Official Title: A Phase III, Randomized, Double-Blind Placebo-Controlled, Multicenter Study To Evaluate the Efficacy and Safety of Baloxavir Marboxil in Combination With Standard-of-Care Neuraminidase Inhibitor in Hospitalized Participants With Severe Influenza

NCT Number: NCT03684044

Document Date: Protocol Version 2: 30-May-2019

PROTOCOL

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BALOXAVIR MARBOXIL IN COMBINATION WITH STANDARD-OF-CARE NEURAMINIDASE INHIBITOR IN HOSPITALIZED PATIENTS WITH SEVERE INFLUENZA**
PROTOCOL NUMBER:	CP40617
VERSION NUMBER:	2
EUDRACT NUMBER:	2018-001416-30
IND NUMBER:	126653
TEST PRODUCT:	Baloxavir marboxil (RO7191686)
MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 17 July 2018
DATES AMENDED:	Version 1 (VHP only): 27 November 2018 Version 2: See electronic date stamp below.

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	30-May-2019 16:10:33

PROTOCOL AMENDMENT, VERSION 2:
RATIONALE

In addition to updates initiated in this Version 2, this amendment contains updates made in a Version 1 (VHP only) amendment approved on 27 November 2018 (applicable to countries under Voluntary Harmonization Procedure [VHP] only). Protocol Version 2 supersedes Protocol Version 1 and Version 1 VHP.

Changes to the protocol are summarized below:

- The study sample size was change from approximately 240 to approximately 366 hospitalized adults and adolescent patients throughout the protocol. This change was based upon a blinded review of the time to clinical improvement (TTCI) data from patients recruited during the northern hemisphere 2018/2019 flu season and the incorporation of a planned futility interim analysis (see Section 6).
- The optional interim analysis was changed to a formal, pre-planned, unblinded, non-binding futility analysis. It will be conducted after approximately 65% of TTCI events and will be based on the TTCI and the Lan-DeMets Pocock beta spending function (Section 6.7.1).
- The endpoint “time to clinical response” was moved from an exploratory endpoint to an additional key secondary endpoint at the request of the FDA (Section 2).
- The palatability and acceptability endpoint was added to address a request from the European Medicines Agency (EMA) Pediatric Committee (PDCO) to assess the acceptability of the baloxavir marboxil granules for oral suspension formulation (Section 2, Section 4.5.15, Section 6.4.5, and Appendix 5).
- The number of sites to enroll patients was updated from approximately 215 global sites to 250 sites to allow for the increase in sample size (Section 3.1).
- Known hypersensitivity to baloxavir marboxil or the drug product excipients was added as an exclusion criterion (Section 4.1.2).
- A section was added to summarize post-marketing safety data that identified hypersensitivity reactions (i.e., anaphylaxis/anaphylactic reactions, angioedema, and urticaria) as adverse drug reactions during post-marketing use of baloxavir marboxil (Section 1.2.4). In the event of a anaphylaxis or other form of hypersensitivity reaction, advice that patients should be withdrawn from study treatment was included (Section 4.6.1).

Other additions and clarifications:

- Summary information was added for intravenous zanamivir (Dectova®), which recently received a positive opinion for use under exceptional circumstances from the EMA for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and pediatric patients (Section 1.1).
- A section was added to summarize results from a Phase III, double-blind, randomized, placebo- and active-controlled study investigating baloxavir marboxil in patients at high risk of developing influenza-related complications (Section 1.2.3).

- The timing of the vital signs and assessments for National Early Warning Score 2 (NEWS2) was clarified, as indicated in the clarification letters sent to sites, to ensure all vital sign parameters and NEWS2 assessments are collected together and that assessment timepoints are spread throughout the study day to reflect the patient's condition over the entire study day, where possible (Sections 4.5.4; Appendix 5 footnotes).
- The vitals sign data to be utilized during screening to calculate the NEWS2 score was clarified, as indicated in the clarification letters sent to sites, to ensure that all data collected closest to but before randomization should be used for the NEWS2 score calculation and assessment of patient eligibility (Section 4.5.6 and Appendix 3).
- Clarification was added that the modified intent-to-treat infected (mITTI) population would be used in efficacy analyses. Clarification was also added that full details of analysis methods will be contained within the Statistical Analysis Plan (Section 6.4).
- The following minor revisions were made for clarification or for consistency across sections/Schedule of Activities:
  - Study Treatment Preparation (Section 4.3.1.1): Text was aligned with Pharmacy Manual following protocol clarification letter.
  - Cautionary Therapy (Section 4.4.2): Dairy products and calcium-fortified beverages was added to the list of cautionary therapies. The word "oral" was added to laxatives and antacids for clarity. In addition, the phrase "where possible" was also added to match wording for this section (i.e., cautionary, not prohibited).
  - Pharmacokinetic Analyses (Section 6.6): The text was updated to describe how patients with 2 or 3 study treatment doses will be analyzed separately. It was also stated that population PK model outcomes would be reported in a separate report.
  - Schedule of Activities: The End of Study (EOS) column was moved so it is included under the Follow-Up Period heading for clarity.
  - Schedule of Activities: The timing of Visit 8 was clarified in a footnote to ensure that Visit 8 did not occur on the same day as Visit 7.
  - Other minor clarifications and corrections were made throughout the protocol for clarify, consistency, or to align text with clarification letters. These are indicated by italicized text.

Updates in line with Xofluza® (baloxavir marboxil) approvals and documentation: Core Data Sheets (CDS), Investigator's Brochure, Drug Safety Update Report (DSUR).

- Rationale for patient population (Section 3.3.2): Text was updated to align with approvals as well as current and potentially future Clinical Development Plan (CDP).
- Safety plan update (Section 5.1): Text was updated to align with the Sponsor's documentation and approvals.

The following updates were made to bring the protocol into alignment with recent updates to the company's protocol model document:

- Text has been modified to account for the fact that special situations (i.e., accidental overdoses and medication errors) are not required to be reported within 24 hours (Sections 5.3.5.11 and 5.4). Note that serious adverse events associated with special situations are still required to be reported within 24 hours.
- Language has been updated to indicate that therapeutic or elective abortions are not considered adverse events unless performed because of an underlying maternal or embryofetal toxicity. In such cases, the underlying toxicity should be reported as a serious adverse event. Language has also been added to clarify that all abortions are to be reported on the paper Clinical Trial Pregnancy Reporting Form (Section 5.4.3.3).
- Language has been added for consistency with Roche's current data retention policy and to accommodate more stringent local requirements (if applicable) (Section 7.5).
- Language has been added to indicate that the study will comply with applicable local, regional, and national laws (Section 8.1).
- Language has been revised to clarify that data posting will not be limited to clinical trial registries and to clarify that redacted Clinical Study Reports are provided only if requirements of Roche's global policy on data sharing have been met (Section 9.5).

The following updates were made in the Version 1 (VHP only) amendment per VHP request, except where noted, and are being carried forward into this Version 2 amendment:

- Known hypersensitivity to baloxavir marboxil or the drug product excipients has been added as an exclusion criterion (Section 4.1.2).
- The Medical Monitor has changed and updated contact information has been provided (Section 5.4.1).
- Language regarding written informed consent for adolescents unable to legally provide consent was revised to accommodate situations where a local regulatory or Independent Review Board/Ethics Committee policy requires written informed consent from both parents (Section 4.5.1). Section 8.2 has been amended accordingly.
- The type of pregnancy test at screening has been changed from a urine pregnancy test to a serum pregnancy test (Section 4.5.7 and Appendix 1). In this Version 2 amendment, the requirement at screening was clarified as follows: serum pregnancy tests for VHP sites and serum or urine pregnancy tests for sites in the rest of the world.
- In order to correct an error in Version 1, text was added stating that patients who discontinue study treatment should continue in the study and complete all scheduled study assessments/visits per protocol, where possible (Section 4.6.1).
- In order to correct an error in Version 1, text was updated to clarify that patients who discontinue from the study will be asked to complete a study discontinuation visit, at

which time the assessments per the end of study visit should be conducted (Section 4.6.2).

- Text was added to clarify the censoring of patients who discontinue for any reason prior to achieving a clinical response event. Text has been added stating that a sensitivity analysis for subjects who discontinue for any reason prior to achieving a clinical response event will be performed to investigate potential confounding factors and detailed in the SAP along with any further sensitivity analyses (Section 6.4.1).

The Schedule of Activities was updated to reflect updates made in the body of the text and to correct minor typographical errors.

Substantive new information from both amendments (i.e., Version 2 and Version 1 [VHP only]) appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BALOXAVIR MARBOXIL IN COMBINATION WITH STANDARD-OF-CARE NEURAMINIDASE INHIBITOR IN HOSPITALIZED PATIENTS WITH SEVERE INFLUENZA**
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MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BALOXAVIR MARBOXIL IN COMBINATION WITH STANDARD-OF-CARE NEURAMINIDASE INHIBITOR IN HOSPITALIZED PATIENTS WITH SEVERE INFLUENZA**
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PHASE:	III
INDICATION:	Influenza
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of baloxavir marboxil in combination with a standard-of-care (SOC) neuraminidase inhibitor (NAI) (i.e., oseltamivir, zanamivir, or peramivir) compared with a matching placebo in combination with a SOC NAI in hospitalized patients with influenza. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to baloxavir marboxil or its matching placebo. Study treatment is given in combination with a SOC NAI.

Primary Objective	Corresponding Endpoint
• To evaluate the clinical efficacy of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI	• TTCI defined as: – Time to hospital discharge OR – Time to NEWS2 of ≤2 maintained for 24 hours
Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the clinical efficacy of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI	**Key Secondary Endpoints:** • Response rates of the 6-point ordinal scale at Day 7 • *Time to clinical response based on temperature ranges, oxygen saturation, respiratory status, heart rate, and hospitalization status* [a] **Other Secondary Endpoints:** • Incidence of mechanical ventilation • Duration of mechanical ventilation • Incidence of ICU stay • Duration of ICU stay • Time to clinical failure, defined as the time to death, mechanical ventilation, or ICU admission, corresponding to ordinal scale categories 6, 5, and 4, respectively, from baseline • Time to hospital discharge • Incidence of post-treatment influenza-related complications [b] • Mortality rate at Day 7 • Mortality rate at Day 28 • Time to NEWS2 of ≤2 maintained for 24 hours
Virology Objectives	**Corresponding Endpoints**
• To evaluate the virological activity of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI	• Time to cessation of viral shedding by virus titer • Time to cessation of viral shedding by RT-PCR • Change from baseline in influenza virus titer and in the amount of virus RNA (RT-PCR) at each timepoint • Proportion of patients with positive influenza virus titer and proportion of patients positive by RT-PCR at each timepoint • AUC in virus titer and in the amount of virus RNA (RT-PCR)
• To evaluate the polymorphic and treatment-emergent amino acid substitutions in the *PA*, *PB1*, *PB2,* and *NA* genes and drug susceptibility in patients with evaluable virus	• Polymorphic and treatment-emergent amino acid substitutions in the *PA*, *PB1*, *PB2,* and *NA* genes • Drug susceptibility in patients with evaluable virus

Safety Objective (cont.)	Corresponding Endpoints (cont.)
•To evaluate the safety of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI in hospitalized patients with influenza	•Compare the incidence and severity of AEs and SAEs •Incidence of AEs leading to discontinuation •Proportion of patients with any post-treatment ALT and AST above baseline and $>3\times$ ULN, $>5\times$ ULN, $>10\times$ ULN
Pharmacokinetic Objective	**Corresponding Endpoints**
•To evaluate the single- and multiple-dose pharmacokinetics of baloxavir	•Plasma concentrations of baloxavir (active metabolite) at specified timepoints •After each dose, concentration at predose and 24 hours postdose will be summarized • Non-compartmental PK parameters such as AUC, C_{max} and $t_{1/2}$ (only for patients undergoing sequential PK sampling)
Exploratory Palatability and Acceptability Objective	***Corresponding Endpoint***
• *To describe the palatability and acceptability of the oral suspension in hospitalized patients with influenza*	• *Number and proportion of patients reporting each palatability and acceptability response at each timepoint*

AE = adverse event; AUC = area under the concentration–time curve; C_{max} = maximum plasma concentration; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; NAI = neuraminidase inhibitor; NEWS2 = National Early Warning Score 2; PK = pharmacokinetic; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; *SOC = standard-of-care;* TTCI = time to clinical improvement; $t_{1/2}$ = half-life; ULN = upper limited normal

[a] *Criteria for each parameter (i.e., temperature, oxygen saturation, respiratory status, heart rate, systolic blood pressure, and hospital discharge) as defined in the protocol.*

[b] Incidence of post-treatment influenza-related complications as defined as pneumonia, myositis or rhabdomyolysis, encephalitis or encephalopathy, myocarditis and/or pericarditis, otitis media, sinusitis, exacerbation of COPD/asthma, sepsis, acute lung injury, or acute respiratory distress syndrome.

Study Design

Description of Study

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy, safety, and pharmacokinetics of baloxavir marboxil in combination with a SOC NAI (i.e., oseltamivir, zanamivir, or peramivir), compared with a matching placebo in combination with a SOC NAI in approximately *366* hospitalized adults and adolescent patients (aged ≥ 12 years) with influenza.

Patients will be randomized as soon as possible after screening *(ideally within 12 hours)*, providing they are within 96 hours of symptom onset and hospitalized (includes assessment in emergency centers pending admission to a hospital ward). Patients will be assigned in a 2:1 ratio to receive baloxavir marboxil or matching placebo. Study treatment must be given in combination with a SOC NAI according to investigator preference (i.e., oseltamivir, zanamivir, or peramivir). Re-screening of patients who fail to meet the inclusion and exclusion criteria will be permitted only once, providing the time from symptom onset to randomization is still within 96 hours.

Baloxavir marboxil will be administered as a weight-based dose (40 mg for patients weighing 40 to <80 kg, 80 mg for patients weighing ≥ 80 kg) on Days 1 and 4, and also on Day 7 if clinical improvement has not occurred at Day 5, per protocol defined criteria. Treatment with a SOC NAI (i.e., oseltamivir, zanamivir, or peramivir) should be administered in accordance with local clinical practice. To fully explore the utility of the combination with baloxavir marboxil, or

matching placebo, the dosing regimen of the SOC NAI should aim to ensure that anti-viral activity is maintained from Day 1 to Day 5. The SOC NAI treatment may be extended to Day 10 or beyond at the discretion of the investigator and in accordance with local clinical practice. The study consists of two periods: a 10-day treatment period and a 25-day follow-up period. Therefore, the maximum study duration for each patient will be 35 days.

The study assessments to be conducted include the following: physical examination, vital signs, assessment of consciousness, presence, or absence of respiratory support, adverse events, concomitant therapies, clinical laboratory tests, nasopharyngeal swabs*, and the palatability and acceptability questionnaire*.

An external independent Data Monitoring Committee (iDMC) will evaluate safety according to policies and procedures detailed in an iDMC Charter.

Number of Patients

Approximately *366* hospitalized adults and adolescent patients (aged ≥12 years) are planned for enrollment at approximately *250* global sites in both Northern and Southern hemispheres.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Adult patients: Signed informed consent by any patient capable of giving consent, or, where the patient is not capable of giving consent, by his or her legal/authorized representative
- Adolescent patients not able to legally consent: written informed consent for study participation is obtained from patient's parents or legal guardian, with assent as appropriate by the patient, depending on the patient's level of understanding and capability to provide assent.
- Age ≥12 years at the time of signing the Informed Consent Form/Assent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Patients who require hospitalization for severe influenza or acquire influenza during hospitalization, the severity of which requires an extension of hospitalization
- Diagnosis of influenza A and/or B by a positive Rapid Influenza Diagnostic Test (RIDT) or reverse transcriptase-polymerase chain reaction (RT-PCR)

  Positive results from local tests are acceptable if conducted within the 24 hours prior to screening.

  A patient with a negative RIDT may be enrolled if influenza is suspected based on local surveillance data or if the patient reports contact with a known case of influenza within the prior 7 days and all other inclusion criteria are met
- The time interval between the onset of symptoms and randomization is within 96 hours

  The onset of symptoms is defined as the time when the patient experiences at least one new general symptom (e.g., headache, feverishness or chills, muscle or joint pain, fatigue), respiratory symptom (e.g., cough, sore throat, nasal congestion), or fever.
- A score of ≥4 based on the National Early Warning Score 2 (NEWS2)
- Patients will require objective criteria of seriousness defined by at least one of the following criteria:
  - Requires ventilation or supplemental oxygen to support respiration
  - Has a complication related to influenza that requires hospitalization (e.g., pneumonia, CNS involvement, myositis, rhabdomyolysis, acute exacerbation of chronic kidney disease, asthma or chronic obstructive pulmonary disease [COPD], severe dehydration, myocarditis, pericarditis, exacerbation of ischemic heart disease)
- For women of childbearing potential: Agreement to remain abstinent (refrain from heterosexual intercourse)

  Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 28 days after the last dose of study

treatment. Hormonal contraceptive methods must be supplemented by a barrier method.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of $<$ 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

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

- Patients who have received more than 48 hours of antiviral treatment for *the current* influenza *infection* prior to screening
- Patients who have received baloxavir marboxil for the current influenza infection
- Known contraindication to neuraminidase inhibitors
- Patients hospitalized for exclusively social reasons (e.g., lack of caregivers at home)
- Patients expected to die or be discharged within 48 hours, according to the investigator's judgement
- Patients weighing $<$ 40 kg
- Patients with known severe renal impairment (estimated glomerular filtration rate $<$ 30 mL/min/1.73 m^2) or receiving continuous renal replacement therapy, hemodialysis, peritoneal dialysis
- Patients with any of the following laboratory abnormalities detected within 24 hours prior to or during screening (according to local laboratory reference ranges:
  - ALT or AST level $>$ 5 times the upper limit of normal (ULN)

    OR
  - ALT or AST $>$ 3 times the ULN and total bilirubin level $>$ 2 times the ULN
- Pregnant or breastfeeding, or positive pregnancy test in a predose examination, or intending to become pregnant during the study or within 28 days after the last dose of study treatment
- Exposure to an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- *Known hypersensitivity to baloxavir marboxil or the drug product excipients*

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The LPLV is expected to occur 35 days after the last patient is enrolled.

Length of Study

The total length of the study, from screening of the first patient to the LPLV, is expected to be approximately *2.5* years.

Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are baloxavir marboxil and its matching placebo as the comparator.

Test Product (Investigational Drug)

Baloxavir marboxil or its matching placebo will be administered orally according to body weight (40 mg for patients weighing 40 to <80 kg; 80 mg for patients weighing ≥ 80 kg), either in tablet form or granules for oral suspension for patients unable to swallow or with a nasogastric tube in situ (e.g., in intubated patients). Dosing will occur on Day 1 and Day 4, with a further dose at Day 7 for patients who have not improved according to *at least 1 of the following* specific criteria at Day 5*:* ongoing mechanical ventilation, persistent fever, severely immunocompromised, *pneumonia, or* confirmed/suspected influenza-related complication.

Non-Investigational Medicinal Product

Standard-of-Care Neuraminidase Inhibitor

The protocol-defined SOC NAIs are oseltamivir, zanamivir, or peramivir.

An open-label SOC NAI should be administered according to local clinical practice (i.e., oseltamivir, peramivir, or zanamivir) to ensure anti-viral activity is maintained from Day 1 through Day 5. The SOC NAI treatment may be extended to Day 10 or beyond at the discretion of the investigator and in accordance with local clinical practice. Special attention is required for dosing in patients with renal impairment, as dose adjustment may be needed.

Statistical Methods

Primary Analysis

The primary efficacy objective for this study is to evaluate the efficacy of baloxavir marboxil plus a SOC NAI, compared with matching placebo plus SOC NAI on the basis of the following endpoint:

- Time to clinical improvement (TTCI; defined as time to hospital discharge or time to NEWS2 of ≤ 2 and maintained for 24 hours, whichever comes first)

The median TTCI will be compared between the baloxavir marboxil plus SOC NAI and matching placebo plus SOC NAI arms using the stratified log-rank test within three regions (i.e., North America; Europe, Middle East, and Africa [EMEA]; rest of world [ROW]), NEWS2 (≤ 7, >7), and time from symptom onset to study treatment (≤ 48 hours, >48 hours) included as the stratification factors. The Kaplan-Meier plot, median time to response, and their 95% CI, and a p-value will be presented.

The log-rank test requires the assumption of proportional hazards to be met. The proportional hazards assumption will be tested graphically using the log cumulative hazard plot by treatment group. The plots for each treatment group will be parallel if the proportional hazard assumption holds. *Using a Cox model, the slope of a linear regression will also be tested and a plot of scaled Schoenfeld residuals against the Kaplan-Meier estimator will be investigated.* Should the proportional hazards assumption be violated*,* the Gehan-Wilcoxon test will be used to analyze the data *as the logrank test can be under powered in this situation. All investigations will be detailed in the statistical section of the CSR.*

The estimand is the median change in TTCI. This absolute measure will be assessed over the duration of the study (35 days). Intercurrent events are those that occur after treatment initiation and either preclude observation of the variable or affect its interpretation. Intercurrent events will be accounted for through censoring rules. Patients who are lost to follow-up, who do not have a clinical response event, who die *or discontinue for any reason prior to achieving a clinical response event* will be censored at their last contact date or date of death, whichever is applicable. No dose reductions or treatment cross-overs are anticipated.

The primary efficacy analysis population will be characterized through the inclusion/exclusion criteria and will be the modified intent-to-treat (influenza-)infected (*m*ITTI) population, which consists of all patients who were randomized to treatment, received a dose of study drug, and were RT-PCR positive for influenza (centrally assessed) *at any timepoint*.

A sensitivity analysis will be conducted where patients who are lost to follow-up or who do not have a clinical response event will be assumed to have had an event at 28 days. *A sensitivity*

analysis for patients who discontinue for any reason prior to achieving a clinical response event will be performed to investigate potential confounding factors. A sensitivity analysis, considering death as a competitive event, using a competing risk model will be conducted if there are a sufficient number of deaths or an imbalance between groups in deaths and reason attributed. These and any further sensitivity analyses will be fully detailed in the SAP.

Missing data handling rules for the components of the NEWS2 score will be specified in the SAP.

Determination of Sample Size

Two new factors influenced the revised sample size: 1) the revised assumption for the placebo plus NAI control-arm TTCI following blinded data review and 2) the faster than anticipated enrollment rate. Integration of these two factors informed a sample size readjustment to approximately 366 randomized patients. Assuming that the RT-PCR–positive rate (tested in a central laboratory) will be 75% of the randomized population and a dropout rate of 4% the mITTI population will be 264 patients (i.e., 176 patients in the baloxavir marboxil group and 88 in the placebo group).

The total number of randomized patients may change based on the percentage of patients who are RT-PCR positive during the study.

The total *m*ITTI sample size of *264* patients provides at least 80% power using the Logrank Chi-Square test to detect a 31-hour difference in TTCI between treatment groups under the following assumptions: median TTCI in the placebo plus NAI group is *94* hours, 840 hours follow-up (35 days) *using 5% alpha. T*he minimal detectable difference is *expected to be around* 23 hours. The *alteration of the* TTCI in *the* placebo plus NAI group *to 94* hours was selected after consideration of the response rates observed in *a blinded review of TTCI including data from 127 patients.*

The increased sample size has the consequential benefit of a larger population for safety analysis of the combination and multiple dose regimen specifically tested in this study for the severely ill hospitalized patient group.

The study power is calculated based on the primary endpoint incorporating a group sequential design (GSD) using a beta spending function with non-binding rule, to allow for one futility interim, without increasing the overall experiment-wise error rate.

Interim Analyses

After approximately 65% of TTCI events, a formal unblinded non-binding futility interim analysis based on the TTCI will be performed. The futility interim analysis will use a Lan-DeMets Pocock beta spending function. If the hazard ratio seen at the interim is below the calculated futility bound, the trial may be declared futile and recruitment will be stopped.

The futility interim is non-binding on the Sponsor, and any deviation from the iDMC recommendation will be fully documented in the CSR. If the study is stopped for futility, at that point the study results will be reported. Full operating characteristics of the IA will be detailed in the SAP.

The interim analysis will be conducted by an *unblinded* external statistical group *(independent Data Coordinating Centre, iDCC)* and reviewed by the iDMC *(also unblinded), whilst the Sponsor will remain blinded until the end of study*. Interactions between the iDMC*/iDCC* and Sponsor will be carried out as specified in the iDMC Charter.

The iDMC Charter will be updated to document this pre-planned interim analysis and potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for futility *or continue the study*), and the iDMC Charter will also be made available to relevant health authorities.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ANCOVA	analysis of covariance
AUC	area under the concentration–time curve *or area under the curve (as appropriate)*
AUC_{inf}	area under the concentration–time curve from time 0 to infinity
AUC_{tau}	area under the plasma concentration–time curve for a dosing interval
BID	twice daily
C_{24}	concentration 24 hours postdose
C_{max}	maximum plasma concentration
C_{trough}	minimum plasma concentration
CL/F	apparent clearance
COPD	chronic obstructive pulmonary disease
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EMEA	Europe, Middle East, and Africa
FiO_2	fraction of inspired oxygen
GSD	*Group Sequential Design*
HA	hemagglutinin complex
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
ICU	intensive care unit
iDCC	*independent Data Coordinating Centre*
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit
M2	matrix-2
*m*ITTI	*modified* intent-to-treat (influenza) infected (population)
MN	mobile nursing
NA	neuraminidase
NAI	neuraminidase inhibitor
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEWS2	National Early Warning Score 2

Abbreviation	Definition
NMPA	*National Medical Products Administration*
PCR	polymerase chain reaction
PK	pharmacokinetic
PRO	patient-reported outcome
RIDT	Rapid Influenza Diagnostic Test
ROW	rest of world
RT-PCR	reverse transcriptase-polymerase chain reaction
SAP	Statistical Analysis Plan
SOC	standard of care
$TCID_{50}$	50% tissue culture infectious dose
TQT	Thorough QT
TTAS	*time to alleviation of symptoms*
TTCI	time to clinical improvement
ULN	upper limit of normal
Vc/F	apparent volume of distribution for the central compartment

1. BACKGROUND

1.1 BACKGROUND ON INFLUENZA

Influenza is an acute respiratory infectious disease caused by a virus of the orthomyxovirus family. Two forms are known to infect humans, influenza A and B. These viruses cause an acute febrile infection of the respiratory tract after an incubation period of 1 to 4 days, characterized by the sudden onset of fever, cough, fatigue, headache, and myalgia. Annual influenza epidemics are thought to result in between 3 and 5 million cases of severe illness, and between 250,000 and 500,000 deaths every year around the world (WHO 2017).

Although the condition is usually self-limiting in healthy adults, it can be associated with substantial morbidity and occasional mortality in children, the elderly, and the immunocompromised (Paules and Subbarao 2017). Hospitalization due to severe influenza is associated with high mortality (4%–8%), intensive care unit (ICU) admission (5%–17%), and prolonged hospital stays of between 5 and 9 days. During a pandemic season, the outcomes may be more serious, with up to 34% of patients requiring ICU care and a mortality rate as high as 15% (Lee and Ison 2012).

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

The following anti-influenza virus drugs are currently available for treatment of acute, uncomplicated influenza in different countries: the M2 ion channel inhibitors amantadine and rimantadine, the RNA polymerase inhibitor favipiravir, and the NA inhibitors (i.e., oseltamivir, zanamivir, and peramivir). Many cases of seasonal influenza infection are resistant to amantadine and rimantadine, hence their use in clinical practice is limited. NA inhibitor (NAI) oral formulations need to be administered for 5 days, potentially resulting in poor patient compliance and convenience, while inhalation formulations can only be used in patients who are able to inhale the drug. These factors contribute to an unmet medical need for new antiviral influenza drugs that can be easily and less frequently administered, particularly in patients who are severely ill and possibly intubated.

In February 2019, intravenous zanamivir (Dectova®) received a positive opinion for use under exceptional circumstances from the European Medicines Agency for the treatment of complicated and potentially life-threatening influenza A or B virus

infections in adult and pediatric patients (aged ≥6 months). Zanamivir is only indicated when the influenza virus is resistant to other antiviral drugs, or when other antiviral drugs are not suitable, and, therefore, have limited scope in treating influenza in hospitalized patients. Currently, there are no *other* licensed drugs *specifically* approved for the treatment of influenza in hospitalized *patients.* Despite this, NAIs are widely used as the mainstay of treatment for hospitalized patients, and evidence shows a potential reduction in mortality in hospitalized patients treated with NAIs, especially if initiated as early as possible (Muthuri et al. 2014).

Influenza viruses are known to mutate during the course of replication and can mutate into a strain resistant to existing antiviral influenza drugs or a strain to which most people are not immune. Certain strains of avian influenza have been found to be highly pathogenic with high rates of NAI-resistance (Hu et al. 2013). New antiviral influenza treatments with novel mechanisms of action may provide alternative therapy options, particularly when used in combination with NAIs, to overcome such highly pathogenic organisms.

1.2 BACKGROUND ON BALOXAVIR MARBOXIL

Baloxavir marboxil is a compound that exerts antiviral effects against influenza. Baloxavir marboxil (also referred to as S-033188) is a pro-drug, which is converted to an active form baloxavir (also referred to BALOXAVIR) through a metabolic process called hydrolysis, in the blood, liver, and small intestine.

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

To date, one Phase II study in *otherwise healthy* adults and *two* Phase III stud*ies* in adults and adolescents *(i.e., one in otherwise healthy patients and one in patients with high risk of influenza-related complications)* have been completed and are summarized below. *Currently, t*he clinical development plan is designed to investigate *additional* indications for post-exposure prophylaxis, the *reduction of influenza transmission, and otherwise healthy pediatrics (<12 years of age). The studies for these additional* indications are not discussed in this protocol.

Baloxavir marboxil is approved for use in Japan (since February 2018) for the treatment of influenza A or B virus infection in all age groups (≥10 kg) and in the United States (since October 2018), Hong Kong (since February 2019), and Thailand (since March 2019). It is approved for the treatment of influenza in otherwise healthy patients aged 12 years and above who have been symptomatic for no more than 48 hours. In addition, baloxavir marboxil is approved in Thailand and Japan for the treatment of influenza in patients aged 12 years and above who have been symptomatic for no more than 48 hours and are at high risk of developing influenza-related complications. Regulatory filings

in other global regions are either completed, ongoing, or planned to gain market authorization for the use of baloxavir marboxil for the treatment of influenza.

Detailed profiles of baloxavir marboxil and its active form, baloxavir, derived from nonclinical and clinical studies are provided in the Baloxavir Marboxil Investigator's Brochure.

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

In this Phase II, double-blind, randomized, placebo-controlled study, the efficacy and safety of baloxavir marboxil in *otherwise healthy Japanese* patients with influenza virus infection was investigated. A single dose of 10, 20, or 40 mg baloxavir marboxil or placebo was administered to 400 patients with influenza virus infection (100 per dose group).

The median times to alleviation of influenza symptoms in the 10-mg, 20-mg, and 40-mg groups were 54.2, 51.0, and 49.5 hours, respectively, compared with 77.7 hours in the placebo group. Using the stratified generalized Wilcoxon test, the prespecified secondary analysis, all three dose groups of baloxavir marboxil showed a significantly greater reduction in the time to alleviation of symptoms compared with the placebo group (2-sided p-values: $p = 0.0085$ for the 10-mg group, $p = 0.0182$ for the 20-mg group, and $p = 0.0046$ for the 40-mg group).

Compared with the placebo group, all of the baloxavir marboxil groups showed a greater reduction in the proportion of patients with positive influenza virus titer, change from baseline in influenza virus titer, and change in amount of influenza virus on Days 2 and 3 using the stratified Wilcoxon test.

Baloxavir marboxil was well tolerated in the study. No deaths, serious adverse events, or treatment-emergent adverse events leading to study withdrawal were reported in any of the groups. Adverse events were reported in 27 of 100 patients (27%, 34 events) in the 10-mg group, 23 of 100 patients (23%, 29 events) in the 20-mg group, and 26 of 100 patients (26%, 29 events) in the 40-mg group compared with 29 of 100 patients (29%, 40 events) in the placebo group. No dose-dependent adverse events were observed. Most adverse events were of mild intensity and resolved. No severe treatment-emergent adverse events were reported in the study.

1.2.2 Phase III Double-Blind Study in Otherwise Healthy Patients (Study 1601T0831, *CAPSTONE 1*)

In this Phase III, double-blind, double-randomized, placebo- and active (oseltamivir)controlled study, the efficacy and safety of baloxavir marboxil- was investigated in otherwise healthy *Japanese and US* adults and adolescents 12 to 64 years of age with influenza. The doses studied were a single dose of 40 mg for patients weighing 40 to < 80 kg and a single dose of 80 mg for patients weighing ≥ 80 kg.

Patients randomized to the active-control arm received 75 mg oseltamivir, twice daily (BID) for 5 days. 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.

The baloxavir marboxil group showed a significantly greater reduction in the time to alleviation of symptoms *(TTAS)* compared with the placebo group *(median difference −26.5 hours [95% CI: -35.8, -17.8];* $p < 0.0001$). In the adult stratum of patients, the median *TTAS* was 53.5 hours in the baloxavir marboxil group compared with 53.8 hours in the oseltamivir group. Of the secondary endpoints, significant decreases in both virus titer and the amount of virus RNA were observed in the baloxavir marboxil group compared with the placebo group.

In addition, the median time to cessation of viral shedding, as determined by virus titer, was significantly shorter ($p < 0.0001$) in the baloxavir marboxil group (24 hours) than in the placebo group (96 hours) and in the oseltamivir group (72 hours).

Beneficial effects of baloxavir marboxil on fever were also demonstrated. The proportion of patients who had fever was reduced more rapidly in the baloxavir marboxil group than in the placebo group following the study drug administration. The median time to resolution of fever was shortened by 17.5 hours in the baloxavir marboxil group compared with the placebo group ($p < 0.0001$).

Baloxavir marboxil was well tolerated in this study. No deaths were reported in any group. Two serious adverse events (i.e., aseptic meningitis and incarcerated inguinal hernia) were reported in 2 of 610 patients (0.3%) in the baloxavir marboxil group. Both serious adverse events resolved and were considered not related to study drug by the investigators. Adverse events were reported in 126 of 610 patients (20.7%, 172 events) in the baloxavir marboxil group, 76 of 309 patients (24.6%, 118 events) in the placebo group, and 127 of 513 patients (24.8%, 179 events) in the oseltamivir group.

The relatively common adverse events (incidence 2% or greater) in any of the groups were bronchitis, sinusitis, diarrhea, and nausea; however, the incidence of each adverse event in the baloxavir marboxil group was lower than or equal to that in the placebo group. In all groups, the majority of the adverse events were categorized as Grade 1 or 2 and resolved.

1.2.3 *Phase III Double-Blind Study in Patients at High Risk of Developing Influenza-Related Complications (Study 1602 T0832, CAPSTONE II)*

In this global, Phase III, double-blind, randomized placebo-, and active (oseltamivir)-controlled study, the efficacy and safety of baloxavir marboxil was investigated in adults and adolescents at high risk of developing influenza-related complications. The patients had to have at least one high-risk factor for developing influenza-related complications (adapted from the Centers for Disease Control and

Prevention's [CDC] criteria). The doses studied were a single dose of 40 mg for patients weighing 40 to <80 kg and a single dose of 80 mg for patients weighing ≥ 80 kg. Patients randomized to the active-control arm received 75 mg oseltamivir, BID for 5 days. A total of 2178 patients received the study drug: 730 in the baloxavir marboxil group, 727 in the placebo group, and 721 in the oseltamivir group.

The primary endpoint was the time to improvement of influenza symptoms (TTIS) in patients with influenza. Since high-risk individuals may have underlying chronic diseases that share some symptoms with those of influenza (e.g., cough in a patient with chronic lung disease), a modification of the TTAS was used to permit assessment of improvement of a symptom that may have been present before the onset of influenza but worsened by influenza, or maintenance of a preexisting symptom that had not been worsened by the onset of acute influenza.

The study met its primary endpoint, demonstrating a clinically meaningful and statistically significant reduction in TTIS in the baloxavir marboxil group compared with the placebo group (median difference –29.1 [95% CI: –42.8, –14.6] hours, p <0.0001). The difference in TTIS between the baloxavir marboxil group and the oseltamivir group was not statistically significant (median difference –7.7 [95% CI: –22.7, 7.9] hours, p =0.8347).

The results for the secondary clinical efficacy and virologic endpoints were supportive of the results for the primary endpoint. There were clinically meaningful reductions in TTAS and time to resolution of fever in the baloxavir marboxil group compared to the placebo group, and no notable differences in the secondary clinical efficacy endpoints between the baloxavir marboxil and oseltamivir groups. The median time to cessation of viral shedding, as determined by virus titer, showed a clear reduction in the baloxavir marboxil group compared with the placebo group (median difference of –48.0 hours, p <0.0001) and also when compared to the oseltamivir group (median difference of –48.0 hours, p <0.0001).

Baloxavir marboxil was well tolerated in patients at high risk of influenza-related complications. Two deaths were reported in the study, one in the oseltamivir group due to a SAE of pneumonia unrelated to study treatment (0.1%) and one in the baloxavir marboxil group due to acute myocardial infarction that developed on Day 1 prior to receiving study treatment (0.1%). SAEs (0.7% to 1.2%) and AEs leading to withdrawal from treatment (0.6% to 0.7%) were reported by similar proportions of patients in all groups. All SAEs in the baloxavir marboxil group were considered to be unrelated to treatment. Approximately 25% of patients experienced at least one AE in the baloxavir marboxil group compared with 30% and 28% of patients in the placebo and oseltamivir groups, respectively. The relatively common AEs (incidence 2% or greater) in any of the groups were bronchitis, sinusitis, diarrhea, and nausea; however, the incidence of each AE in the baloxavir marboxil group was lower than or equal to that in the placebo and oseltamivir groups.

1.2.4 *Post-Marketing Safety Data*

Hypersensitivity reactions have been observed in the postmarketing setting which include reports of anaphylaxis/anaphylactic reactions and less severe forms of hypersensitivity reactions including angioedema and urticarial.

Refer to Section 6 *of* the Baloxavir Marboxil Investigator's Brochure for *current* details *related* to *post-marketing safety information.*

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Influenza virus infection can lead to severe outcomes in patients with underlying medical comorbidities or in other vulnerable groups at risk of complications. For example, influenza predisposes individuals to secondary bacterial infection, which may progress in severity leading to poor prognosis (Rothberg and Haessler 2010). Other serious complications can also develop, including cardiac and neurological complications.

There are no approved drugs licensed for the treatment of patients hospitalized with influenza; however, treatment guidelines endorse the use of NAIs, such as oseltamivir, in the hospitalized population (Harper et al. 2009; CDC 2018). Baloxavir marboxil appears to have significant virological efficacy, offering the potential to treat influenza in the hospitalized population more effectively than currently available treatments.

Preclinical studies of baloxavir marboxil used in combination with NAIs have shown synergistic effects on inhibition of viral replication (Kitano et al. 2017). Baloxavir marboxil in combination with a NAI is expected to produce a greater reduction in viral load than either baloxavir marboxil or a NAI alone.

The results of the clinical studies outlined above have demonstrated clinical efficacy and safety of baloxavir marboxil in the treatment of influenza virus infections in otherwise healthy adult and adolescent patients*, and in adult and adolescent patients at high risk of developing influenza-related complications supporting a positive benefit-risk assessment in both populations. With demonstrated clinical efficacy and well tolerated safety profile,* a placebo-controlled study in combination with a standard-of-care (SOC) NAI to assess the efficacy and safety of baloxavir marboxil in hospitalized patients with influenza is justified to address the high unmet need and burden of disease in this severely ill population.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of baloxavir marboxil in combination with a SOC NAI (i.e., oseltamivir, zanamivir, or peramivir) compared with a matching placebo in combination with a SOC NAI in hospitalized patients with influenza. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

In this protocol, "study treatment" refers to baloxavir marboxil or its matching placebo. Study treatment is given in combination with a SOC NAI.

Table 1 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
• To evaluate the clinical efficacy of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI	• TTCI defined as: – Time to hospital discharge OR – Time to NEWS2 of ≤ 2 maintained for 24 hours
Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the clinical efficacy of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI	**Key Secondary Endpoints:** • Response rates of the 6-point ordinal scale at Day 7 • *Time to clinical response based on temperature ranges, oxygen saturation, respiratory status, heart rate, and hospitalization status* [a] **Other Secondary Endpoints:** • Incidence of mechanical ventilation • Duration of mechanical ventilation • Incidence of ICU stay • Duration of ICU stay • Time to clinical failure, defined as the time to death, mechanical ventilation, or ICU admission, corresponding to ordinal scale categories 6, 5, and 4, respectively, from baseline • Time to hospital discharge • Incidence of post-treatment influenza-related complications [b] • Mortality rate at Day 7 • Mortality rate at Day 28 • Time to NEWS2 of ≤ 2 maintained for 24 hours

Table 1 Objectives and Corresponding Endpoints (cont.)

Virology Objectives	Corresponding Endpoints
• To evaluate the virological activity of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI	• Time to cessation of viral shedding by virus titer • Time to cessation of viral shedding by RT-PCR • Change from baseline in influenza virus titer and in the amount of virus RNA (RT-PCR) at each timepoint • Proportion of patients with positive influenza virus titer and proportion of patients positive by RT-PCR at each timepoint • AUC in virus titer and in the amount of virus RNA (RT-PCR)
• To evaluate the polymorphic and treatment-emergent amino acid substitutions in the *PA*, *PB1*, *PB2,* and *NA* genes and drug susceptibility in patients with evaluable virus	• Polymorphic and treatment-emergent amino acid substitutions in the *PA*, *PB1*, *PB2,* and *NA* genes • Drug susceptibility in patients with evaluable virus
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI in hospitalized patients with influenza	• Compare the incidence and severity of AEs and SAEs • Incidence of AEs leading to discontinuation • Proportion of patients with any post-treatment ALT and AST above baseline and >3 × ULN, >5 × ULN, >10 × ULN
Pharmacokinetic Objective	**Corresponding Endpoints**
• To evaluate the single- and multiple-dose pharmacokinetics of baloxavir	• Plasma concentrations of baloxavir (active metabolite) at specified timepoints • After each dose, concentration at predose and 24 hours postdose will be summarized • Non-compartmental PK parameters such as AUC, C_{max} and $t_{1/2}$ (only for patients undergoing sequential PK sampling)
Exploratory Palatability and Acceptability Objective	***Corresponding Endpoint***
• *To describe the palatability and acceptability of the oral suspension in hospitalized patients with influenza*	• *Number and proportion of patients reporting each palatability and acceptability response at each timepoint*

AE = adverse event; AUC = area under the concentration–time curve; C_{max} = maximum plasma concentration; ICU = intensive care unit; NAI = neuraminidase inhibitor; NEWS2 = National Early Warning Score 2; PK = pharmacokinetic; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SOC = standard-of-care; $t_{1/2}$ = half-life; TTCI = time to clinical improvement; $t_{1/2}$ = half-life; ULN = upper limited normal.

[a] *Criteria for each parameter noted in Section 6.4.2.*

[b] Incidence of post-treatment influenza-related complications as defined in Section 6.4.3.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy, safety, and pharmacokinetics of baloxavir marboxil in combination with a SOC NAI (i.e., oseltamivir, zanamivir, or peramivir), compared with a matching placebo in combination with a SOC NAI in approximately *366* hospitalized adults and adolescent patients (aged ≥12 years) with influenza.

Patients will be randomized as soon as possible after screening *(ideally within 12 hours)*, providing they are within 96 hours of symptom onset and hospitalized (includes assessment in emergency centers pending admission to a hospital ward). Patients will be assigned in a 2:1 ratio to receive baloxavir marboxil or matching placebo. Study treatment must be given in combination with a SOC NAI according to investigator preference (i.e., oseltamivir, zanamivir, or peramivir). Re-screening of patients who fail to meet the inclusion and exclusion criteria will be permitted only once, providing the time from symptom onset to randomization is still within 96 hours.

Baloxavir marboxil will be administered as a weight-based dose (40 mg for patients weighing 40 to <80 kg, 80 mg for patients weighing ≥80 kg) on Days 1 and 4, and also on Day 7 if clinical improvement has not occurred at Day 5, per protocol defined criteria (see Section 4.3.2.1). Treatment with a SOC NAI (i.e., oseltamivir, zanamivir, or peramivir) should be administered in accordance with local clinical practice. To fully explore the utility of the combination with baloxavir marboxil, or matching placebo, the dosing regimen of the SOC NAI should aim to ensure that anti-viral activity is maintained from Day 1 to Day 5. The SOC NAI treatment may be extended to Day 10 or beyond at the discretion of the investigator and in accordance with local clinical practice.

The study consists of two periods: a 10-day treatment period and a 25-day follow-up period. Therefore, the maximum study duration for each patient will be 35 days.

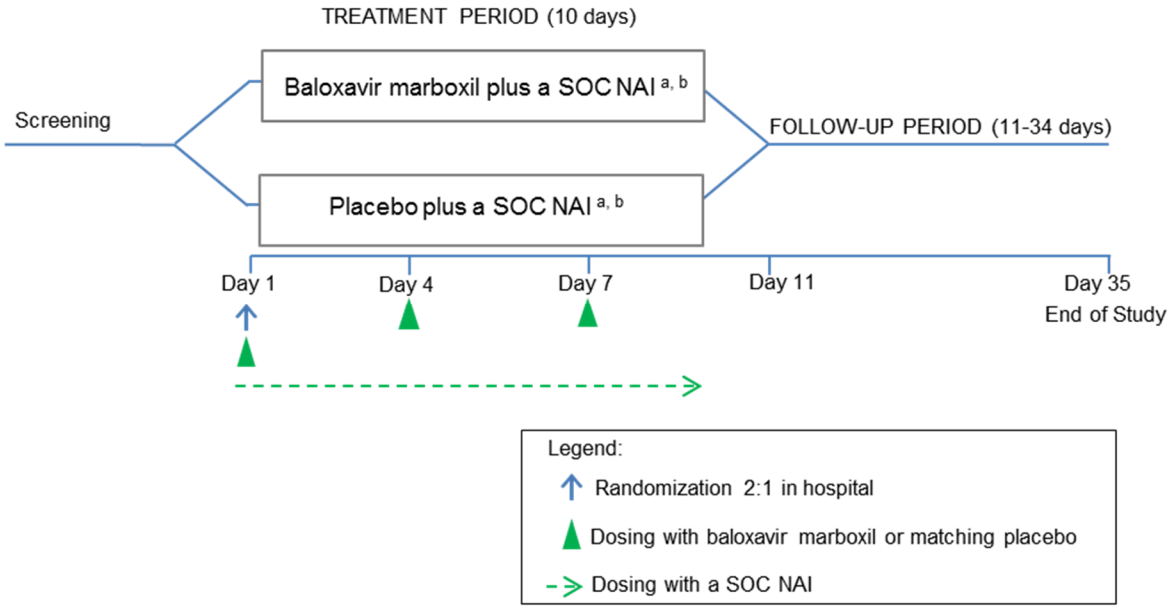
The study assessments to be conducted include the following: physical examination, vital signs, assessment of consciousness, presence or absence of respiratory support, adverse events, concomitant therapies, clinical laboratory tests, nasopharyngeal swabs*, and the palatability and acceptability questionnaire*. Please see Appendix 1 for details concerning the timing of these assessments.

This study will be conducted at approximately *250* global sites in both Northern and Southern hemispheres.

An external independent Data Monitoring Committee (iDMC) will evaluate safety according to policies and procedures detailed in an iDMC Charter.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



NAI = neuraminidase inhibitor; SOC = standard-of-care.

[a] All patients will receive at least two doses of baloxavir marboxil or its matching placebo (i.e., Days 1 and 4). A third dose may also be administered on Day 7 if clinical improvement is not observed at Day 5 according to protocol defined criteria (Section 4.3.2.1).

[b] A SOC NAI should be administered to cover a minimum of treatment exposure from Day 1 to Day 5. This treatment may be extended to Day 10 or beyond, at the discretion of the investigator and in accordance with local clinical practice.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The LPLV is expected to occur 35 days after the last patient is enrolled.

The total length of the study, from screening of the first patient to the LPLV, is expected to be approximately *2.5* years.

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

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Baloxavir Marboxil Dose and Schedule

The safety and efficacy of baloxavir marboxil in otherwise healthy *and high-risk* adult and adolescent patients with influenza virus infection have been demonstrated in

previous studies using baloxavir marboxil tablets (10 mg and 20 mg) dosed at 40 mg and 80 mg according to body weight.

In this study, baloxavir marboxil will be available in two forms. A tablet formulation will be administered to patients who can swallow. Granules for oral suspension formulation will be administered to patients who are intubated and have a nasogastric tube in situ as well as to patients who are unable to swallow tablets for other reasons.

Baloxavir marboxil will be administered as a 40-mg dose in patients weighing 40 to <80 kg or an 80-mg dose in patients weighing ≥ 80 kg. Dosing of baloxavir marboxil will be given, on Day 1 and Day 4 for all patients, with an additional dose on Day 7 in the absence of clinical improvement when assessed on Day 5. Specific criteria for extended dosing to Day 7 include ongoing mechanical ventilation, persistence of fever, severely immunocompromised, *pneumonia, or* confirmed/suspected influenza-related complication.

Seriously ill patients who are hospitalized with influenza demonstrate prolonged viral shedding compared with otherwise healthy patients with influenza (Lee et al. 2009). Therefore, the repeat-dose regimen is to ensure that plasma baloxavir concentrations remain above a target-threshold concentration for a longer duration in severely ill patients owing to the greater potential of a protracted influenza illness.

Administration of up to three doses of baloxavir marboxil separated by 3 days is planned (i.e., Days 1, 4, and 7). The dosing interval of 3 days approximates terminal disposition half-life (~70 hours) of baloxavir, thus higher drug exposure on Day 4 or 7 relative to the first dose is expected, under the assumption of linear pharmacokinetics. Model-based simulation indicates that the population-median accumulation in terms of maximum plasma concentration (C_{max}) and minimum *plasma* concentration (C_{trough}) prior to next dose on Day 7 (third consecutive dose) would be approximately 1.5 and 1.7 times greater than after the first dose, respectively. Based on the worst-case arithmetic mean Bayesian estimate of 126 ng/mL for C_{max} in Phase III (Asian >80 kg), the highest peak plasma concentration after a third consecutive dose (Day 7) is not expected to exceed the peak drug levels observed in Japanese patients receiving 80 mg in the Thorough QT (TQT) study. Likewise, total drug exposure simulated on Day 7 area under the plasma concentration–time curve for a dosing interval (AUC_{tau}) is not expected to exceed area under the concentration–time curve from Time 0 to infinity (AUC_{inf}) of the TQT, regardless of dose. However, for certain individual Asian patients receiving 80 mg, total drug exposure on Day 7 (AUC_{tau}) may approach similar overall exposures as seen in the TQT.

3.3.2 Rationale for Patient Population

The safety and efficacy of baloxavir marboxil has been investigated in otherwise healthy adult and adolescent populations*, and in adult and adolescent patients at high risk of influenza-related complications. Baloxavir marboxil has been approved in several*

countries, including Japan and the United States. Given the significant unmet need in patients hospitalized with *severe* influenza, this study is designed to evaluate the efficacy and safety of baloxavir marboxil in this population.

Baloxavir marboxil has been well tolerated in adults and adolescents in previous studies, with a pharmacokinetic (PK) profile supportive of the inclusion of these age groups in this study. *There are a number of pediatric studies in progress that are designed to* confirm the safety and pharmacokinetics of baloxavir marboxil in otherwise healthy children with influenza aged <12 years. Depending on the outcome of these additional pediatric studies and this current study in hospitalized patients, younger hospitalized patients may be studied in a future protocol.

Morbidity and mortality are particularly high for elderly patients and immunocompromised patients admitted to hospital with influenza. This study will, therefore, include both of these groups, with no upper age limit or restriction on the degree of immunocompromise. Patients with severe renal or severe liver impairment will be excluded based on the current unknown PK profile and tolerability of repeated doses of baloxavir marboxil.

3.3.3 Rationale for Control Group

It is not ethical to withhold active treatment from patients hospitalized with influenza, given the potential severity and poor outcomes in this patient group. NAIs are well-established and well-characterized antiviral agents used as the SOC in many patients hospitalized with influenza and are supported in published guidelines for antiviral treatment of these patients (Harper et al. 2009; Fiore et al. 2011). All patients in this study will receive a SOC NAI treatment (i.e., oseltamivir, zanamivir, or peramivir). In addition, patients will be randomized in a 2:1 ratio to receive baloxavir marboxil or its matching placebo. Therefore, at a minimum, all patients will be treated with a SOC NAI for influenza.

3.3.4 Rationale for Endpoints

There is no validated clinical end-point for assessing improvement in patients hospitalized due to influenza. Consequently, *three* measures of clinical improvement are used in this study: "*time* to clinical improvement" as the primary endpoint*, "response* rates of the 6-point ordinal scale" *and "time* to clinical response" as *key secondary endpoints. The primary and both key secondary endpoints* will be *tested in a hierarchical chain to control the experiment-wise error rate (alpha).*

The primary endpoint for this study will be the time to clinical improvement (TTCI), defined as time to hospital discharge or time to National Early Warning Score 2 (NEWS2) of ≤ 2 maintained for 24 hours, whichever occurs first. This endpoint will provide objective evidence of improvement in a patient's condition, which is likely to be a reasonable surrogate to overall clinical status improvement.

The original NEWS was created in the United Kingdom by the Royal College of Physicians in 2012 to standardize the process of recording, scoring, and responding to changes in routinely measured physiological parameters in acutely ill patients. The score has been widely implemented across the National Health Service in the United Kingdom, and in other healthcare settings across the world. NEWS2 is a similar but updated score (Royal College of Physicians 2017) to incorporate an additional oxygen scale for patients at risk of hypercapnic respiratory failure (target oxygen saturation of 88%–92%, rather than the standard target of ≤96%).

Six physiological parameters are routinely recorded:

- Respiration rate
- Oxygen saturation
- Systolic blood pressure
- Pulse rate
- Level of consciousness and new confusion (ACVPU: A=alert, C=new confusion, V=responsive to voice, P=responsive to pain, U=unconscious)
- Temperature

In addition, a weighting score of 2 is added for patients requiring supplemental oxygen to maintain their prescribed oxygen saturation range.

NEWS2 was developed for patients aged ≥16 years; however, children aged 12–16 years have very similar physiological parameter ranges as adults. In this study, NEWS2 is not being used as an early warning system to identify patients who may need escalating levels of care; rather, it is being used to standardize vital sign collection which will facilitate setting severity levels for inclusion and demonstrating response to treatment. Most pediatric early warning scores are complex and designed to detect critical illness in younger children. For the purposes of this study, a patient achieving a NEWS2 of ≤2 is likely to represent a meaningful degree of clinical improvement (i.e., clinically stable and potentially eligible for discharge). Importantly as well, the method of statistical analysis and the selection of a clinically meaningful difference between treatment groups are possible for an endpoint of this design.

The *first* key secondary endpoint will be the proportion of patients per category in the 6-point ordinal scale at Day 7. The categories within this scale (see Section 4.5.16) reflect the clinical status of patients during their hospital stay. The clinical status should be assessed to reflect the most accurate condition of the patient from a medical perspective, to minimize the effects of administrative or non-medical factors (e.g., the hospital bed availability may lead to patients not being cared for in the ward most suitable for their condition). This endpoint has received considerable interest for use in this patient population. There is as yet no definition of a minimum clinically relevant difference between treatment groups; however, the 6-point ordinal scale will be used in

this study to investigate the change in clinical state of patients as the key secondary endpoint.

The second of the two key secondary endpoints will be "time to clinical response". This endpoint is defined by the time to hospital discharge or the time to vital sign parameter stabilization. Vital sign stabilization is based on achieving a set temperature, combined with achieving a set oxygen saturation, plus two out of three other parameters related to respiratory status, blood pressure or heart rate (see Section 6.5).

This endpoint was defined in a previous intravenous zanamivir or oral oseltamivir clinical study, the largest randomized, double-blind clinical trial of any NAI in hospitalized patients with severe influenza to date (Marty et al. 2017). In the study by Marty et al., the "time to clinical response" (primary endpoint) was not met, and numerical non-significant differences were noted and warrant further investigation.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study aims to enroll approximately *366* adult and adolescent patients. The study is designed to assess the safety and clinical activity of baloxavir marboxil when given in combination with a SOC NAI in patients hospitalized due to severe influenza.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Adult patients: Signed informed consent by any patient capable of giving consent, or, where the patient is not capable of giving consent, by his or her legal/authorized representative
- Adolescent patients not able to legally consent: written informed consent for study participation is obtained from patient's parents or legal guardian, with assent as appropriate by the patient, depending on the patient's level of understanding and capability to provide assent
- Age ≥ 12 years at the time of signing the Informed Consent Form/Assent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Patients who require hospitalization for severe influenza or acquire influenza during hospitalization, the severity of which requires an extension of hospitalization
- Diagnosis of influenza A and/or B by a positive Rapid Influenza Diagnostic Test (RIDT) or reverse transcriptase-polymerase chain reaction (RT-PCR)

  Positive results from local tests are acceptable if conducted within the 24 hours prior to screening.

  A patient with a negative RIDT may be enrolled if influenza is suspected based on local surveillance data or if the patient reports contact with a known case of influenza within the prior 7 days and all other inclusion criteria are met

- The time interval between the onset of symptoms and randomization is within 96 hours

  The onset of symptoms is defined as the time when the patient experiences at least one new general symptom (e.g., headache, feverishness or chills, muscle or joint pain, fatigue), respiratory symptom (e.g., cough, sore throat, nasal congestion), or fever.

- A score of ≥4 based on the NEWS2 (see Appendix 3)
- Patients will require objective criteria of seriousness defined by at least one of the following criteria:
  - Requires ventilation or supplemental oxygen to support respiration
  - Has a complication related to influenza that requires hospitalization (e.g., pneumonia, CNS involvement, myositis, rhabdomyolysis, acute exacerbation of chronic kidney disease, asthma or chronic obstructive pulmonary disease [COPD], severe dehydration, myocarditis, pericarditis, exacerbation of ischemic heart disease)
- For women of childbearing potential: Agreement to remain abstinent (refrain from heterosexual intercourse)*:*

  Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 28 days after the last dose of study treatment. Hormonal contraceptive methods must be supplemented by a barrier method.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

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

- Patients who have received more than 48 hours of antiviral treatment for *the current* influenza *infection* prior to screening
- Patients who have received baloxavir marboxil for the current influenza infection
- Known contraindication to neuraminidase inhibitors
- Patients hospitalized for exclusively social reasons (e.g., lack of caregivers at home)

- Patients expected to die or be discharged within 48 hours, according to the investigator's judgement
- Patients weighing <40 kg
- Patients with known severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2) or receiving continuous renal replacement therapy, hemodialysis, peritoneal dialysis
- Patients with any of the following laboratory abnormalities detected within 24 hours prior to or during screening (according to local laboratory reference ranges:
  - ALT or AST level >5 times the upper limit of normal (ULN)

    OR
  - ALT or AST >3 times the ULN and total bilirubin level >2 times the ULN
- Pregnant or breastfeeding, or positive pregnancy test in a predose examination, or intending to become pregnant during the study or within 28 days after the last dose of study treatment
- Exposure to an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- *Known hypersensitivity to baloxavir marboxil or the drug product excipients*

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Following completion of screening and after all patient eligibility requirements are confirmed, patients will undergo randomization in a 2:1 ratio stratified by three regions (i.e., North America; Europe, Middle East, and Africa [EMEA]; and rest of world [ROW]), NEWS2 score (≤ 7, >7; see Appendix 3), and time from symptom onset to study treatment (≤ 48 hours, >48 hours).

All patients will receive either baloxavir marboxil or its matching placebo.
A permuted-block randomization method will be used to obtain an approximate 2:1 ratio between the active treatment arm and the placebo arm within each stratum. The placebo and active kits are filled and packaged to look identical.

All study site personnel and patients will be blinded to the baloxavir marboxil versus placebo treatment assignment throughout the study; the SOC NAI will be open label. The Sponsor and its agents will also be blinded to the baloxavir marboxil assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their responsibilities during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and iDMC members.

While PK samples must be collected from patients assigned to the comparator placebo arm, PK assay results for these patients are not needed for the safe conduct or proper interpretation of this study. Laboratories responsible for performing study drug PK assays will be unblinded to patients' treatment assignments in order to identify appropriate samples to be analyzed. PK samples from patients assigned to the placebo arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing).

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly (see Section 5.4.1 for contact information). The investigator should document and provide an explanation for any non-emergency unblinding. After discussion and agreement with the Medical Monitor, the investigator will subsequently be allowed to break the treatment code by contacting the IxRS.

In accordance with health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all suspected unexpected serious adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are baloxavir marboxil and its matching placebo as the comparator.

4.3.1 Study Treatment and NAI Formulation, Packaging, and Handling

4.3.1.1 Baloxavir Marboxil and Matching Placebo (Study Treatment)

Baloxavir marboxil and matching placebo will be supplied by the Sponsor as tablets or granules for oral suspension. *In order to maximize the study blind, it is mandated that each site delegates the preparation of baloxavir marboxil and placebo granules to dedicated site personnel that are not involved in any other study related assessments or procedures. The administration of the granule formulation can be performed by study personnel.*

For information on the formulation and handling of baloxavir marboxil and matching placebo, see the pharmacy manual.

4.3.1.2 Standard-of-Care Neuraminidase Inhibitor

For sites where the SOC NAI is oseltamivir, the oseltamivir will be supplied by the Sponsor as capsules or powder for oral suspension. For information on the formulation and handling of oseltamivir, see local prescribing information.

All other SOC NAIs (i.e., zanamivir or peramivir) will be supplied by the study sites and will be reimbursed by the Sponsor. For information on the formulation, packaging, and handling of SOC NAIs, see local prescribing information.

4.3.2 Study Treatment and SOC NAI Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

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

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.1.

4.3.2.1 Baloxavir Marboxil and Matching Placebo (Study treatment)

Baloxavir marboxil or matching placebo will be administered orally according to body weight (40 mg for patients weighing 40 to $<$80 kg; 80 mg for patients weighing $\geq$80 kg) either in tablet form (20-mg tablets) or granules for oral suspension for patients unable to swallow or with a nasogastric tube in situ (e.g., in intubated patients).

Dosing will occur on Day 1 and Day 4, with a further dose at Day 7 for patients who have not improved according to *at least 1 of the following* specific criteria at Day 5*:*

- *O*ngoing mechanical ventilation
- *P*ersistent fever
- *S*everely immunocompromised
- *Pneumonia*
- *Confirmed*/suspected influenza-related complication

4.3.2.2 Standard-of-Care Neuraminidase Inhibitor

In general, choice of dose, regimen, and any period of extended dosing or dose alterations for the SOC NAI (i.e., oseltamivir, zanamivir, or peramivir) should be made in accordance with local clinical practice. However, due to the design of the trial, wherever possible, treatment with the chosen SOC NAI should be sufficient to ensure exposure of active drug such that anti-viral activity is maintained from Day 1 through Day 5. Table 2

provides guidance on the choice of dose and regimen to achieve this goal. If required, the investigator may choose to follow local practice instead of these guidelines. Special attention is required for dosing in patients with renal impairment, as dose adjustment may be needed.

The above recommendation is regardless of whether the patient has already received antiviral treatment within 48 hours prior to screening (i.e., a minimum of 5 days administration of the NAI beginning at Day 1 is recommended).

Table 2 Guidance for Dose and Dosing Regimen for Neuraminidase Inhibitors

NAI	Dose	Regimen	Duration of Dosing from Day 1	Comments
Oseltamivir	75 mg	BID	5 days	
Zanamivir	10 mg	BID	5 days	Lowest age for dosing to be in line with local prescribing information
Peramivir	Adults: 600 mg Adolescents: 10 mg/kg up to, a maximum of 600 mg	QD	5 days	Peramivir dosing regimen has been selected in line with the study conducted in hospitalized patients (deJong et al. 2014) and is, therefore, higher than the generally approved dose in uncomplicated influenza

BID = twice daily; NAI = neuraminidase inhibitor; QD = once daily.

Treatment with all NAIs may be extended to Day 10 or beyond, at the discretion of the investigator and in accordance with local clinical practice. Special attention is required for dosing in patients with renal impairment, as dose adjustment may be needed.

Note: For sites where the SOC NAI is oseltamivir; from the point of randomization, Sponsored-supplied capsules or suspension should be used, *where possible*.

4.3.3 Investigational Medicinal Product Accountability

The IMPs to be used in this study (i.e., baloxavir marboxil and its matching placebo) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied *investigational medicinal product (*IMP*)* is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.4 Continued Access to Baloxavir Marboxil

Currently, the Sponsor does not have any plans to provide the Roche IMP (baloxavir marboxil) or any other study treatments or interventions to patients who have completed the study. The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

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

4.4 CONCOMITANT THERAPY AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

All therapies required for the management of the patient's acute illness are permitted except for those listed below in Section 4.4.3 (Prohibited Therapy).

4.4.2 Cautionary Therapy

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

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Investigational therapy (other than the protocol-mandated study treatment) is prohibited within 5 half-lives or 30 days (whichever is longer) prior to initiation of study treatment and during *the* study
- Approved or experimental influenza treatments other than the protocol-mandated NAIs (i.e., oseltamivir, zanamivir, or peramivir) from the point of randomization
- Concomitant use of herbal therapies is prohibited as their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown

4.5 STUDY ASSESSMENTS

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

Patients will be closely monitored for safety and tolerability throughout the study. Patients' liver function should be assessed prior to each dose of baloxavir marboxil or matching placebo; therefore, dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

At applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional or by staff from study site (if local processes are in place) at the patient's home or another suitable location, to improve access and convenience for patients participating in the study following hospital discharge.

The Sponsor may select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Appendix 1) specifies the assessments that may not be performed by an MN professional.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). If a patient cannot provide consent on his or her own, informed consent by legal/authorized representatives may be obtained only if allowed by and in accordance with local regulations and Independent Review Board (IRB)/Ethics Committee (EC) policies and procedures. If a patient gains the ability to consent on his or her own during the course of the study, he or she must re-consent. For adolescents unable to legally provide consent, written informed consent for participation in the study must be obtained from the child's parent*(s)* or legal guardian *in accordance with local regulations and IRB/EC policies and procedures* before performing any study-related procedures (including screening evaluations). The written Assent Form should also be signed and dated by those children who are considered to have a sufficient level of understanding as well as the capability to provide assent.

Informed Consent Forms (and Assent Forms where appropriate) for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

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

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, home oxygen use, and use of alcohol and drugs of abuse will be recorded at the baseline visit. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Recorded demographic data will include age, sex, and self-reported race/ethnicity.

Race/ethnicity data is to be obtained only if allowed by and in accordance with local regulations. Race/ethnicity data, where collected, will be used as a variable within the PK analysis. In the Phase III study (1601T0831), a difference was observed in the baloxavir plasma concentration 24 hours postdose (C_{24}) measurement when assessed according to reported race (see Baloxavir Marboxil Investigator's Brochure for details).

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

4.5.3 Physical Examinations

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

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

Limited, symptom-directed physical examinations may be performed by an MN professional.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, peripheral oxygen saturation, systolic and diastolic blood pressures, and body temperature. Body temperature should be measured using the same methodology throughout the study.

For patients requiring supplemental oxygen, the oxygen flow rate (L/min) and/or fraction of inspired oxygen (FiO_2) should be recorded.

All of the vital sign parameters should be recorded *together* four times per day for the duration of the hospitalization throughout the treatment period (Day 1/Visit 1 to Day 10*). It is recommended that the collection timepoints for vital signs and assessments (specific to NEWS2, Section 4.5.4) are spread throughout the study day to reflect the patient's condition over the entire study day, where possible. Following hospital discharge during the treatment period (Day 1 to Day 10) these parameters should be recorded once at each return visit to the clinic.* Patients who remain hospitalized during the follow-up period (Day 11+) require daily collection of vital signs for the purpose of the study. During the follow-up period in patients who have been discharged, vital sign measurements and temperature are to be recorded at the investigators' discretion (e.g., if symptoms and signs persist during follow-up). Vital sign measurements may be performed by an MN professional.

4.5.5 Assessments Specific to National Early Warning Score 2

In addition to the vital measurements, the patient's consciousness level and the presence or absence of respiratory support must be recorded. The NEWS2 parameter for respiratory support is the selection of either air or oxygen –"oxygen" can include other forms of ventilation to maintain oxygen saturation (see Appendix 3).

These should be recorded at the same time points as the vital sign measurements (see Section 4.5.4 and Appendix 1).

4.5.6 National Early Warning Score 2

The NEWS2 should be calculated by the site at screening only based upon vital sign values and assessments related to National Early Warning Score 2 (see Section 4.5.5) recorded during the patient assessment. Should these assessments be conducted more than once during the screening period (per site patient care), all data collected closest to but before randomi*zation should be used for the NEWS2 score calculation and assessment of patient eligibility.* See Appendix 3 for calculation instructions.

After screening, the NEWS2 values do not need to be calculated by the site, but will be calculated electronically by the Sponsor based on vital sign parameters and NEWS2-related assessments recorded by the investigator in the appropriate eCRF.

4.5.7 Laboratory and Other Biological Samples

Samples for the following laboratory tests will be sent to local laboratories for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH
- Liver chemistry panel: total bilirubin, ALP, ALT and/or AST

- Pregnancy test
  - All women of childbearing potential will have a pregnancy test at screening *(urine or serum). For those countries under VHP (i.e., Belgium, Czech Republic, Estonia, Finland, France, Germany, Hungary, Romania, Spain, and Sweden), as well as Netherlands, a serum pregnancy test is mandated 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 serum pregnancy test.

The following samples will be sent to the Sponsor or a designee for analysis:

- Plasma samples for PK analysis (see Appendix 2)
- Serum antibody titers for influenza A and B viruses
- Nasopharyngeal swabs for influenza virology tests (i.e., RT-PCR, 50% tissue culture infectious dose [$TCID_{50}$], phenotyping and genotyping according to the resistance analysis plan, drug susceptibility testing) and non-influenza respiratory *bacterial and* virus coinfections panel (only at the screening visit)

Blood and urine sample collection may be performed by an MN professional. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

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

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

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

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

4.5.8 Liver Function Monitoring

Patients should be assessed for liver function prior to each dose of baloxavir marboxil or matching placebo.

On Day 1 and Day 4, the assessment is mandatory. On Day 1, the local laboratory full blood chemistry panel required as part of screening can be used for this assessment or prior blood results if tests conducted within 24 hours prior to screening. On Day 4, the

protocol-required local laboratory blood liver chemistry panel should be used for this assessment.

On Day 7, the local laboratory blood liver chemistry panel and associated review of liver chemistry is only required if the patient will receive baloxavir marboxil or matching placebo on this study day.

Results must be reviewed by the investigator before dose administration. Dosing will occur only if the clinical assessment and local laboratory liver chemistry panel values are acceptable (see Appendix 4).

4.5.9 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1) and may be obtained at unscheduled timepoints.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and, if possible, should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.5.10 Chest X-Rays/CT scan

If a chest X-ray has not been taken within the 24 hours prior to screening, it must be performed on Day 1. If a chest X-ray was performed within 24 hours prior to screening, no additional chest X-ray needs to be performed. If the SOC is a chest CT scan, this can be used as alternative to the chest X-ray.

Chest X-ray/CT scan findings should be recorded on the appropriate eCRF at baseline. If additional chest X-rays/CT scans are taken per local practice, this information should be provided in the CRF.

4.5.11 Rapid Influenza Diagnostic Test

For patients to be eligible for this study, a RIDT or RT-PCR is required to be performed to inform a diagnosis of influenza. A patient with a negative RIDT may be enrolled if influenza is suspected based on local surveillance data or the patient reports contact

with a known case of influenza within the prior 7 days and this is documented; the patient must meet all other inclusion criteria.

The RIDT will be provided by the Sponsor for sites that do not have access to a local RIDT kit or who do not perform RIDT as standard of care. If a site has performed a RIDT or RT-PCR test within the 24 hours prior to screening, the local RIDT or RT-PCR result can be used, and the test result will be entered into the eCRF.

4.5.12 Nasopharyngeal Samples

Nasopharyngeal samples collected from both nostrils will be used for influenza virology tests for all patients and sent to a central laboratory. It may only be possible to access one nostril if a patient has a nasogastric tube in place, in which case sites may collect a sample from one nostril only.

Nasopharyngeal samples should be taken at screening and sent to a central laboratory **in addition** to any local swabs taken for RIDT or RT-PCR used for patient eligibility purposes. Phenotyping and genotyping will be performed according to the resistance analysis plan.

4.5.13 Endotracheal Aspirates

For patients who are intubated, endotracheal aspirates should be taken on the same day as nasopharyngeal samples (see Appendix 1), in accordance with local techniques for endotracheal aspiration. If bronchoalveolar lavage is being performed for reasons not related to the study, samples should also be collected for influenza RT-PCR assessment, if possible, for central laboratory testing.

4.5.14 Meals

Study treatment can be taken with or without food. The time of last food intake prior to each study treatment on Days 1, 4, and 7 (if additional treatment administered on Day 7) as well as the fasting period after each study treatment intake will be recorded in the eCRF.

It is recommended that dairy products and calcium-fortified beverages should not be taken with baloxavir marboxil, where possible. (see Section 4.4.2).

4.5.15 *Palatability and Acceptability Assessment*

Patients that are awake, compos mentis, and take the study treatment (baloxavir marboxil or matching placebo) oral suspension will be asked to assess palatability and acceptability through a questionnaire (Appendix 5). The time of assessment completion should be approximately 1 minute after swallowing the study treatment solution, and before rinsing the mouth, on Day 1 and Day 4 (as well as Day 7 if an additional dose is required).

4.5.16 Ordinal Scale Determination

Assessment of patient status using an ordinal scale will be recorded at baseline on Day 1, and again once daily every morning (between 8 am and 12 pm) while hospitalized. The ordinal scale categories are as follows:

1. Discharged (or "ready for discharge")
2. Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen/non-invasive ventilation
3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen/non-invasive ventilation
4. ICU without mechanical (invasive) ventilation (or "ready for ICU admission")
5. Mechanical (invasive) ventilation
6. Death

Patients who are ready to be discharged (e.g., still hospitalized due to non-medical or administrative reasons) will be assigned an ordinal scale of 1

Patients in non-ICU hospital ward that are eligible for ICU care based on clinical presentation but awaiting ICU care will be assigned an ordinal scale of 4.

Patients in ICU for administrative or non-medical reasons, who are ready for a non-ICU hospital ward, will be assigned an ordinal scale of 2 (if not requiring supplemental oxygen/ non-invasive ventilation) or 3 (requiring supplemental oxygen/ non-invasive ventilation).

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Abnormal liver function test results (please refer to Appendix 4
- *Anaphylaxis or other form of hypersensitivity reaction*
- Pregnancy

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

Patients who discontinue study treatment should be continued in the study and complete all scheduled study assessments/visits per protocol, where possible.

4.6.2 Patient Discontinuation from Study

Patients who discontinue *from the study* will be asked to *complete* a study discontinuation visit. *At study discontinuation, assessments per the end of study (EOS) visit should be conducted.*

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

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

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

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety and efficacy of baloxavir marboxil has been investigated in otherwise healthy adult and adolescent populations as well as adult and adolescent patients at high risk of influenza-related complications. Baloxavir marboxil has been approved in several countries, including Japan and the United States (see Section 1.2). The safety plan for patients in this study is based on clinical experience with baloxavir marboxil in completed and ongoing studies*, as well as analysis of cumulative adverse events reporting from post-marketing surveillance.* Please refer to the Baloxavir Marboxil Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Management of Patients Who Experience Adverse Events

5.1.1.1 Dose Modifications

No dose modification will be permitted during the study.

5.1.1.2 Treatment Interruption

Treatment interruption is not allowed in this study. Study treatment should be discontinued in patients who meet the criteria listed in Section 4.6.1.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see

Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined as follows:

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4, Section 5.5, and Section 5.6. The investigator is also responsible for reporting any occurrence of accidental overdose or medication error (see Section 5.3.5.11).

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

5.3.1 Adverse Event Reporting Period

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

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

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

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

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

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

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

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

5.3.5.4 Abnormal Laboratory Values

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

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

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

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

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

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

5.3.5.5 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.6 Abnormal Liver Function Tests

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

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

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

In addition, liver function abnormalities meeting any of the following criteria need to be managed according to Appendix 4:

- AST or ALT $>5\times$ ULN
- AST or ALT $>3\times$ ULN and total bilirubin $>2\times$ ULN or INR >1.5, if INR is measured
- AST or ALT $>3\times$ ULN with signs and symptoms compatible with hepatitis or hypersensitivity

5.3.5.7 Deaths

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

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

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

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

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of Influenza

Medical occurrences or symptoms of deterioration that are anticipated as part of influenza, such as fluctuations in symptoms, should only be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an

unanticipated worsening of influenza on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of influenza").

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization following initial discharge (i.e., in-patient admission to a hospital) or prolonged hospitalization (i.e., after the current study hospitalization) should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

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

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

The patient has not experienced an adverse event.

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

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours
- Adverse events that would otherwise not require hospitalization

5.3.5.11 Reporting Requirements for Cases of Accidental Overdose or Medication Error

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

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

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

Special situations are not in themselves adverse events but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For baloxavir

marboxil *and matching placebo*, adverse events associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with baloxavir marboxil *and matching placebo*, 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 adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)

- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 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 IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information**:**

PPD 24-Hour Safety Hotline:

- North America: +1 888 483 7729
- EMEA/APAC: +44 (0) 1223 374 240
- Latin America: +55 11 4504 4801

Roche Medical Monitor/ Medical Responsible: [redacted] M.D.

Mobile Telephone No.: [redacted]

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the

electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 28 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, 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 submit a Clinical Trial

Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient 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.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), 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 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a SAE, 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 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to 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 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- Baloxavir Marboxil Investigator's Brochure

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

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

An iDMC will monitor the incidence of the events listed in Section 5.2.3 during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Efficacy analyses will be conducted for the modified intent-to-treat infected (mITTI) population. This is defined as all patients randomized who received at least one dose of study drug and were centrally assessed as RT-PCR positive for influenza at any timepoint, with patients grouped according to the treatment assigned at randomization.

Safety analyses will be conducted for the safety population. This is defined as all patients who received at least one dose of study drug, with patients grouped according to the treatment received.

The analysis will occur at the end of the study (as defined in Section 3.2).

Detailed specifications of the statistical methods will be described in the Statistical Analysis Plan (SAP).

The global population will include all patients enrolled during the global enrollment phase (If patients from China are enrolled, a China subpopulation will include all patients enrolled at National Medical Products Administration [NMPA]-recognized sites). Separate analyses may be performed for the global population and the China subpopulation (see Section 6.8 for information on the China subpopulation analyses).

6.1 DETERMINATION OF SAMPLE SIZE

Two new factors influenced the revised sample size: 1) the revised assumption for the placebo plus NAI control-arm TTCI following blinded data review (Section 6.1.1) and 2) the faster than anticipated enrollment rate. Integration of these two factors informed a sample size readjustment to approximately 366 randomized patients. Assuming that the RT-PCR–positive rate (tested in a central laboratory) will be 75% of the randomized population and a dropout rate of 4%, the modified intent-to-treat (influenza) infected (mITTI) population will be 264 patients (i.e., 176 patients in the baloxavir marboxil group and 88 in the placebo group). The total number of randomized patients may change based on the percentage of patients who are RT-PCR positive during the study.

The total mITTI sample size of 264 patients provides at least 80% power using the Logrank Chi-Square test to detect a 31-hour difference in TTCI between treatment groups under the following assumptions: median TTCI in the placebo plus NAI group is 94 hours, 840 hours follow-up (35 days) using 5% alpha. The minimal detectable difference is expected to be around 23 hours. The alteration of the TTCI in the placebo plus NAI group to 94 hours was selected after consideration of the response rates observed in a blinded review (see Section 6.1.1) of TTCI including data from 127 patients.

The increased sample size has the consequential benefit of a larger population for safety analysis of the combination and multiple dose regimen specifically tested in this study for the severely ill hospitalized patient group.

The study power is calculated based on the primary endpoint incorporating a group sequential design (GSD) using a beta spending function with non-binding rule, to allow for one futility interim, without increasing the overall experiment-wise error rate.

6.1.1 ***Blinded Sample Size Re-Assessment***

The TTCI of 84 hours for the placebo plus NAI arm was selected in the initial study design (i.e., protocol version 1) after consideration of response rates observed in prior hospitalized studies with similar clinical response endpoints (Marty et al. 2017; de Jong et al. 2014).

After the first northern hemisphere flu season recruitment, a blinded evaluation of the protocol defined TTCI for all available data was conducted to improve the accuracy of assumptions of the length of TTCI in the placebo plus NAI group. The pooled median TTCI of this blinded review (94 hours) was selected as the revised assumption for the placebo plus NAI group, which resulted in the adjustment of the study sample size (Section 6.1).

Given the blinded nature of the evaluation, this has no impact on the overall alpha for the study.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who are randomized, who are RT-PCR positive, *who are treated,* and who discontinue or complete the study will be summarized by treatment group. Reasons for premature study withdrawal will be summarized.

Eligibility criteria deviations and other major protocol deviations will be listed and summarized by treatment group.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race, region, NEWS2, RT-PCR status, time from symptom onset to study treatment) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by treatment group. These will be summarized for the modified-ITTI and safety populations.

6.4 EFFICACY ANALYSES

Efficacy analyses will *use the mITTI population, which* include*s* all patients randomized who received at least one dose of study drug with patients grouped according to the

treatment assigned at randomization and are centrally assessed RT-PCR positive for influenza *at any timepoint*.

In addition to the analyses described in Section 6.4.1 and Section 6.4.2, the following analyses will be performed for the primary efficacy endpoint and the key secondary efficacy endpoint*s, as appropriate*. Details of these analyses will be described in the SAP:

- Sensitivity analyses to evaluate the robustness of results to the primary analysis methods (e.g., handling of dropouts)
- *Descriptive subgroup* analyses to evaluate the consistency of results across prespecified subgroups (e.g., based on age, sex, race/ethnicity, stratification factors*, and patients taking anti-influenza drugs prior to enrollment*)

Hypothesis tests will be two-sided at the 5% significance level, unless stated otherwise.

To manage the overall type I error, the endpoints will be tested sequentially. The order of testing will be as follows:

- TTCI
- Response rates of the 6-point ordinal scale at Day 7
- *Time to Clinical Response*

If the primary efficacy analysis hypothesis test result is not statistically significant *(i.e. $p > 0.05$),* the hypothesis below that result in the hierarchical chain will be considered exploratory and no claims of statistical significance will be made. *The same rules apply to the next endpoint in the chain.*

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of baloxavir marboxil plus a SOC NAI, compared with matching placebo plus SOC NAI on the basis of the following endpoint:

- TTCI (defined as time to hospital discharge or time to NEWS2 of ≤ 2 and maintained for 24 hours, whichever comes first)

The median TTCI will be compared between the baloxavir marboxil plus SOC NAI and matching placebo plus SOC NAI arms using the stratified log-rank test within three regions (i.e., North America, EMEA, ROW), NEWS2 (≤ 7, >7), and time from symptom onset to study treatment (≤ 48 hours, >48 hours) included as the stratification factors. The Kaplan-Meier plot, median time to response, 95% CIs, and p-values will be presented.

The log-rank test requires the assumption of proportional hazards to be met. The proportional hazards assumption will be tested graphically using the log cumulative hazard plot by treatment group. The plots for each treatment group will be parallel if the

proportional hazard assumption holds. *Using a Cox model, the slope of a linear regression will also be tested and a plot of scaled Schoenfeld residuals against the Kaplan-Meier estimator investigated.*

Should the proportional hazards assumption be violated, the Gehan-Wilcoxon test will be used to analyze the data *as the logrank test can be under powered in this situation. All investigations will be detailed in the statistical section of the CSR.*

The estimand is the median change in TTCI. This absolute measure will be assessed over the duration of the study (35 days). Intercurrent events are those that occur after treatment initiation and either preclude observation of the variable or affect its interpretation. Intercurrent events will be accounted for through censoring rules. Patients who are lost to follow-up, who do not have a clinical response event, who die or discontinue for any reason prior to achieving a clinical response event will be censored at their last contact date or date of death, whichever is applicable. No dose reductions or treatment cross-overs are anticipated.

As specified in Section 6.4, the primary efficacy analysis population will be the modified-ITTI population, which consists of all patients who were randomized to treatment, received a dose of study drug, and were RT-PCR positive for influenza *at any timepoint*.

A sensitivity analysis will be conducted where patients who are lost to follow-up or who do not have a clinical response event will be assumed to have had an event at 28 days. A sensitivity analysis for *patients* who discontinue for any reason prior to achieving a clinical response event will be performed to investigate potential confounding factors. *A sensitivity analysis, considering death as a competitive event, using a competing risk model will be conducted if there are a sufficient number of deaths or an imbalance between groups in deaths and reason attributed. These and any further sensitivity* analyses will be fully detailed in the SAP.

Missing data handling rules for the components of the NEWS2 score will be specified in the SAP.

6.4.2 Key Secondary Endpoints

6.4.2.1 *6-Point Ordinal Scale Measured at Day 7*

For the key secondary endpoint *of* 6-point ordinal scale *the response rate of the scale will be* measured at Day 7. The 6-point ordinal scale will be analyzed using the Cochran-Mantel-Haenszel test statistic stratified by region (i.e., North America, EMEA, ROW), NEWS2 (≤ 7, >7), and time from symptom onset to study treatment (≤ 48 hours, >48 hours).

For the ordinal endpoint, missing data will be imputed by using the patient's last non-missing score for any patient with a missing response at Day 7. If the patient died

prior to Day 7, the patient will be included in the death category. The proportion of patients with a response in each category will be summarized by treatment group and Cochran-Mantel-Haenszel test statistic result presented.

A sensitivity analysis will be conducted where missing scores at Day 7 will be replaced by the patient's last non-missing score +1 *(i.e., one ordinal category worse)*. If the patient died prior to or on Day 7, the patient will be included in the death category.

6.4.2.2 *Time to Clinical Response*

The additional key secondary endpoint of the "time to clinical response" will be based upon hospital discharge, fever, and oxygen saturation, and two or more of the following: improved respiratory status, heart rate, or systolic blood pressure. The exact criteria for each parameter are as follows:

Temperature:[a]

- ≤36·6°C (≤97·9°F)–axillary, or
- ≤37·2°C (≤99°F)–oral, or
- ≤37·7°C (≤99·9°F)– rectal, core, or tympanic

AND

Oxygen Saturation:[b,c]

- ≥95% (without supplemental oxygen)

AND two of the following three:

Respiratory Status:

- Return to pre-morbid oxygen requirement (patients with chronic oxygen use), OR
- Need for supplemental oxygen (given in any way–ventilator, non-invasive ventilation, facemask, face-tent, or nasal cannula) to no need for supplemental oxygen, OR
- Respiratory rate ≤24 per min (without supplemental oxygen)

Heart Rate:

- ≤100 beats per min

Systolic blood pressure:[d]

- ≥90 mmHg

OR

Hospital Discharge

[a] Without the use of antipyretics within 8 hours.

[b] A patient with a history of chronic hypoxia (without supplemental oxygen) will satisfy the normalization criteria for oxygen saturation if the value (without supplemental oxygen) is $\leq 2\%$ from the patient's historical oxygen saturation before enrollment as documented in the patient's medical records, if available

[c] This requirement is waived for patients with a history of chronic supplemental oxygen requirement who have an oxygen saturation $< 95\%$ with supplemental oxygen documented in the patients' medical records within 12 months of enrollment.

[d] Without inotropic support given within 2 hours of assessment.

For patients who achieve four of the five vital sign resolution criteria above, both the temperature and oxygen saturation response criteria must be maintained for 24 hours for the clinical response endpoint to be met.

Time to clinical response will be analyzed using *similar* method*s* and sensitivity analyses as specified for the primary endpoint. Patients who are lost to follow-up, who do not have a clinical response, or who die will be censored at their last contact date or date of death, whichever is applicable. *Further details on methods and missing data rules will be fully detailed in the SAP.*

6.4.3 Secondary Efficacy Endpoints

The *other* secondary endpoints for this study are as follows:

- The incidence of mechanical ventilation
- Duration of mechanical ventilation
- Incidence of ICU stay
- Duration of ICU stays
- Time to clinical failure (defined as the time to death, mechanical ventilation, or ICU admission, corresponding to ordinal scale categories 6, 5, and 4, respectively, from baseline)
- Time to hospital discharge
- Incidence of influenza-related complications (pneumonia, myositis or rhabdomyolysis, encephalitis or encephalopathy, myocarditis and/or pericarditis, otitis media, sinusitis, exacerbation of COPD/asthma, sepsis, acute lung injury, or acute respiratory distress syndrome)*
- Mortality rate at Day 7
- Mortality rate at Day 28
- Time to NEWS2 of ≤ 2 maintained for 24 hours

* Specific complication eCRF pages with diagnostic criteria for the complications of pneumonia, myositis or rhabdomyolysis, encephalitis or encephalopathy, myocarditis and/or pericarditis, otitis media, sinusitis, exacerbation of COPD/asthma, sepsis, acute lung injury, or acute respiratory distress syndrome will be utilized for these events reported as adverse events after the initiation of study treatment. This data will be subject to a blinded manual medical review of events together with other related eCRF data (e.g., serious adverse event forms as applicable and medical history).

Secondary efficacy *incidence* and rate endpoints will be analyzed using the Cochran-Mantel-Haenszel test statistic stratified by region (North America, EMEA, ROW), NEWS2 (≤7, >7) and time from symptom onset to study treatment (≤48 hours, >48 hours).

Time to event secondary efficacy endpoints will be analyzed using *similar* method*s* as specified for the primary endpoint. Patients who are lost to follow-up, who do not have a response, or who die will be censored at their last contact date or date of death, whichever is applicable.

Mortality rates and duration of ICU stays and ventilation will be analyzed descriptively.

6.4.4 Virology Endpoints

The virology endpoints for this study are as follows:

- Time to cessation of viral shedding by *virus titer and by* RT-PCR

  The time to cessation of viral shedding will be analyzed using *similar methods* as specified for the primary endpoint. Patients who are lost to follow-up, who do not have cessation of viral shedding, or who die will be censored at their last contact date or date of death, whichever is applicable.
- Change from baseline in influenza virus titer and in the amount of virus RNA (RT-PCR) at each timepoint
- Proportion of patients with positive influenza virus titer and proportion of patients positive by RT-PCR at each time point
- Area under the curve (AUC) over time in virus titer and amount of virus RNA (RT-PCR)

For the incidence and rate endpoints, missing data imputations will be specified in the SAP.

For incidence and rate endpoints, the difference in proportions, 95% CIs, and the p-values will be presented.

Continuous endpoints, such as change from baseline endpoints, will be analyzed using an analysis of covariance (ANCOVA) model with region (North America, EMEA, ROW*)*, NEWS2 (≤7, >7), and time from symptom onset to study treatment (≤48 hours, >48 hours) as stratification variables, and the baseline value of the studied measure as a covariate.

The additional virology endpoints are as follows:

- Polymorphic and treatment-emergent amino acid substitutions in the *PA*, *PB1*, *PB2,* and *NA* genes
- Drug susceptibility in patients with evaluable virus

The additional virology endpoints will be summarized descriptively. Further details will be described in a resistance analysis plan.

6.4.5 *Exploratory Palatability and Acceptability Endpoint*

The palatability and acceptability endpoint for patients that receive the study treatment (baloxavir marboxil or matching placebo) oral suspension on Days 1, 4, and 7 (if additional study treatment is administered on Day 7) will be summarized descriptively.

The number and proportion of patients within each response category for the palatability and acceptability questions from the questionnaire (Appendix 5) will be presented for the following:

- *Overall taste on a scale of 1 to 5*
- *Whether the patient would be happy to take the medicine again (yes, no, not sure/no answer)*

No formal statistical analyses will be performed.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

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

Safety will be assessed through descriptive summaries of adverse events, vital sign measurements, and laboratory test results (serum chemistry and hematology including complete blood count with differential and platelet counts).

A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug.

Separate summaries will be generated for serious adverse events, deaths, adverse events leading to discontinuation of study drug, and adverse events of special interest. Adverse events will be summarized by MedDRA term, appropriate thesaurus level, and toxicity grade.

Descriptive summaries of laboratory values at baseline and throughout the study will be tabulated by treatment arm. For selected parameters, changes from baseline and the proportion of patients experiencing clinically significant changes relative to baseline will be summarized by treatment arm.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients who provided at least one measurable postdose concentration at a scheduled visit timepoint. Patients may be excluded from the PK analysis population only if they significantly violate the inclusion or exclusion criteria or deviate significantly from the protocol, or if data are unavailable or incomplete. Decisions on patient exclusion from the PK analysis population will be made prior to database closure by the clinical pharmacologist. Excluded patients will be documented, together with the reason for exclusion.

For all patients, individual baloxavir concentration data will be listed by day and by timepoint postdose. Plasma levels of baloxavir will be summarized (i.e., mean, standard deviation, coefficient of variation, median, minimum, and maximum) by day and timepoint postdose. Individual and mean plasma baloxavir concentrations versus time data will be plotted (i.e., a separate figure panel for each of the three doses). In addition, for patients who provided sparse PK data, the distribution of plasma baloxavir concentrations will also be presented by means of a boxplot (i.e., a separate figure for each dose, X-axis category time postdose).

Non-compartmental PK parameters (e.g., AUC, time to maximum concentration, C_{max}, half-life) will only be derived for patients who underwent the non-sparse (sequential) PK sampling regimen (Appendix 2) and who provided sufficient data to allow estimation of such parameters. *The following non-compartmental PK parameters will be derived for each individual after the first and second dose: $AUC_{0\text{-}72h}$, C_{max}, C_{24}, and terminal half-life (as appropriate for data collected). AUC_{inf} and clearance at steady state will be reported after the first dose, only. Drug accumulation will be assessed based on the AUC0-72h ratio between the second and first baloxavir marboxil dose. Estimates for these parameters will be tabulated and summarized (i.e., mean, standard deviation, coefficient of variation, median, minimum, and maximum). Inter-patient variability will be evaluated based on the summary statistics of the individual PK parameter estimates.*

All tables, listings, and figures derived from PK data (concentrations or parameters) obtained from patients who underwent the sequential PK sampling (Appendix 2) will be presented separately (*i.e.,* not pooled with data from patients who underwent sparse PK *sampling*).

Non-linear mixed effect modelling will be used to characterize the population pharmacokinetics of `baloxavir` in the target population. The population typical PK model parameters (e.g., apparent clearance [CL/F], apparent volume of distribution for the central compartment [Vc/F]), and their covariates will be estimated. Individual PK parameters may also calculated using post hoc Bayesian estimation for each patient, and plotted against significant covariates identified (e.g., body weight, age). The derived PK parameters will be tabulated and summarized (i.e., by mean, standard deviation, coefficient of variation, median, and minimum and maximum). PK exposure and

response (e.g., virus titers) relationships will be explored. *The population PK model outcomes will be reported in a stand-alone report outside of the clinical report.*

Additional PK analyses will be conducted as appropriate.

6.7 INTERIM ANALYSIS

6.7.1 Planned Interim Analysis

After approximately 65% of TTCI events, a formal unblinded non-binding futility interim analysis based on the TTCI will be performed. The futility interim analysis will use a Lan-DeMets Pocock beta spending function. If the hazard ratio seen at the interim is below the calculated futility bound, the trial may be declared futile and recruitment will be stopped.

The futility interim is non-binding on the Sponsor, and any deviation from the iDMC recommendation will be fully documented in the CSR. If the study is stopped for futility, at that point the study results will be reported. Full operating characteristics of the interim analysis will be detailed in the SAP.

The interim analysis will be conducted by an *unblinded* external statistical group *(independent Data Coordinating Centre [iDCC])* and reviewed by the iDMC *(also unblinded), whilst the Sponsor will remain blinded until the end of study.* Interactions between the iDMC*/iDCC* and Sponsor will be carried out as specified in the iDMC Charter.

The iDMC Charter will be updated to document this pre-planned interim analysis and potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for futility *or continue the study*), and the iDMC Charter will also be made available to relevant health authorities.

6.8 CHINA SUBPOPULATION ANALYSES

If patients in China are enrolled, the China subpopulation will include all patients enrolled at *NMPA*-recognized sites. Results from these analyses *may* be summarized in a separate clinical study report.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the *applicable* laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. Food and Drug Administration regulations and applicable local, state, and federal laws. Studies

conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) *and applicable local, regional, and national laws*.

8.2 INFORMED CONSENT

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

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will

be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

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

Approximately *250* sites *globally* in both Northern and Southern hemispheres will participate to enroll approximately *366* patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

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

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

10. REFERENCES

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Appendix 1
Schedule of Activities

		Treatment Period[a]									Follow-Up Period			
Day(s)	D1		D2	D3	D4	D5	D6	D7	D8	D9	D10 (±2 day)[b]	Hosp Day 11+[c]	Discharged D11–30[d]	*EOS D35 (± 3 day)*[d]	Unsched Visit
Visits	Screening[e]	Random/ V1	V2	V3	V4	V5		V6			V7		V8	*V9*	
Administrative Procedures															
Informed consent and assent	x														
Inclusion/Exclusion criteria	x														
Baseline characteristics	x														
Medical history	x														
Concomitant medication monitoring	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Clinical Procedures															
Physical examination[f]	x[f]	x	x	x	x	x	x	x	x	x	x	x	x[g]	x[g]	x[h]
Body weight	x												*x*[g]		
Vital sign measurements[i, j, k]	x	x	x	x	x	x	x	x	x	x	x	x	x[g]	x[g]	x[h]
Assessment of consciousness[i, j, k]	x	x	x	x	x	x	x	x	x	x	x	x	x[g]	x[g]	x[h]
Presence or absence of respiratory support[i, j, k]	x	x	x	x	x	x	x	x	x	x	x	x	x[g]	x[g]	x[h]
Full blood hematology and chemistry[l]	x[m]										x	x[g]	x[g]	x[g]	x[h]
Blood liver chemistry[l]					x[m]			x[m]							
Electrocardiogram[n]	x		x												
Chest X-ray/CT Scan[o]	x	(x)													

Appendix 1
Schedule of Activities (cont.)

		Treatment Period[a]									Follow-Up Period			
Day(s)	D1		D2	D3	D4	D5	D6	D7	D8	D9	D10 (±2 day)[b]	Hosp Day 11+[c]	Discharged D11–30[d]	*EOS D35 (± 3 day)[d]*	Unsched Visit
Visits	Screening[e]	Random/ V1	V2	V3	V4	V5		V6			V7		V8	*V9*	
Nasopharyngeal swabs for local testing (RIDT or RT-PCR)[p]	x														
Nasopharyngeal swabs for central testing (non-influenza respiratory virus coinfections; RT-PCR; titer; phenotyping and genotyping, drug susceptibility test)[q]	x		x	x	x	x		x			x	x [g]	x[g]	x[g]	x[h]
Blood for influenza antibody titer		x												*x*	
Pregnancy test[r]	x													x	x[h]
Adverse events[s]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ordinal scale recording[t]		x	x	x	x	x	x	x	x	x	x	x	x		
Study Drug Administration															
Baloxavir marboxil/placebo[u]		x[m]			x[m]			x[m]							
SOC NAI[v]		x					x								
Meal intake documentation[w]		x			x			x							
Palatability & acceptability assessment[z]		*x*			*x*			*x*							
Pharmacokinetic Assessments															
Plasma PK samples for baloxavir[w, x, y]		x	x		x	x		x				x			

Appendix 1
Schedule of Activities (cont.)

CT = computed tomography; D = day; EOS = end of study; Hosp = Hospitalized; NAI = neuraminidase inhibitor; PK = pharmacokinetics; NEWS2 = National Early Warning Score 2; Random = Randomization; RIDT = Rapid Influenza Diagnostic Test; RT-PCR = reverse transcription polymerase chain reaction; SOC = standard-of-care; Unsched = Unscheduled; V = visit; *VHP = Voluntary Harmonization Procedure.*

a. During the treatment period, Visits 1–7 should be performed for all patients regardless if they remain hospitalized or have been discharged. On non-visit Days 6, 8, and 9, procedures are only to be conducted for patients who remain hospitalized.
b. A visit window of ± 2 days applicable for discharged patients only.
c. Hospitalized Days 11+: procedures are to be conducted for patients who remain hospitalized, only.
d. The follow-up visit, Visit 8, should occur after hospital discharge, but not before Day 11 or within 5 days before the EOS visit. *Visit 8 should occur after Visit 7.* The EOS visit should occur approximately 28 days after the last dose of study drug.
e. Randomization should occur as soon as possible, ideally within 12 hours, after screening.
f. A complete physical examination should be conducted at screening. At post-baseline visits and as clinically indicated, limited, symptom-directed physical examinations should be performed. Examinations should occur on a daily basis during the hospitalization and at each return visit after discharge. See Section 4.5.3 for definitions of complete and limited, symptom-directed physical examinations.
g. Clinical procedures/nasopharyngeal swabs may be undertaken at investigator's discretion if symptoms and signs persist beyond the treatment period or if viral shedding is detected beyond Day 10.
h. Perform assessments at any unscheduled visits based upon the cause of the visit and the investigator's discretion.
i. During the study treatment period (Day 1/Visit 1 to Day 10), *all* vital sign measurements (i.e., respiratory rate, pulse rate, peripheral oxygen saturation, systolic and diastolic blood pressures, and body temperature) and NEWS2-specific assessments (i.e., consciousness and presence or absence of respiratory support) should be recorded *together* four times per day*, and spread throughout the day,* for the duration of the hospitalization and once at each return visit to the clinic following hospital discharge up to Day 10 (Visit 7). During the follow-up period, for patients who remain in hospital, vital sign measurements and NEWS2-specific assessments should be conducted once per day. In patients who have been discharged, vital sign measurements and NEWS2-specific assessments are to be recorded at the investigators' discretion (e.g., if symptoms and signs persist during follow-up).
j. Should be assessed according to NEWS2 parameters (see Appendix 3). Presence or absence of respiratory support per the NEWS2 parameter may be air or oxygen; "oxygen" can include other forms of ventilation to maintain oxygen saturations.
k. The NEWS2 should be calculated by the site at screening only to determine patient eligibility based upon vital sign values and assessments related to National Early Warning Score 2 (see Section 4.5.5) recorded during the patient assessment. *Should these assessments be conducted more than once during the screening period (per site patient care), all data collected closest to but before randomization should be used for the NEWS2 score calculation and assessment of patient eligibility.* See Appendix 3 for calculation instructions.
l. See Section 4.5.7 for tests included in laboratory panels.
m. Local laboratory liver function test results to be reviewed by the investigator before baloxavir marboxil, or its matching placebo, is administered. On Day 1 *and* Day 4*, the assessment is mandatory*. On Day 1, the local laboratory full blood chemistry panel required as part of screening can be used for this assessment or prior blood results if tests conducted within 24 hours prior to screening. On Day 4, the protocol required local laboratory blood liver chemistry panel should be used for this assessment. *On Day 7, the local laboratory blood liver chemistry panel and associated review of liver chemistry is only required* if the patient will *receive baloxavir marboxil or matching placebo on this study day.*

Appendix 1
Schedule of Activities (cont.)

n. This assessment cannot be conducted by a mobile nurse.

o. If a chest X-ray has not been taken within the 24 hours prior to screening, it must be performed on Day 1. If a chest X-ray was performed within 24 hours prior to screening, no additional chest X-ray needs to be performed. If the SOC is a chest CT scan, this can be used as alternative to the chest X-ray. The chest X-ray/CT scan must not be performed any later than Day 1. This assessment cannot not be conducted by a mobile nurse.

p. Nasopharyngeal swabs for RIDTs or RT-PCR: Rapid influenza test or RT-PCR should be performed at screening or conducted within 24 hours prior to screening, and can be undertaken by a local test kit or Sponsor-provided kit.

q. Patients who are intubated will have endotracheal samples (*aspirates*) taken for virological assessment, in addition to two nasopharyngeal swabs at each timepoint, including at the screening visit.

r. All women of childbearing potential will have a pregnancy test at screening *(urine or serum). For those countries under VHP (i.e., Belgium, Czech Republic, Estonia, Finland, France, Germany, Hungary, Romania, Spain, and Sweden), as well as the Netherlands, a serum pregnancy test is mandated at screening.* Urine pregnancy tests (for all women of childbearing potential) will be *performed* at the end of study visit and at unscheduled visits (as required). If a urine *pregnancy* test is positive, a serum pregnancy test must be performed.

s. Adverse events should be recorded on a daily basis during the hospitalization and at each return visit after discharge.

t. Assessment of patient status using the ordinal scale should be recorded at baseline on Day 1/Visit 1 then again daily every morning (between 8 am and 12 pm) for patients who remain hospitalized.

u. Study treatment dosing will occur on Day 1 and Day 4, with a further dose at Day 7 for patients who have not improved at Day 5. Specific criteria must be met for additional dosing at Day 7 include ongoing mechanical ventilation, persistence of fever, severely immunocompromised, confirmed/suspected influenza-related complication, or pneumonia. Study treatment will be given in the hospital setting due to the requirement for pre-dose liver function monitoring. *In order to maximize the study blind, it is mandated that each site delegates the preparation of baloxavir marboxil and placebo granules to dedicated site personnel that are not involved in any other study related assessments or procedures.* Dose administration cannot be conducted by a mobile nurse.

v. The SOC NAI should to be administered to cover the minimum treatment exposure from Day 1 through Day 5*, where possible*. This may be extended to Day 10 or beyond, at the discretion of the investigator and in accordance with clinical practice *(*see Section 4.3.2.2 for further guidance*)*.

w. The time of last food intake prior to dosing with study treatment and the fasting period following study treatment should be recorded on Days 1 and 4, as well as on Day 7 if additional study treatment is administered.

x. Sparse PK samples: See Appendix 2.

y. Sequential PK samples: See Appendix 2. Although sequential PK sampling is optional the protocol aim is to attempt to collect it from a maximum of 12 patients.

z *Palatability and acceptability assessments are to be conducted for patients that take study treatment as an oral suspension, and are awake and compos mentis during administration on Day 1 and Day 4 (as well as Day 7 if an additional dose is required). The time of assessment should be completed approximately 1 minute after swallowing the drug solution, and before rinsing the mouth.*

Appendix 2
Schedule of Pharmacokinetic Samples

Visit	Timepoint	Sample Type
Sparse PK Sampling (all patients)		
Post-randomization/ Visit 1 (Day 1)	0.5–2 hours, 4–6 hours, and 10–12 hours postdose	plasma
Visit 2 (Day 2)	24 (±2) hours postdose	plasma
Visit 4 (Day 4)	**pre-dose** [a]	plasma
Visit 5 (Day 5)	24 (±2) hours postdose	plasma
Visit 6 (Day 7)	**pre-dose** (=72 hours postdose) [b]	plasma
Visit 8 (Days 11–30 or Hospital Day 11+)	Collect one sample during the washout/follow-up period	plasma
Rich (sequential) PK samples (optional in a total of maximum 12 patients)		
Post-randomization/V1 (Day 1)	30 (±15) min, 2 hours (±15 min), 4 hours (±30 min), and 10 (±1) hours postdose	plasma
Visit 2 (Day 2)	24 (±2) hours postdose	plasma
Visit 4 (Day 4)	**pre-dose** [a], 30 (±15) min, 2 hours (±15 min), 4 hours (±30 min), and 10 (±1) hours postdose	plasma
Visit 5 (Day 5)	24 (±2) hours postdose	plasma
Visit 6 (Day 7)	**pre-dose** (=72 hour postdose) [b] and 4 hours (±30 min) [c] postdose	plasma
Day 8	24 (±2) hours postdose [c]	plasma
Visit 8 (Days 11–30 or Hospital Day 11+)	Collect one sample during the washout/follow-up period	plasma

PK = pharmacokinetic.

Note: All PK samples are for determining plasma levels of baloxavir.

[a] Collect sample **immediately prior** ***(within 3 hours)*** **to dosing** on Day 4.

[b] Collect sample **immediately prior** ***(within 3 hours)*** **to dosing** on Day 7. If no dose is given on Day 7, take sample as a 72-hour *(± 3 hours) after Day 4* dose sample.

[c] Collect sample only if a dose is administered on Day 7.

Appendix 3
National Early Warning Score 2 (NEWS2)

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Reference

Royal College of Physicians. National early warning score (NEWS) 2 Standardizing the assessment of acute-illness severity in the NHS. London: RCP, 2017.

At screening, the NEWS2 should be calculated based upon vital sign values recorded during the patient assessment. *Should these vital signs assessments be recorded more than once during the screening period (per site patient care) all data collected closest to but before randomization should be used for the NEWS2 score calculation and assessment of patient eligibility.*

The oxygen saturation should be scored according to either the SpO_2 Scale 1 or 2 presented in the table above. The SpO_2 Scale 2 is for patients with a target oxygen saturation requirement of 88%–92% (e.g., in patients with hypercapnic respiratory failure related to advanced lung diseases, such as chronic obstructive pulmonary disease [COPD]). This should only be used in patients confirmed to have hypercapnic respiratory failure by blood gas analysis on either a prior or their current hospital admission.

The decision to use the SpO_2 Scale 2 should be made by the treating physician and should be recorded in the eCRF. In all other circumstances, the SpO_2 Scale 1 should be used.

Appendix 3
National Early Warnig Score 2 (NEWS2) (cont.)

For physiological parameter “Air or Oxygen?”: Any patients requiring the use of oxygen or other forms of ventilation to maintain oxygen saturations and support respiration should be assigned a score of 2.

The consciousness level should be recorded according to the best clinical condition of the patient during the assessment. Patients who are assessed as “Alert” (A) should be assigned a score of 0. Patients assessed as “New Confusion” (C), “Responsive to Voice” (V), “Responsive to Pain” (P), or “Unconscious” should be assigned a score of 3.

Scores should be assigned for respiratory rate, systolic blood pressure, pulse, and temperature according to the table above.

The NEWS2 should be recorded in the eCRF at the screening visit to ensure patients meet the eligibility criteria. In addition to the total NEWS2, the individual components of the score should also be recorded in the eCRF. Additional NEWS2 values will be calculated electronically throughout the study by the Sponsor based upon entry of vital sign parameters by the investigator in the appropriate eCRF.

Example Case Calculation:

A 82-old lady was admitted to an acute medical unit from a residential care home. Her taken observations and corresponding NEWS2 score are as follows:

Physiological Parameter	Observation	Component Score
Respiratory rate (per min)	26	3
Oxygen saturations (SpO_2 %)	95%	1
Supplemental Oxygen	No	0
Systolic blood pressure (mmHg)	140	0
Pulse Rate (bpm)	109	1
Conscious level	Alert	0
Temperature (^oC)	39	1
	Total NEWS2 Score	**6**

Appendix 4
Management Criteria for Abnormal Liver Function Tests

Management Criteria for Abnormal Liver Function tests have been designed to ensure patient safety and evaluate liver event etiology (see Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, FDA: 2009; available from: https://www.fda.gov/downloads/Guidances/UCM174090.pdf).

Abnormal Liver Chemistry Criteria

The investigator or subinvestigator must review study patient laboratories to identify if any levels meet the following criteria:

- AST or ALT $>5\times$ upper limit of normal (ULN)
- AST or ALT $>3\times$ ULN and total bilirubin (TBL) $>2\times$ ULN or INR >1.5, if INR is measured
- AST or ALT $>3\times$ ULN with signs or symptoms compatible with hepatitis or hypersensitivity (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, eosinophilia [$>5\%$])

Action to be Taken by Investigator

If any abnormal liver chemistry criterion is met, the investigator or subinvestigator must do the following:

- Patients must be instructed to discontinue study medication immediately.
- Following the initial observed elevation, every effort should be made to have the patient return to the clinic within 72 hours (if already discharged from hospital) to repeat liver function chemistries and for further hepatic evaluation.
- Every effort should be made to have the patients monitored 2 to 3 times per week until liver function chemistries (i.e., ALT, AST, ALP, TBL) resolve, stabilize *per investigator judgement*, or return to within the normal range or to baseline levels.
- Consultation with a specialist, such as a hepatologist, and liver imaging (i.e., ultrasound, magnetic resonance imaging [MRI], computerized tomography) should be considered for worsening laboratory values or symptoms.

Appendix 5
Palatability and Acceptability Assessment of Study Drug

Questionnaire A: Adolescent (Age 12 to 15 Years) Palatibility and Acceptability Assessment of Study Treatment Suspension (Baloxavir Marboxil or Placebo)

STUDY CP40617

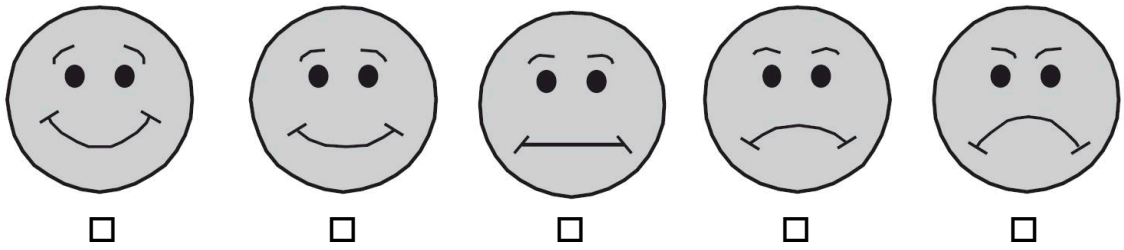
Site Number: ☐☐☐☐☐☐ *Visit Number:* ☐☐

Patient Number: ☐☐☐☐☐ *Date:* ☐☐ ☐☐ ☐☐☐☐
Date *Month* *Year*

Instructions:

- *Questionnaire A is to be utilized for adolescents aged 12–15 years unless they are considered to have a sufficient level of understanding to complete Questionnaire version B (Adolescents 16 years and above and adults).*
- *The questions below are to be completed approximately 1 minute after swallowing the drug solution and before rinsing the mouth.*
- *For Question 1, patients are encouraged to select, from the 5-point visual hedonic scale below, the face that best reflects how much he or she liked the taste of the ingested study drug solution.*
- *This questionnaire can be given to the patient to complete or the form can be completed by study personnel. The patient must provide answers to the questions.*

1. *How was the taste of the medicine?*



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

2. *Would you be happy to take the medicine again?*

☐ *yes*

☐ *no*

☐ *not sure/no answer*

Appendix 5
Palatability and Acceptability Assessment of Study Drug (cont.)

Questionnaire B: Adult and Adolescent (Age 16 Years and Above) Palatability and Acceptability Assessment of Study Treatment Suspension (Baloxavir Marboxil or Placebo)

STUDY CP40617

Site Number: ☐☐☐☐☐☐ *Visit Number:* ☐☐

Patient Number: ☐☐☐☐☐ *Date:* ☐☐ ☐☐ ☐☐☐☐
Date *Month* *Year*

Instructions:

- *Questionnaire B is to be utilized for adults and adolescents (age 16 years and above).*
- *The questions below are to be completed approximately 1 minute after swallowing the drug solution and before rinsing the mouth.*
- *This questionnaire can be given to the patient to complete or the form can be completed by study personnel. The patient must provide answers to the questions.*

1. *How would you rate the overall taste of the medicine at this moment? Please tick a box between 1 (very pleasant) and 5 (very unpleasant).*

☐	☐	☐	☐	☐
1 (very pleasant)	*2*	*3*	*4*	*5 (very unpleasant)*

2. *Would you be happy to take the medicine again?*

☐ *yes*

☐ *no*

☐ *not sure/no answer*