exposed to an investigational drug within 90 days prior to the initial screening visit.
- Participants who have received baloxavir marboxil previously.

- Participants who are considered inappropriate for the study by the Principal Investigator or subinvestigator.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

- Participants are required to fast approximately 10 hours prior to study drug administration and up to 4 hours postdose.

- Participants have to refrain from food items with well-known CYP3A perpetrator potential (such as grapefruit [juice], Seville oranges, pomelos, and St. John's wort-containing products) within 72 hours prior to Day -1.

5.3.2 Caffeine, Alcohol, and Tobacco

- Participants will have to refrain from alcohol and caffeine-containing products within 72 hours prior to Day -1 and during the study.The use of tobacco- or nicotine-containing products is not allowed between 24 weeks prior to screening and Day -1 and throughout the study.

5.3.3 Activity

- Participants must abstain from strenuous exercise for 96 hours before admission and before each blood collection for clinical laboratory tests during the follow-up period.

- Donation of > 400 mL of blood within 12 weeks or > 200 mL of blood within 4 weeks prior to screening by the participant, or donation of any amount of blood between screening and Day -1 is prohibited.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled to the study treatment.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screen failures.

If a participant fails to fulfill eligibility requirement due to a transient and non-clinical significant condition at screening, the Principal Investigator may repeat the relevant screening assessment(s) within the 28-day screening period. If the participant fails a second time they will be classed as a screen failure and cannot be re-screened.

Re-screening is allowed for participants who were screened in the study and met eligibility requirements but failed to be enrolled within 28 days after the start of screening period because the enrollment was suspended. In order to re-screen such a participant, all eligibility requirements should be re-evaluated and all applicable screening

assessments repeated if done more than 28 days prior to the enrollment (Appendix 1 [Section 1.3]).

5.5 RECRUITMENT PROCEDURES

Participants will be identified for potential recruitment using pre-screening enrollment logs, clinical database and Independent Ethics Committees (IEC) approved newspaper/radio/social-media advertisements prior to consenting to take part in the study.

6. TREATMENTS

Study drug is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a participant according to the study protocol.

All the study drug (baloxavir marboxil) required for completion of this study will be provided by the Sponsor. The study drug will be administered at the study center under the supervision of study center's staff.

6.1 TREATMENTS ADMINISTERED

Baloxavir marboxil is a prodrug of polycyclic pyridone compound that is expected to have anti-influenza activity. Table 4 summarizes the treatment administered.

Table 4 Summary of Treatment Administered

Study Drug Name:	Baloxavir marboxil
Dosage Formulation:	Baloxavir marboxil will be provided as a film-coated oral tablet in 20 mg strength. The tablet composition includes lactose monohydrate, croscarmellose sodium, povidone, microcrystalline cellulose, sodium stearyl fumarate, hypromellose, talc, and titanium oxide.
Unit Dose Strength/Dosage Levels:	Baloxavir marboxil is available as 20 mg tablet
Route of Administration:	Baloxavir marboxil will be administered orally on Day 1 only.
Dosing Instructions:	Baloxavir marboxil is to be taken orally once with a glass of water. The study drug will be given after an overnight fast of approximately 10 hours followed by a fast of at least 4 hours postdose.
Packaging and Labeling	Study drug will be provided in blister packaging in a carton box.
Manufacturer:	Shionogi & Co., Ltd. Settsu plant, Japan

Please see the IB for more details.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study drug packaging will be overseen by the F. Hoffmann-La Roche Ltd and Shionogi & Co., Ltd clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labeling of the study drug will be in accordance with F. Hoffmann-La Roche Ltd and Shionogi & Co., Ltd standard and local regulations.

The investigational study center will acknowledge receipt of the study drug and confirm the shipment condition and content. Any damaged shipments will be replaced.

Upon arrival of the study drug at the study center, the personnel will complete the following:

- Check the study drug for damage.
- Verify proper identity, quantity, integrity of seals and temperature conditions.
- Report any deviations or product complaints to the Monitor upon discovery.

The investigator or delegate must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.

Only participants enrolled in the study will receive the study drug and only authorized study center staff will supply or administer correct dose of the study drug. All study drugs 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 study center staff.

The Principal Investigator is responsible for accountability of study drug, reconciliation, and record maintenance (i.e., receipt, reconciliation and final disposition records).

Study drugs will either be disposed of at the study center according to the study center’s institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The study center's method of study drug destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used study drug for safety reasons. The study center must obtain written authorization from the Sponsor before any drug is destroyed, and the study drug destruction must be documented on the appropriate form.

Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

This is an open-label study. Participants will be randomized to 40 mg or 80 mg baloxavir marboxil in a 1:1 ratio. The randomization list will be generated by the Sponsor or its designee. The randomized treatment assignment will be allocated from the list sequentially to participants in the order in which they are enrolled. The study center will record the treatment assignment on the applicable eCRF.

6.3.2 Blinding

This is an open-label study.

6.4 TREATMENT COMPLIANCE

The study drug will be administered in the study center by the authorized study center staff. The investigator or designee will record the correct dose, date, and time of administration on the Drug Accountability Record.

6.5 CONCOMITANT THERAPY

Concomitant therapies are defined as therapies taken after the initiation of the drug. In the case that any therapies are used during the study, the investigator or subinvestigator will record the following information for all therapies used after the first dose of the study drug till end of the study in the eCRF:

- Name of used drug or used procedures
- Change in dose, as-needed use, and route of administration (if a drug is administered)
- Duration of treatment
- Reason for use

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All concomitant medications should be reported to the investigator and recorded on the page of concomitant medications eCRF.

6.5.1 Permitted Therapy

Any medication which is considered necessary for participant's welfare and medications for treatment of adverse events are permitted and may be given at the discretion of the Principal Investigator.

All therapy and/or medication administered to manage adverse events should be recorded on the adverse event and concomitant page of the eCRF.

6.5.2 Prohibited Therapy

The use of drugs (e.g., prescription or OTC drugs, herbal and dietary supplements, vitamins) is prohibited for 14 days prior to admission (Day -1).

The use of drugs (e.g., prescription or OTC drugs, herbal and dietary supplements, vitamins) and procedures without any medication is prohibited from admission until completion of the post-dosing observation period (or early termination).

6.6 DOSAGE MODIFICATION

There will be no dose modification during the study. Two dose levels of the study drug will be evaluated. Sixteen participants in each group will receive either the 40 mg or 80 mg of study drug in parallel.

6.7 TREATMENT AFTER THE END OF THE STUDY

The Sponsor does not intend to provide the study drug or other study interventions to participants after conclusion of the study or any earlier participant withdrawal.

7. DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY DRUG

This is a single-dose study therefore there are no criteria for study drug discontinuation for a given participant once the study drug has been administered.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants have the right to voluntarily withdraw from the study at any time for any reason.

In addition, the Principal Investigator has the right to withdraw a participant from the study for medical conditions that the Principal Investigator or Sponsor determines, may jeopardize the participant's safety if he or she continues in the study.

If possible, information on reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Participants will not be followed for any reason after consent has been withdrawn.

When a participant voluntarily withdraws from the study, or is withdrawn by the Principal Investigator, samples collected until the date of withdrawal will be analyzed, unless the participant specifically requests for these to be discarded or local laws require their immediate destruction. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Participants who withdraw from the study for safety reasons will not be replaced. Participants who withdraw from the study for other reasons will be replaced.

See SoA (Section 1.3) for data to be collected at the time of follow-up visits, and for any further evaluations that need to be completed.

7.3 LOST TO FOLLOW-UP

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

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

- The study center 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 and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant. 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 to have withdrawn from the study.

Discontinuation of study center or of study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timepoints are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should be administered the study drug.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the Informed Consent Forms may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time-frame defined in the SoA.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

- At time-points when several assessments coincide, the following sequence is suggested; at the discretion of the investigator, the order can be adjusted to optimize site personnel and participant's time management.

  Urine collection

  ECG recordings

  Vital signs

  PK and safety blood sampling

  Study drug administration

8.1 EFFICACY ASSESSMENTS

Not applicable.

8.2 SAFETY ASSESSMENTS

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological, neurological, and musculoskeletal system in addition to head, eyes, ears, nose, throat, neck, and lymph nodes. Height and weight will be measured and recorded at screening. Additionally, weight will be measured on Days -1, 4, and 6. Further examination of other body systems may be performed in case of evocative symptoms at the investigator's discretion.

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

- Investigators should pay special attention to clinical signs related to previous serious illnesses.

- Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Changes from baseline abnormalities should be recorded in participant's notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the adverse event eCRF.

8.2.2 Vital Signs

- Body temperature, pulse rate, blood pressure, and respiratory rate will be assessed.
- Blood pressure and pulse measurements will be assessed in a supine position with a completely automated device and will be measured at each timepoint on the same arm. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of one pulse and three blood pressure measurements (three consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the three blood pressure readings will be recorded on the eCRF.

8.2.3 Electrocardiograms

- 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the pulse rate and measures PR, QRS, QT, and QTc intervals. *Triplicate 12-lead ECGs can be performed at specified timepoints if deemed necessary by investigator.*
- At each timepoint at which triplicate ECGs are required, three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- To minimize variability, it is important that participants be in a resting position (for approximately ≥ 10 minutes) prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. Electrocardiogram should be performed prior to any scheduled vital sign measurements and blood draws. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.
- If at a particular postdose timepoint the mean QTcF is > 500 ms and/or 60 ms longer than the baseline value, another triplicate ECG must be recorded, ideally within the next 5 minutes, and triplicate ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. The investigator should also evaluate the participant for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).
- For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the participant's source documents at the study center.

8.2.4 Clinical Safety Laboratory Assessments

- See Appendix 4 for the list of clinical laboratory tests to be performed and the SoA (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 Section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 15 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Medical Monitor.
  If such values do not return to normal/baseline within a period judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

- All protocol-required laboratory assessments, as defined in Appendix 4, must be conducted in accordance with the Laboratory Manual and the SoA.

- If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant's management or are considered clinically significant by the investigator (e.g., serious adverse event s or adverse events or dose modification), then the results must be recorded in the eCRF. Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts.

- Additional blood or urine samples may be taken at the discretion of the investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor participant safety.

- Where the clinical significance of abnormal laboratory results is considered uncertain, screening laboratory tests may be repeated before randomization to confirm eligibility.

- If there is an alternative explanation for a positive urine or blood test for drugs of abuse, e.g., previous occasional intake of a medication or food containing for example, codeine, benzodiazepines or opiates, the test could be repeated to confirm washout.

8.2.5 Medical History and Demographic Data

- Medical history includes clinically significant diseases surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 3 days prior to the screening visit or 14 days prior to admission.

- Demographic data will include age, sex, and self‑reported race/ethnicity.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 2. The non-serious adverse events of special interest are discussed in Sections 8.3.6.

The investigator and any qualified designees are responsible for ensuring that all AEs (including assessment of seriousness, severity and causality; see Appendix 2) are recorded on the AE page of eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2.

Procedures used for recording AEs are provided in Appendix 3

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

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Investigators will seek information on AEs at each visit. All AEs, whether reported by the participant or noted by study center staff, will be recorded in the participant's medical record and on the AE eCRF as follows:

After informed consent has been obtained **but prior to initiation of study drug**, only SAEs caused by a protocol-mandated intervention should be reported. Any other AEs should not be reported.

After initiation of study drug: all AEs, regardless of relationship to study drug, will be reported until 14 days after the last dose of study drug.

Post-study adverse events and serious adverse events: The investigator is not required to actively monitor participants for AEs after the end of the AE reporting period (14 days after the last dose of study drug).

However, if the investigator learns of any SAE (including a death) or other AEs of concern that are believed to be related to prior treatment with study drug, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the Sponsor. For the procedure of reporting, see Appendix 2.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all participant evaluation timepoints.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the event is otherwise explained, the participant is lost to follow-up (Section 7.3), or the participant withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or study-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the AE eCRF and in the participant's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the AE eCRF.

All pregnancies in the partner of a male participant reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 8.3.5.

8.3.3.2 Sponsor Follow-Up

For SAEs, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow-up by telephone, fax, electronic mail, 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.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IEC, and investigators.

Investigator safety reports must be prepared for sudden unexpected serious adverse reaction according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then, file it along with the IB and will notify the IEC, if appropriate according to local requirements.

For immediate and expedited reporting requirements from investigator to Sponsor and from Sponsor to Health Authority, investigators, and IEC, see Appendix 2.

8.3.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitor is available 24 hours a day 7-days a week. Medical Monitor's contact details will be available on a separate list generated by the study management team.

8.3.5 Pregnancy

Male participants will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study or within 28 days after the last dose of study drug.

Female participants will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the administration of baloxavir marboxil.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the pregnancy reporting process as detailed in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs (Appendix 5).

8.3.6 Non-Serious Adverse Events of Special Interest

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2 for reporting instructions).

Non-serious adverse events of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Appendix 3.
- Suspected transmission of an infectious agent by the study drug, as defined below:

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

8.3.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8 Management of Specific Adverse Events

Not applicable.

8.4 TREATMENT OF OVERDOSE

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects (see Sections 5 and 5.2 of Appendix 2 for further details).

For this study, any dose of study drug greater than prescribed within a 24-hour time period from previous dose will be considered an overdose.

As per IB, there is no specific antidote for the study drug. In the event of overdose, general supportive measures should be initiated based on the participant's signs and symptoms.
In the event of an overdose, the investigator should:

1. Contact the Sponsor's Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved.
3. Obtain a blood sample for PK analysis within 24 hours from the date of the last dose of study drug, if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose, as well as the duration of the overdose, in the eCRF.

8.5 PHARMACOKINETICS

The PK of the study drug is being evaluated in this study. Blood samples for determination of plasma PK will be collected during the study at the timepoints specified in Table 2. The plasma obtained from the PK blood sample will be stabilized before freezing to block ex-vivo pro-drug conversion to baloxavir. Baloxavir marboxil and baloxavir will be analyzed by a validated LC-MS/MS assay.

The remaining plasma samples will be destroyed within 2 years after the date of final Clinical Study Report. Remaining PK samples may be used for exploratory analyses, if required. Details on sampling procedures, sample storage and shipment are given in the Laboratory Manual.

8.6 PHARMACODYNAMICS

Pharmacodynamic parameters are not evaluated in this study.

8.7 GENETICS/PROTEOMICS

Pharmacogenomics assessments are not performed in this study.

8.8 BIOMARKERS

Biomarkers are not evaluated in this study.

8.9 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health Economics or Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.10 TIMING OF STUDY ASSESSMENTS

8.10.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study−specific screening tests or evaluations. Informed Consent Forms for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study center.

All screening and pre-treatment assessments must be completed and reviewed to confirm that participants meet all the eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screen failure.

An Eligibility Screening Form documenting the investigator's assessment of each screened participant with regard to the protocol's eligibility requirement is to be completed by the investigator and kept at the study center.

Screening and pre-treatment assessments will be performed within -28 to -2 days prior to Day 1.

8.10.2 Assessments during In-house Period

Under no circumstances will participants who enroll in this study and have completed treatment as specified, be permitted to re-enroll in the study.

All assessments must be performed as per SoA (see Section 1.3). Assessments scheduled on the day of study drug administration should be performed prior to administration of study drug, unless otherwise noted in the SoA (e.g., postdose PK samples).

8.10.3 Assessments at Study Completion/Early Termination Visit

Participants who discontinue from the study early will be asked to return to the study center14 days after the dose of study drug for a follow‑up visit. Assessments conducted at Day 15 will be performed at the early termination visit. (See SoA, Section 1.3).

8.10.4 Post-Dosing and Follow-Up Assessments

Post-dosing and follow-up assessments will be conducted on Days 6, 8, 10, 12, and 15 as specified in SoA (see Section 1.3). After the study completion or early termination visit, adverse event AEs should be followed as outlined in Sections 8.3.1 and 8.3.3.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Not applicable.

9.2 SAMPLE SIZE DETERMINATION

A total of 32 Chinese participants will be enrolled in this study with 16 participants in each group of 40 mg and 80 mg baloxavir marboxil.

The number of participants (16 participants for each dose level) is chosen based on practical clinical judgment, the PK variability observed (AUC and C_{max} in Caucasian and Japanese healthy participants), anticipated drop-rate, and China's regulatory requirements.

9.3 POPULATIONS FOR ANALYSES

The populations for analysis are defined in section 9.4.3 and 9.4.4.

9.4 STATISTICAL ANALYSES

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

9.4.1 Summaries of Treatment Group Comparability

Demographics and baseline characteristics will be summarized with descriptive statistics for all randomized participants, presented overall and by dosing regimen.

9.4.2 Efficacy Analyses

This study does not evaluate efficacy analyses.

9.4.3 Safety Analyses

All participants who received at least 1 dose of the study drug, whether prematurely withdrawn from the study or not, will be included in the safety analysis population. Participants will be grouped by the actual dose regimen they received.

All safety analyses will be based on the safety analysis population.

The safety statistical analysis methods are presented in Table 5.

Table 5 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Method
Adverse events	The original terms recorded on the eCRF by the investigator for adverse events will be coded by the Sponsor. Adverse events will be classified by system organ class and preferred terms using MedDRA.
Clinical laboratory tests	All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI unit) by individual listings with flagging of abnormal results. Summary tables of change from baseline over time will be displayed for selected parameters.
Vital signs	Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries may be provided, as appropriate.
Concomitant medications	The original terms recorded on the participant's eCRF by the investigator for concomitant medications will be standardized by the Sponsor by assigning preferred terms. Concomitant medications will be presented in summary tables and listings.

CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; NCI = National Cancer Institute

Electrocardiogram data will be presented in by-patient listings. In addition, tabular summaries will be used, as appropriate.

9.4.4 Pharmacokinetic Analyses

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

Analyses will be carried out on the PK analysis population.

Individual plasma concentrations at each sampling timepoint for baloxavir marboxil and its major metabolite, baloxavir will be presented by listings and appropriate descriptive summary statistics by dose, including arithmetic means, geometric means, medians, minimums-maximums, SD, and coefficients of variation. Individual and mean plasma concentration versus time data will be plotted by dose on linear as well as semi-logarithmic scales.

All PK parameters will be presented by individual listings and summary statistics by dose including arithmetic means, geometric means, medians, minimums-maximums, SDs, and coefficients of variation.

The primary baloxavir marboxil and baloxavir PK study parameters will be the C_{max} and the area under the concentration-time curve from Time 0 to infinity ($AUC_{0\text{-}inf}$) if it can be derived accurately, otherwise a truncated as appropriate. All other PK parameters will be regarded as secondary.

Non-compartmental analysis using WinNonlin software will be used to calculate PK parameters where appropriate. Non-compartmental analysis will be employed for estimation of the following PK parameters:

- T_{max}: Time to maximum observed plasma concentration
- C_{max}: Maximum observed plasma concentration
- $AUC_{0\text{-}inf}$: Area under the plasma concentration-time curve between Time 0 extrapolated to infinity
- $AUC_{0\text{-}last}$: Area under the plasma concentration-time curve between Time 0 and the time of the last quantifiable concentration
- $AUC_{0\text{-}t}$: Area under the plasma concentration-time curve between Time 0 and the time t. Time t may be chosen as a time point where evaluable concentrations are available in at least 90% of participants
- $t_{1/2}$: Terminal elimination half-life
- CL/F: Apparent total oral clearance

- Vz/F: Apparent oral volume of distribution based on the terminal phase
- Plasma concentration at 24, 48, and 72 hours postdose.

9.5 INTERIM ANALYSES

No interim analysis is planned for this study.

9.6 SUMMARIES OF CONDUCT OF STUDY

The number of participants who complete the study and the number of participants who enroll, discontinue or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized by dose levels. Protocol deviations will be listed and evaluated for their potential impact on interpretation of study results. Study drug administration will be summarized by in-house period. Descriptive statistics will be used in evaluating the conduct of the study.

10. REFERENCES

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The following section includes standard appendices such as Appendix 1 (for regulatory, ethical and study oversight considerations), Appendix 2 (for AE definitions, reporting) and Appendix 3 (procedures of recording), and Appendix 5 (contraceptive guidance and collection of pregnancy information). Additional study-related appendices are in order of appearance in the protocol.

Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

1. REGULATORY AND ETHICAL CONSIDERATIONS

1.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

1.2. INSTITUTIONAL ETHICS COMMITTEE

This protocol, the Informed Consent Forms (ICFs), any information to be given to the participant (e.g. advertisements, diaries etc), and relevant supporting information must be submitted to the Independent Ethics Committee (IEC) by the Principal Investigator and reviewed and approved by the IEC before the study is initiated. In addition, any participant recruitment materials must be approved by the IEC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC. Investigators are also responsible for promptly informing the IEC of any protocol amendments (Section 2.3.1 of this Appendix).

The investigator should follow the requirements for reporting all adverse events to the Sponsor. Investigators may receive written investigational new drug safety reports or other safety‑related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with Health Authority requirements and the policies and procedures established by their IEC, and archived in the study centers study file.

1.3. INFORMED CONSENT

The Sponsor's Master ICF in local language will be provided to each study center. 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, local regulations, ICH guidelines, where applicable, and the IEC or study center. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate Consent Forms proposed by the study center (collectively, the "Consent Forms") before IEC submission. The final IEC‑approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant or the participant's legally authorized representative.

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

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to take part. The final revised IEC approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

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

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

Re-screening is allowed for participants who were screened in the study and met study eligibility requirements but failed to be enrolled within 28 days after the start of screening period because the enrollment was suspended. These participants will have to sign another ICF, if the re-screening occurs within 28 days from the previous ICF signature date.

1.4. CONFIDENTIALITY

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; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her 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 the participant.

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

The participant must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

1.5. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (i.e., LPLV).

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

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

The Principal Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Principal Investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.

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

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center 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, ICH GCP, and all applicable regulatory requirements.

2.1.2 Source Data Records

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

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

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

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial‑related monitoring, Sponsor audits, and IEC review. The investigational study center must also allow inspection by applicable Health Authorities.

2.1.3 Use of Computerized Systems

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

2.2. RETENTION OF RECORDS

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Principal Investigator for at least 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.

2.3. STUDY RECORDS

The Principal Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully reconstructed, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IEC and governmental approval.

Roche shall also submit an Annual Safety Report once a year to the IEC and CAs according to local regulatory requirements and timelines of each country participating in the study.

2.3.1. Protocol Amendments

Any substantial protocol amendments will be prepared by the Sponsor. Substantial protocol amendments will be submitted to the IEC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IEC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or any non-substantial changes, as defined by regulatory requirements.

2.3.2. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Principal Investigator agrees to submit all manuscripts or abstracts to the Sponsor for approval prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Principal Investigator.

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 multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Principal Investigator and the appropriate Sponsor personnel.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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

2.3.3. Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the regulatory authorities a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

2.3.4. Study Center Inspections

Study center visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The Principal Investigator will permit national and local Health Authorities, Sponsor monitors, representatives, and collaborators, and the IECs to inspect facilities and records relevant to this study.

3. ADMINISTRATIVE STRUCTURE

3.1. INDEPENDENT REVIEW COMMITTEE (IRC)

Not applicable.

3.2. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

Not applicable.

3.3. INTERNAL MONITORING COMMITTEE (IMC)

Not applicable.

3.4. CLINICAL EVENTS COMMITTEE (CEC)

Not applicable.

4. STUDY AND STUDY CENTER CLOSURE

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

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

The Sponsor will notify the Principal Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

Study center will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Principal Investigator may initiate study center 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 center by the Sponsor or Principal Investigator may include but are not limited to:

- Failure of the Principal Investigator to comply with the protocol, the requirements of the IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Principal Investigator.
- Discontinuation of further study drug development.

Appendix 2
Adverse Events: Definitions and Procedures for Evaluating, Follow-up and Reporting

1. DEFINITION OF ADVERSE EVENTS

According to the E2A International Council for Harmonisation guideline for Good Clinical Practices, an adverse event is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events Meeting the Adverse Event Definition:

- Any deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., ECG, X−ray) that is associated with symptoms or leads to a change in study drug or concomitant treatment or discontinuation from study drug.
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study drug (e.g., screening invasive procedures such as biopsies).

Events NOT Meeting the Adverse Event Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/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 an adverse event.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

2. DEFINITION OF SERIOUS ADVERSE EVENTS

If an event is not an AE per definition above, then it cannot be a serious adverse event (SAE) even if serious conditions are met (e.g., hospitalization for signs/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 which hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see Appendix 3).

  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 serious 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 or significant disability/incapacity**

  Disability means substantial disruption of the participant'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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Other significant events**:

  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.

3. RECORDING OF ADVERSE EVENT AND/OR SERIOUS ADVERSE EVENT

When an adverse event/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/serious adverse event information in the electronic Case Report Form (eCRF).

It is not acceptable for the investigator to send photocopies of the participant's medical records to Medical Monitor in lieu of completion of the eCRF.

There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. 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 Sponsor or designee.

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

3.1. ASSESSMENT OF SEVERITY

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study and assign it to one of the categories provided in Table 6 (as a guidance for assessing adverse event severity).

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

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

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

Table 6 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event.

3.2. ASSESSMENT OF CAUSALITY

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug.
- Known association of the event with the study drug or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

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

4. FOLLOW-UP OF AES AND SAES

The Principal Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee 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, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the Principal Investigator will provide the Sponsor or designee with a copy of any post-mortem findings including histopathology. New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information.

5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies (see Section 8.3.5)
- Accidental overdoses or medication errors (see Appendix 2, Section 5.2 for details on reporting requirements)

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

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

Investigators must also comply with local requirements for reporting serious adverse events to the local Health Authority and IEC.

5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS AND NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST

Events that Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Events that Occur after Study Drug Initiation

For reports of serious adverse events and non-serious adverse events of special interest (Section 8.3.6) that occur after initiation of study drug (Section 8.3.1), investigators

should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest/ Serious Adverse Event eCRF form and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Reporting of Post-Study Adverse Events and Serious Adverse Events

If the investigator becomes aware of any other serious adverse event occurring after the end of the adverse event reporting period, if the event is believed to be related to prior to the study drug, then the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event Reporting Form using the fax number or e-mail address provided to the investigators.

5.2 REPORTING REQUIREMENTS FOR CASES OF ACCIDENTAL OVERDOSE OR MEDICATION ERROR

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

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

Special situations are not in themselves adverse events, but may result in adverse events. All special situations associated with baloxavir marboxil, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

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

- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

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

6. EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse event of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IECs, and applicable Health Authorities based on applicable legislation.

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

- Baloxavir marboxil IB

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.

Appendix 3
Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event electronic Case Report Form (eCRF). Avoid colloquialisms and abbreviations.

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

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

1.1. INFUSION/INJECTION-RELATED REACTIONS

Not applicable.

1.2. OTHER 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.

2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, adverse events occurring 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. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events 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 subsequent fracture, all three 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.

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 of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

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

4. ABNORMAL LABORATORY VALUES

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

- Accompanied by clinical symptoms.
- Results in a change in study drug (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- 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., alkaline phosphatase and bilirubin five times the upper limit of normal (ULN) associated with cholecystitis), only the diagnosis (i.e., cholecystitis) 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 if 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5. ABNORMAL VITAL SIGN VALUES

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

6. ABNORMAL LIVER FUNCTION TESTS

Drug-induced liver injury has been the most frequent single cause of safety-related drug marketing withdrawals or limitation of use, as well as discontinuation of clinical development programs. Hence, detection and reporting of liver function abnormalities that might herald a signal of severe drug-induced liver injury are conducted for any product in clinical development, irrespective of its expected liability for this risk.

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. 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 4 of this Appendix) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.1 of Appendix 2).

7. DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5 of Appendix 2), regardless of relationship to the study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor. This includes death attributed to progression of Condition being Studied.

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").

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”).

9. LACK OF EFFICACY OR WORSENING OF CONDITION BEING STUDIED

Not applicable.

10. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Appendix 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
- Planned hospitalization required by the protocol (hospitalization from Day -1 to Day 4 for study drug administration).
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The participant has not suffered 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 for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

11 PATIENT-REPORTED OUTCOME DATA (CLINICAL OUTCOME ASSESSMENT DATA REPORTED DIRECTLY BY PATIENT)

Not applicable.

Appendix 4
Clinical Laboratory Tests

The tests detailed in Table 7 will be performed by the local laboratory

Protocol-specific eligibility requirements of participants are detailed in Sections 5.1 and 5.2, respectively, of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Principal Investigator or required by local regulations.

Table 7 Protocol-Required Safety Laboratory Assessments

All study-required laboratory assessments will be performed by a local laboratory:

Laboratory Assessments	Parameters
Hematology	• Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
Clinical Chemistry	• Sodium, potassium, chloride, bicarbonate, glucose (fasting), urea, creatinine, total protein, serum albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, LDH.
Coagulation	• INR, aPTT, PT.
Viral Serology	• HIV, HBsAg, HCV and syphilis (*Treponema pallidum*) antibody.
Lipids	• Total Cholesterol, triglycerides
Thyroid Hormones	• Free T4, TSH.
Pregnancy Test	• All women of childbearing potential (including those who have had a tubal occlusion) will have a blood pregnancy test at screening. {Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.} • {Serum or urine} human chorionic gonadotropin (hCG) pregnancy test (as-needed for women of childbearing potential).
Urinalysis	• Specific gravity • Dipstick: pH, glucose, protein, blood, leukocyte If there is a clinically significant positive result (confirmed by a positive repeated sample), urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy and culture. • Microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal.

Other Screening Tests	• Breath alcohol, urine test for cotinine, and urine drug screen (amphetamines, barbiturates, cocaine, opiates, methadone, cannabinoids and benzodiazepines).

ALP = alkaline phosphatase, eGFR = estimated glomerular filtration rate, FSH = follicle-stimulating hormone, GGT = gamma-glutamyl transferase, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, TSH = thyroid stimulating hormone.

The results of each test must be entered into the eCRF.

Investigators must document their review of each laboratory safety report.

Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

Roche and Shionogi & Co., Ltd standard reference ranges, rather than the reference ranges of the Principal Investigator, will be used for all parameters. For most parameters, the measured laboratory test result will be assessed directly using the Roche and Shionogi & Co., Ltd standard reference range. Certain laboratory parameters will be transformed to Roche and Shionogi & Co., Ltd's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of investigator ranges, e.g., enzyme tests that include AST, ALT, and alkaline phosphatase and total bilirubin. Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

- Definition of Laboratory Abnormalities

For all laboratory parameters included, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in participant listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for each laboratory parameter. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a participant, the midpoint of the standard reference range will be used as the participant's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as "HH" for very high or "LL" for very low.

Appendix 5
Contraceptive Guidance and Collection of Pregnancy Information

1. DEFINITIONS

- **Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

- **Women in the following categories are considered to be Woman of Non-Childbearing Potential**

a) Pre-menarchal

b) Pre-menopausal female with one of the following:

– Documented hysterectomy.

– Documented bilateral salpingectomy.

– Documented bilateral oophorectomy.

Note: Documentation can come from the study center's personnel's review of participant's medical records, medical examination, or medical history interview.

c) Post-menopausal female

– A postmenopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient.

– Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

2. CONTRACEPTION GUIDANCE

- **Female partners of male participants**

Female partners of male participant must use a highly effective method of contraception consistently and correctly as described in Table 8 below.

Table 8 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User-Dependent [a] (Failure rate of < 1% per year when used consistently and correctly)
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User-Independent[a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner *A vasectomy is a highly effective contraception method provided that the vasectomized partner is the sole male sexual partner of the women of childbearing potential P and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

3. PREGNANCY TESTING

As women of child bearing potential are not enrolled in the study, pregnancy testing will not be done.

4. COLLECTION OF PREGNANCY INFORMATION

- **Male participants with partners who become pregnant**

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study (see Section 8.3.5). This applies only to male participants who receive the study drug.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to the study drug. The investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. When permitted by the study center, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy when available. An investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- **Female participants who become pregnant**

This section is not applicable as WOCBP are not enrolled in the study.

- The investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study (see Section 8.3.5). Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, which will be forwarded to the Sponsor. Monitoring of the participant should continue until conclusion of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, and should not be recorded on the adverse event electronic Case Report Form (eCRF), any pregnancy complication will be reported as an adverse event or serious adverse event. A spontaneous abortion is always considered to be a serious adverse event and will be reported as such. Any post-study pregnancy related

serious adverse event considered reasonably related to the study drug by the investigator, will be reported to the Sponsor as described in Appendix 2. While the investigator is not obligated to actively seek this information in former study participants, he/she may learn of a serious adverse event through spontaneous reporting.

5 ABORTIONS

Any spontaneous abortion in the female partner of male participant should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Any induced abortion due to maternal toxicity and/or embryo-fetal toxicity should also be classified as serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Elective abortion not associated with toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female partner of a male participant exposed to the study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2.

Appendix 6
Protocol Amendment History

Document History

Documents	Dates	Substantial	Region
Version 2 (Amendment 1)	06 December 2018	Yes	China
Version 1 (Original Protocol)	07 August 2018	-	-

SPONSOR SIGNATORY FORM

TITLE:	**A PHASE I, SINGLE-CENTER, OPEN-LABEL, PARALLEL, TWO DOSE LEVEL STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY FOLLOWING A SINGLE DOSE OF BALOXAVIR MARBOXIL IN HEALTHY CHINESE VOLUNTEERS**
PROTOCOL NUMBER:	YP40902
VERSION NUMBER:	2
TEST PRODUCT:	Baloxavir marboxil (RO7191686)
SPONSOR:	F. Hoffmann-La Roche Ltd and Shionogi & Co., Ltd

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

[redacted]
Sponsor's Name (print)

[redacted]
Sponsor's Signature

15 Jan 2019
Date