

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

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STATISTICAL ANALYSIS PLAN

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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STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

Date and Time(UTC)	Reason for Signing	Name
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STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This Statistical Analysis Plan (SAP) has been amended to incorporate the following changes:

Endpoint	Update
6-Point Ordinal Scale Measured at Day 7	<ul style="list-style-type: none"> • Included clarification of the analysis to be conducted, including details of exploratory analysis • Included sensitivity analysis to add a score of 1 to the last non-missing value (except if last non-missing was death) as per protocol.
ECG	<ul style="list-style-type: none"> • Included Section 4.7.5 to present ECG data.
Urinalysis	<ul style="list-style-type: none"> • Removed urinalysis as this data is not being collected. • Included pregnancy listing.
Definition of immunocompromised patient population	<ul style="list-style-type: none"> • Update to appendix 6 criteria which outlines the criteria used to define the immunocompromised subgroup analysis of the TTCI primary endpoint
Incidence and duration of ICU stay and mechanical ventilation	<ul style="list-style-type: none"> • Included additional analysis to include patients who had incidence of ICU stay/mechanical ventilation prior to randomization and who continued to be in ICU/on mechanical ventilation after receiving first treatment.

Additional minor changes have been made to improve clarity and consistency.

1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for the clinical efficacy, clinical safety and pharmacokinetic (PK) data for Study CP40617, Protocol Version(v) 2.0.

Baloxavir marboxil (also referred to as S-033188, Shionogi Compound Identification Number) is a pro-drug that is converted to an active form (baloxavir, S-033447) in the blood, liver, and small intestine through a metabolic process called hydrolysis.

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

2. STUDY DESIGN

2.1 DESCRIPTION OF THE STUDY

Study CP40617 is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy, safety, and PK 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 approximately 366 hospitalized adults and adolescent patients (aged ≥ 12 years) with influenza.

Patients will be randomized 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).

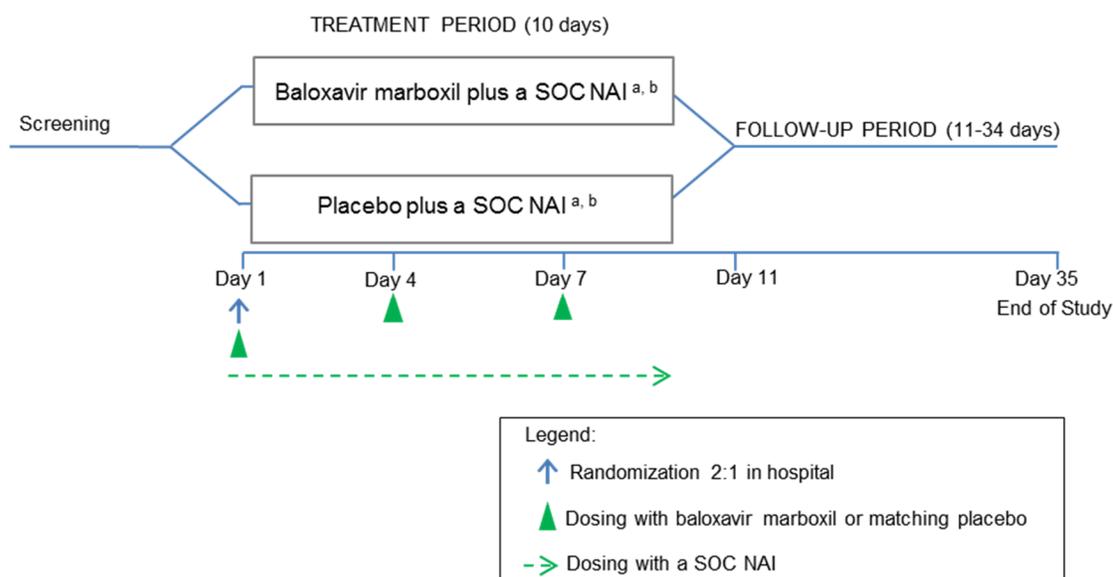
The study consists of two periods: a 10-day treatment period and a 25-day follow-up period. Therefore, the maximum study duration for each patient will be 35 days.

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. Additionally, the iDMC will review the primary efficacy data for futility at time of interim analysis.

[Figure 1](#) presents an overview of the study design. A schedule of activities is provided in [Appendix 2](#) .

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.
- ^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.

2.2 PROTOCOL SYNOPSIS

The Protocol Synopsis is in [Appendix 1](#) and includes the study objectives, inclusion and exclusion criteria, outcome measures, and statistical methods as stated in the Protocol.

2.3 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](#).

Table 1 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
<ul style="list-style-type: none"> To evaluate the clinical efficacy of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI 	<ul style="list-style-type: none"> TTCI defined as: <ul style="list-style-type: none"> Time to hospital discharge OR Time to NEWS2 of ≤ 2 maintained for 24 hours
Efficacy Objectives	Corresponding Endpoints
<ul style="list-style-type: none"> To evaluate the clinical efficacy of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI 	<p>Key Secondary Endpoint:</p> <ul style="list-style-type: none"> 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 <p>Other Secondary Endpoints:</p> <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To evaluate the virological activity of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI 	<ul style="list-style-type: none"> 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)
<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Polymorphic and treatment-emergent amino acid substitutions in the PA, PB1, PB2, and NA genes Drug susceptibility in patients with evaluable virus

Table 1 Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
<ul style="list-style-type: none"> To evaluate the safety of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI in hospitalized patients with influenza 	<ul style="list-style-type: none"> 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 $>3 \times \text{ULN}$, $>5 \times \text{ULN}$, $>10 \times \text{ULN}$
Pharmacokinetic Objective	Corresponding Endpoints
<ul style="list-style-type: none"> To evaluate the single- and multiple-dose pharmacokinetics of baloxavir 	<ul style="list-style-type: none"> 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 Objective	Corresponding Endpoint
<ul style="list-style-type: none"> To evaluate palatability of the oral suspension in hospitalized patients with influenza 	<ul style="list-style-type: none"> 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; TTCl=time to clinical improvement; ULN=upper limited normal.

^a Criteria for each parameter noted in Section 6.4.2 of the Clinical Study Protocol (CSP).

^b Incidence of post-treatment influenza-related complications as defined in Section 6.4.3 of the CSP.

2.4 DETERMINATION OF SAMPLE SIZE

The required sample size of the modified intent-to-treat infected (mITTI) population is 264 patients (176 patients in the baloxavir marboxil group and 88 in the placebo group). It is assumed that the reverse transcriptase polymerase chain reaction (RT-PCR)-positive rate (tested in a central laboratory) will be 75% of the randomized population; hence, approximately 366 patients will be randomized to ensure an adequate number of patients in the mITTI population and to allow for a 4% dropout rate. 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 log-rank Chi-Square test to detect a 31-hour difference in the time to clinical improvement (TTCl) between treatment groups under the following assumptions: median TTCl in the placebo plus NAI group is 94 hours, 840 hours follow-up (35 days), using an alpha of 5%, and the minimal detectable difference is 23 hours. The TTCl in the placebo plus NAI group of 94 hours was selected after consideration of the response rates observed in a blinded review of TTCl including data from 127 patients.

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.

2.5 ANALYSIS TIMING

The primary study analysis will occur when the last patient has either withdrawn or completed Day 35 visit, and will be based on cleaned data for all patients up to and including this point.

2.5.1 Planned Interim Analyses

After approximately 65% of TTCl events, a formal unblinded non-binding futility interim analysis (IA) based on the TTCl will be performed on the mITTI population. Enrollment will continue during the IA conduct.

The IA will be conducted by an unblinded external statistical group (independent Data Coordinating Centre [iDCC]) and reviewed by the iDMC (also unblinded), while 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 details the 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).

The futility interim analysis will use a Lan-DeMets Pocock beta spending function. The TTCl will be compared between treatment groups using a log-rank test adjusting for the stratification factor applied at randomization (i.e. region, National early warning score 2 [NEWS2] score, and time from symptom onset to study treatment), if the assumption of proportional hazards holds.

If the p -values seen at the interim is above the calculated futility bound ($\sim p=0.077$), and the iDMC members agree, based on their expert opinion, that there is no clinically meaningful difference in the TTCl, the trial may be declared futile and recruitment will be stopped. The futility bound will be re-calculated based on the final percentage of events in the IA.

Should the proportional hazards assumption be violated, the Gehan Wilcoxon test will be used to analyze the data. If the p -value is above the calculated futility bound ($\sim p$ -value=0.077) and the iDMC members agree, based on their expert opinion, that there is no clinically meaningful difference in the TTCl, the trial may be declared futile and recruitment will be stopped.

As the interim analysis is non-binding, the iDMC may choose to continue the study despite the futility boundary being crossed if they determine that there appears to be some evidence of a treatment effect from their evaluation of all the available TTCl data.

The expected RT-PCR positive rate of 75% will be continuously monitored prior to the IA to ensure this RT-PCR positive rate assumption is correct. The timing of the IA will be adjusted accordingly.

The futility interim is non-binding on the Sponsor, and any deviation from the iDMC recommendation will be fully documented in the Clinical Study Report (CSR). If the study is stopped for futility, all recorded data up to that point will be reported for inclusion in a full study report.

3. STUDY CONDUCT

3.1 RANDOMIZATION, STRATIFICATION 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), 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 group and the placebo group within each stratum. The placebo and active kits are filled and packaged to look identical.

Patients, investigators, and the Sponsor will be blinded to treatment assignment.

At study completion, stratification variables recorded in the Interactive Voice/Web Response System (IxRS) will be compared to the stratification variables recorded on the electronic Case Report Form (eCRF) to identify any mis-stratifications. These will be listed for all patients. If it is found that $> 10\%$ of mis-stratifications occurred, a sensitivity analysis will be carried out on the primary endpoint, using the eCRF stratification variables in the model.

3.2 SAFETY DATA MONITORING

An iDMC will evaluate safety during the study on a regular basis. All summaries and analyses by treatment group for the iDMC review are prepared by an external iDCC. Members of the iDMC are external to the Sponsor and follow a separate iDMC Charter that outlines their roles and responsibilities. Further details can be found in the iDMC charter.

3.3 DEVIATIONS FROM PROTOCOL

Since the finalization of the Protocol v2.0, the following updates have been made to the planned analysis:

Planned Interim Analysis

The statistic used to determine futility in the planned interim analysis per Protocol v2.0 was the hazard ratio:

- 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.

This has been updated to the p-value, to ensure consistency between the proportional hazards and non-proportional hazards scenarios in the analysis:

- If the p-value seen at the interim is above the calculated futility bound, the trial may be declared futile and recruitment will be stopped.

Clinical Response Definition

Clinical Response is defined per protocol as:

- For patients who achieve four of the five vital sign resolution criteria, both the temperature and oxygen saturation response criteria must be maintained for 24 hours for the clinical response endpoint to be met or hospital discharge, whichever occurs first.

This has been updated to:

- Clinical response is defined as resolution of at least 4 of the 5 vital signs within the respective resolution criteria, maintained for at least 24 hours, or hospital discharge, whichever occurs first.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

4.1.1 ITT Population

The intent-to-treat (ITT) population is defined as all randomized patients, whether or not the patient received the assigned treatment. The ITT patients will be analyzed according to the treatment assigned at randomization.

4.1.2 Modified Intent-to-Treat Infected Population

Efficacy analyses will be conducted for the 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.

4.1.3 Pharmacokinetic Population

The PK population will consist of patients who received any amount of study treatment and who provided at least one measurable post-dose concentration at a scheduled visit

timepoint. Patients may be excluded from the PK population only if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete. Decisions on patient exclusion from the PK population will be made prior to database closure by the clinical pharmacologist. Excluded patients will be documented, together with the reason for exclusion.

4.1.4 Sparse Pharmacokinetic Population

The sparse PK population comprises all patients in the PK population who did not provide informed consent to intensive PK sampling. Decisions on patient exclusion from the sparse PK population will be made prior to database closure by the clinical pharmacologist. Excluded patients will be documented, together with the reason for exclusion. Patients with a dose modification during the course of the treatment will be fully documented but will not be excluded from the population PK analysis.

4.1.5 Extensive Pharmacokinetic Population

The extensive PK population comprises all patients in the PK population who provided informed consent to intensive PK sampling.

4.1.6 Safety Population

The safety population is defined as patients who received any amount of study treatment. Patients will be analyzed according to the treatment received. Patients who were randomized to the study but who did not receive any study drug will not be included in the safety population.

4.2 ANALYSIS OF STUDY CONDUCT

The number of patients who are randomized (ITT population), who are RT-PCR positive, who are treated (safety population), who are included in the mITT population and who discontinue or complete the study will be summarized by treatment group. Reasons for premature study withdrawal from treatment and from study will be both summarized.

Major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

To descriptively assess the comparability of treatment arms at baseline, summary tables will be produced for both the safety and mITTI population for clinically important baseline demographics and disease characteristics by treatment group.

These summary tables will include number of patients, mean, standard deviation, median, minimum, maximum, first and third quartiles (Q1 and Q3) for continuous demographic/disease characteristics and number and percentage of patients for categorical characteristics.

Demographic and baseline disease characteristics will be summarized as described in the following sections.

4.3.1 Baseline stratification factors

Baseline stratification factors as recorded in the IxRS will be presented as follows:

- NEWS2 (≤ 7 , >7)
- Time from symptom onset to study treatment (≤ 48 hours, >48 hours)
- Regions (i.e., North America; EMEA; and ROW)

4.3.2 Demographics

Frequency tabulations for:

- Age:
 - (<65 , ≥ 65 years)
 - (<80 , ≥ 80 years)
- Sex (male, female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
 - Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Unknown)
 - Region (North America; EMEA; and ROW)
 - Female fertility status (Childbearing Potential, Surgically Sterile, Post-menopausal, Pre-menarchal)
 - Tobacco use history (never, current, previous)
 - Alcohol use history (never, current, previous)
 - Current substance use (yes, no)

will be presented by treatment group.

Descriptive statistics for age and weight will be presented.

4.3.3 Disease Characteristics and Influenza History

- RT-PCR status (positive, negative)
- Influenza Subtype
- Time from symptom onset to study treatment
- Reason for hospitalization (Current Influenza Episode or Other (Prolonged Hospitalization))
- Seriousness criteria:
 - Required ventilation or supplemental oxygen to support respiration at baseline
 - Complication requiring hospitalization

- Complication by body system category (Cardiac, Central Nervous System [CNS], Hepatic, Renal, Respiratory, Gastrointestinal, Metabolic, Musculoskeletal, Other)
- NEWS2 at baseline
- intensive care unit (ICU) status at baseline
- Chronic Hypoxia History (Yes, No, Unknown)
- Co-infections (identified via the non-influenza respiratory bacterial and virus co-infection panel)
- Previous anti-influenza treatments
 - Vaccination history (within last 6 months, within last 12 months)
 - Antiviral treatment within 48 hours prior to screening. Type of antiviral treatment utilized will be presented e.g: Oseltamivir/oseltamivir phosphate, peramivir, zanamivir, Laninamivir, Arbidol, Favipiravir, Amantadine, Rimantadine,
- Ordinal scale at Day 1 (categories 1 – 6, see Section 4.5.2.1)

Medical history data, including surgery and procedures and ongoing baseline conditions will be summarized descriptively by treatment group using the safety population. Additionally, ongoing baseline conditions present in >5% of patients in any treatment arm will be presented. Descriptive summaries of any previous and concomitant treatment will be produced by treatment group for the safety population.

4.4 VISIT WINDOWS

Visit windows will only be applied to scheduled time points for laboratory parameters. This will include full blood hematology and chemistry assessments at Day 1 and Day 10, and blood liver chemistry assessment before dosing with the study treatment on Day 1, Day 4 and Day 7 (if study treatment is planned on Day 7) (Table 2). No other visit windows will be used in the study analysis.

Table 2 Acceptable Time Windows – Laboratory Parameters

Time Point (Scheduled Time Point)	Acceptable Time Window
Visit 1 (Day 1)	pre-dose Day 1
Visit 4 (Day 4)	Between Day 3 and Day 5 as follows: -if patient presents on Day 4 this will be classed as Visit 4; -if patient presents on Day 3 with no Day 4, and no Day 5 this will be classed as Visit 4; -if patient presents on Day 5 with no Day 4, and no Day 3 this will be classed as Visit 4; provided this is the day study treatment was received.
Visit 6 (Day 7)	Between Day 6 and Day 8 as follows: -if patient presents on Day 7 this will be classed as Visit 6; -if patient presents on Day 6 with no Day 7, and no Day 8 this will be classed as Visit 6; -if patient presents on Day 8 with no Day 7, and no Day 6 this will be classed as Visit 6; provided this is the day study treatment was received, per protocol guidance.
Visit 7 (Day 10)	Between Day 8 and Day 12

Measurements collected within the acceptable time window for each scheduled assessment time point, including data obtained at the time of withdrawal, will be used for the analyses at each assessment time point. For all patients with multiple values within a visit window, the value obtained closest to the target time point (Day 1 and Day 10) will be used for the full blood chemistry and haematology evaluations. The value obtained prior to the target time (Day 4 and Day 7) will be used for the pre-study treatment blood liver chemistry. The assessment time point having no measurements within the corresponding acceptable time window will be considered as missing.

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

4.5 EFFICACY ANALYSIS

Efficacy analyses will be conducted for the mITTI population. Hypothesis tests will be two-sided at the 5% significance level, unless stated otherwise.

To manage the overall type I error, the primary and key secondary 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.

4.5.1 **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 based on the following endpoint:

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

TTCI is calculated as per [Table 3](#).

Table 3 TTCI Calculations

TTCI based on	TTCI (hours)
NEWS2 ≤ 2 for 24 hours	date time of initial NEWS2 assessment ≤ 2 - start treatment date time
NEWS2 ≤ 2 prior to discharge*	date time of initial NEWS2 assessment ≤ 2 - start treatment date time
Hospital discharge	date time of hospital discharge - start date time of treatment

*when a patient met the NEWS2 ≤ 2 and was discharged from hospital during the 24 hour period of stability confirmation, the time of achieving TTCI was defined as the initial time at which the NEWS2 ≤ 2 and not the time of hospital discharge.

NEWS2 (National early warning score 2) is the sum of the score of each of the following assessments, as described in [Appendix 4](#): respiration rate (per minute), oxygen saturation (SpO₂%) according to scale 1 or scale 2, supplemental oxygen or room air, systolic blood pressure (mmHg), pulse rate (bpm), consciousness level, temperature (°C).

Missing data for the calculation of the NEWS2 will not be imputed for the following reasons:

1. TTCI endpoint can be met through hospital discharge.
2. The physiological components of the NEWS2 can be highly heterogeneous in the study patient population and therefore the process of imputation would not be relevant.

The 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 score at baseline (≤ 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 is most appropriate when the assumption of proportional hazards is 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. Should the proportional hazards assumption be violated, the Gehan Wilcoxon test will be used to analyze the data.

The estimand is the difference in distributions between baloxavir marboxil plus SOC NAI and matching placebo plus SOC NAI arms in the mTTi for the TTCI using appropriate method, as described above. This absolute measure will be assessed over the duration of the study (35 days). The median TTCI for each treatment group and difference between treatment groups will be presented. Intercurrent events are those that occur after treatment initiation and either preclude observation of the variable or affect its interpretation. Intercurrent events, such as patients who are lost to follow-up, die or discontinue for any reason prior to achieving a clinical improvement or do not have a clinical improvement event, will be accounted for through censoring rules, as described in [Table 4](#) below.

Table 4 TTCI and Censoring

Event	Censor	Date and Time
Clinical improvement (based on NEWS2 \leq 2 for 24 hours)	No	vital signs assessment where NEWS2 \leq 2 at start of 24 hour period
Clinical improvement (based on NEWS2 \leq 2 prior to discharge)	No	first vital signs assessment where NEWS2 \leq 2 prior to discharge
Clinical improvement (based on hospital discharge)		
- hospital discharge and hospital re-admission within 24 hours) and discontinue study on same day	Yes	hospital discharge
- hospital discharge and hospital re-admission within 24 hours) and continue study	Yes	hospital discharge
- hospital discharge against medical advice (i.e. self-discharge)	Yes	hospital discharge
- all other hospital discharge	No	hospital discharge
Death prior to achieving a clinical improvement	Yes	last vital signs assessment prior to death
Discontinuation for any reason prior to achieving a clinical improvement	Yes	last vital signs assessment prior to discontinuation
Lost to follow-up	Yes	last vital signs assessment
No clinical improvement	Yes	last vital signs assessment

TTCI= Time to clinical improvement; NEWS2= National early warning score

4.5.1.1 Sensitivity Analysis

The following sensitivity analyses will be conducted:

1. to examine the effect of subjects who discontinue for any reason prior to achieving a clinical response event
 - patients who are lost to follow-up or who do not have a clinical response event will be censored at 35 days.
 - any imbalance in demographics, disease characteristics and influenza history between treatment arms will be assessed in relation to reasons for discontinuation to identify any confounding factors. Identified confounding factors will be adjusted for in 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 (~10%) or an imbalance between groups in deaths and reason attributed.
2. to examine the effect of artificial support, defined as receiving non-invasive mechanical ventilation, mechanical ventilation, Extracorporeal membrane oxygenation (ECMO) and/or inotropic support
 - patients who met the NEWS2 criteria (≤ 2 for 24 hours) and received artificial support during this time period will be censored at the vital signs assessment where $\text{NEWS2} \leq 2$ at start of 24 hour period.

4.5.2 Key Secondary Efficacy Endpoints

4.5.2.1 6-Point Ordinal Scale Measured at Day 7

For the key secondary endpoint of 6-point ordinal scale, which is recorded after randomization on Day 1, and again once daily every morning (between 8 am and 12 pm) while hospitalized, the response rate of the scale will be measured at Day 7. 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).

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 at baseline (≤ 7 , > 7), and time from symptom onset to study treatment (≤ 48 hours, > 48 hours) for the mITTI population.

For the ordinal endpoint, missing data will be imputed as per the following rules as described in [Table 5](#) below:

Table 5 Ordinal Scale and Missing Data

Event	Imputation Rule
Patient Discontinued or Lost to follow-up (prior to Day 7)	Impute to last ordinal assessment if either 'Discharged' or 'Death' otherwise not imputed
Patient ongoing but Missing Day 7	Impute to the higher scale score of the prior and subsequent assessment

The proportion of patients with a response in each category will be summarized by treatment group and Cochran-Mantel-Haenszel test statistic result presented. Additionally, a stacked bar-chart will present the ordinal scale responses over time by treatment.

An exploratory analysis using an ordinal outcome logistic regression model will be conducted.

4.5.2.2 Sensitivity Analysis

To examine the effect of missing ordinal scale data subjects with a missing score at any timepoint will have that score imputed to last non-missing score +1. The proportion of patients with a response in each category will be summarized by treatment group and Cochran-Mantel-Haenszel test statistic result presented. Additionally, a stacked bar-chart will present the ordinal scale responses over time by treatment.

4.5.2.3 Time to Clinical Response

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 ([Marty et al. 2017](#)). Time to clinical response is defined as the time from start of study treatment until the timepoint where "clinical response", as defined below, is met.

Patient should meet conditions A and B, and (2 of C, D and E) OR F below. For patients who achieve four of the five vital sign resolution criteria above each of these must be maintained for 24 hours for the clinical response endpoint to be met. As for the primary endpoint, missing data will not be imputed.

A. Temperature

$\leq 38.6^{\circ}\text{C}$ ($\leq 101.9^{\circ}\text{F}$) if axillary, or

$\leq 37.2^{\circ}\text{C}$ ($\leq 99^{\circ}\text{F}$) if oral, or

$\leq 37.7^{\circ}\text{C}$ ($\leq 100^{\circ}\text{F}$) if rectal, core, temporal or tympanic

- without use of antipyretics within 8 hours (missing antipyretics will be assumed to have been taken)

B. Oxygen Saturation

$\geq 95\%$ (without supplemental oxygen)*+

*This requirement will be waived for patients with a history of chronic supplemental oxygen requirement who had a baseline oxygen saturation $< 95\%$ with supplemental oxygen, within 12 months of enrolment as documented in the patient's medical records.

+A patient with a history of chronic hypoxia (without supplemental oxygen) can satisfy the normalisation criteria for oxygen saturation if the value (without supplemental oxygen) was $\leq 2\%$ from patient's historical oxygen saturation baseline as recorded within 12 months before enrolment and documented in the patient's medical records.

C Respiratory Status:

- I. Return to pre-morbid oxygen requirement (patients with chronic oxygen use), OR
- II. 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
- III. Respiratory rate ≤ 24 per min (without supplemental oxygen)

D Heart Rate

≤ 100 beats per min

E Systolic blood pressure

≥ 90 mmHg, without inotropic support given within 2 hours of assessment

OR

F Hospital Discharge

TTCR is calculated as per [Table 6](#).

Table 6 TTCR Calculation

TTCR based on	TTCR (hours)
A and B and (2 of C, D and E) met for 24 hours	date time of initial vital signs assessment where 4 out of 5 criteria initially met and subsequently maintained for 24 hours - start treatment date time
A and B and (2 of C, D and E) met prior to discharge*	date time of initial vital signs assessment where 4 out of 5 criteria initially met and subsequently discharged - start treatment date time
Hospital discharge	date time of hospital discharge - start date time of treatment

TTCR=Time to Clinical Response.

*when a patient met vital sign criteria and was discharged from hospital during the 24 hour period of stability confirmation, the time of achieving TTCR was defined as the initial time at which vital signs were resolved and not the time of hospital discharge.

The time to clinical response 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 at baseline (≤ 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 is most appropriate when the assumption of proportional hazards is 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. Should the proportional hazards assumption be violated the Gehan Wilcoxon test will be used to analyze the data.

The estimand is the difference in distributions between baloxavir marboxil plus SOC NAI and matching placebo plus SOC NAI arms in the mITTi for the time to clinical response, using appropriate method, as described above. This absolute measure will be assessed over the duration of the study (35 days). The median TTCR for each treatment group and difference between treatment groups will be presented.

Intercurrent events are those that occur after treatment initiation and either preclude observation of the variable or affect its interpretation. Intercurrent events, such as patients who are lost to follow-up, die or discontinue for any reason prior to achieving a clinical improvement or do not have a clinical improvement event, will be accounted for through censoring rules, as described in [Table 7](#) below.

Table 7 TTCR and Censoring

Event	Censor	Date and Time
Clinical Response (based on vital signs assessments)	No	first vital signs assessment where 4 out of 5 criteria initially met and subsequently maintained for 24 hours period
Clinical Response (based on vital signs criteria met prior to discharge)	No	first vital signs assessment where 4 out of 5 criteria initially met and maintained prior to discharge
Clinical Response (based on hospital discharge)		
- hospital discharge to another hospital (i.e. hospital admission within 24 hours) and discontinue study on same day	Yes	hospital discharge
- hospital discharge to another hospital (i.e. hospital admission within 24 hours) and continue study	Yes	hospital discharge
- hospital discharge against medical advice	Yes	hospital discharge
- all other hospital discharge	No	hospital discharge
Death prior to achieving a clinical response	Yes	last vital signs assessment prior to death
Discontinuation for any reason prior to achieving a clinical response	Yes	last vital signs assessment prior to discontinuation
Lost to follow-up	Yes	last vital signs assessment
No clinical response	Yes	last vital signs assessment

4.5.2.3.1 Sensitivity Analysis

The following sensitivity analyses may be conducted if appropriate based on evaluation of data:

1. To examine the effect of subjects who discontinue for any reason prior to achieving a clinical response event
 - patients who are lost to follow-up or who do not have a clinical response event will be censored at 35 days.
2. To examine the effect of antipyretics on achieving clinical response
 - the restriction of antipyretics use within 8 hours on temperature condition will be removed
3. To examine the effect of inotropic support on achieving clinical response.
 - the restriction of no inotropic support within 2 hours.

4.5.3 Other Secondary Efficacy Endpoints

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

Incidence of mechanical ventilation

Incidence of mechanical ventilation, as defined as being on non-invasive mechanical ventilation, mechanical invasive ventilation or ECMO, will be assessed from the vital signs assessment log where the patients need for mechanical ventilation is documented. It will be assumed, unless the mechanical ventilation status has changed, that the first occurrence is continuous and as such will be counted as one event. This will also be the case for each subsequent event. If there is a missing status, and the prior and subsequent status are the same, it can be assumed this is the one continuous incidence of mechanical ventilation.

The number of incidences of mechanical ventilations between start of treatment and end of study, as well as number and percentage of patients, will be presented.

As an additional analysis, patients whose mechanical ventilation had started before being randomized into the study, who continued to be on mechanical ventilation after receiving first treatment will also be included in the number of incidences of mechanical ventilations. The number and percentage of patients will also be presented.

Duration of mechanical ventilation

Duration of mechanical ventilation, in hours, will be assessed from the vital signs assessment log where the patients need for mechanical ventilation is documented. The duration of mechanical ventilation will be defined as sum of the duration of each mechanical ventilation incidence. The duration of each incidence is defined as the date and time of the first occurrence of mechanical ventilation until the next date and time where the patient mechanical ventilation status has changed on the vital signs log. It will be assumed that, unless the mechanical ventilation status has changed, the first occurrence is continuous and as such will be counted as one event. This will also be the case for each subsequent event. Duration is calculated for events between start of treatment and end of study.

Patients who are on mechanical ventilation at the last vital signs assessment will use the imputation rules defined in [Table 8](#) below for calculation of the duration of last mechanical ventilation incidence. Missing and partial vital dates will be imputed based on available data, following a conservative approach.

Table 8 Duration of Mechanical Ventilation and Missing Data

Event	Imputation Rule
Patient Discontinued or Lost to follow-up	duration of last incidence uses date of discontinuation or date lost to follow up as the end date
Patient died	duration of last incidence uses date of death as the end date

The analysis of duration of mechanical ventilation will be repeated to include patients whose mechanical ventilation had started before being randomized into the study, who continued to be on mechanical ventilation after receiving first treatment. The duration will be calculated as specified above, except it will start from the start date of mechanical ventilation.

Incidence of ICU stay

Incidence of ICU will be assessed from the ICU admissions log. It will be assumed that, unless a discharge date is available, the first ICU admission is continuous and as such will be counted as one event. This will also be the case for each subsequent event. The number of incidences of ICU stay as well as number and percentage of patients with ICU stay, between start of treatment and end of study will be presented.

This analysis will be repeated to include patients who were admitted to ICU prior to randomization in the study, but remained in ICU after first treatment. The number of incidences of ICU stay, and the number and percentage of patients with ICU stay whilst on treatment will be presented.

Duration of ICU stays

Duration of ICU stay will be calculated in hours as the sum of the duration of ICU stay, based on the admission and discharge date and time of the ICU admissions log: (ICU discharge datetime – ICU admission datetime).

Patients who are in ICU until end of study will be censored at last available date and time. Patients who die will be censored at their date of death.

Partial admission and discharge dates and times will be imputed based on available data, following a conservative approach.

This analysis will be repeated to also include patients who were admitted to ICU prior to randomization in the study, but remained in ICU after first treatment.

Time to clinical failure

Time to clinical failure, in hours, is defined as the time from start of treatment to death, mechanical ventilation, or ICU admission, corresponding to ordinal scale categories 6, 5, and 4, respectively.

For patients who are on mechanical ventilation, or in ICU without mechanical (invasive) ventilation at start of treatment the time to clinical failure is calculated as time to worsening condition i.e. for patients with ordinal scale of 4 (ICU admission without mechanical [invasive] ventilation) at start of treatment worsening is defined as a mechanical ventilation or death), for patients with ordinal scale 5 (mechanical ventilation) at start of treatment worsening defined as a death.

Intercurrent events, such as patients who are lost to follow-up, or discontinue for any reason prior to clinical failure or do not have clinical failure, will be accounted for through censoring rules, as described in [Table 9](#) below.

Table 9 Time to Clinical Failure and Censoring

Event	Censor	Date and Time
Clinical Failure (death, mechanical ventilation, or ICU admission)	No	first occurrence of death, mechanical ventilation, or ICU admission post baseline
Death	No	date of death
Discontinuation but subsequently reported death	No	date of death
Discontinuation for any reason prior to having clinical failure	Yes	censored at last vital signs assessment
Lost to follow-up	Yes	last available date
No clinical failure	Yes	last available date

Time to hospital discharge

Time to hospital discharge, in hours, is defined as the time from start of treatment to time of discharge from hospital. Patients who are lost to follow-up, die or discontinue for any reason prior to discharge or who are not discharged will be censored at the time of their last assessment or date of death, whichever is applicable, as per rules presented in [Table 10](#) below.

Table 10 Time to hospital discharge and Censoring

Event	Censor	Date and Time
Hospital discharge	No	hospital discharge
- hospital discharge to another hospital (i.e. hospital admission within 24 hours) and discontinue study on same day	Yes	hospital discharge
- hospital discharge to another hospital (i.e. hospital admission within 24 hours) and continue study	Yes	hospital discharge
- hospital discharge against medical advice (i.e. self-discharge)	Yes	hospital discharge
- all other hospital discharge	No	hospital discharge
Death prior to hospital discharge	Yes	last vital signs assessment prior to death
Discontinuation for any reason prior to hospital discharge	Yes	last vital signs assessment prior to discontinuation
Lost to follow-up	Yes	last vital signs assessment
No hospital discharge	Yes	last vital signs assessment

Incidence of influenza-related complications

Influenza-related complications are recorded on specific complication eCRF pages with diagnostic questions 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. These eCRF pages will be utilized for these specific events when they are reported as adverse events after the initiation of study treatment. This data will be subject to an internal blinded manual medical review of events together with other related eCRF data (e.g. serious adverse event forms as applicable and medical history). The objective of the review is to ensure that sufficient clinical evidence for each individual reported complication event has been provided through the recorded CRF data to support the diagnosis.

The number and percentage of patients, as well as the number of events, will be presented by treatment group as follows:

- all events,
- internally adjudicated events,
- investigator assessed related to influenza events and
- investigator assessed related to influenza and internally adjudicated events will be presented.

The process by which internal adjudication of influenza related complications will be conducted is outlined in a separate charter.

Mortality rate at Day 7

The mortality rate is defined as the number of patients who died on or before Day 7.

If date of death is not recorded for any patient who has died, the last known date where the patient was alive will be used to ascertain if they were alive at Day 7.

Mortality rate at Day 28

The mortality rate is defined as the number of patients who died on or before Day 28.

If date of death is not recorded for any patient who has died, the last known date where the patient was alive will be used to ascertain if they were alive at Day 28.

Time to NEWS2 of ≤ 2 maintained for 24 hours

Time to NEWS2 of ≤ 2 maintained for 24 hours is defined as the time from start of treatment to the point at which NEWS2 assessment score ≤ 2 is reached and must be maintained for 24 hours. Patients who are lost to follow-up, die or discontinue for any reason prior to achieving NEWS2 of ≤ 2 for 24 hours will be censored at the time of their last assessment or date of death, whichever is applicable, as per rules presented in [Table 11](#) below.

Table 11 Time to NEWS2 of ≤ 2 maintained for 24 hours and Censoring

Event	Censor	Date and Time
NEWS2 ≤ 2 for 24 hours	No	vital signs assessment where NEWS2 ≤ 2 at start of 24 hour period
NEWS2 ≤ 2 prior to discharge	No	first vital signs assessment where NEWS2 ≤ 2 prior to discharge
Death prior to achieving NEWS2 ≤ 2 for 24 hours	Yes	last vital signs assessment prior to death
Discontinuation for any reason prior to achieving NEWS2 ≤ 2 for 24 hours	Yes	last vital signs assessment prior to discontinuation
Lost to follow-up	Yes	last vital signs assessment
No NEWS2 ≤ 2 for 24 hours	Yes	last vital signs assessment

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

Time to event secondary efficacy endpoints will be analyzed using the same method and sensitivity analyses (where required) as specified for the primary endpoint (see Section 4.5.1).

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

4.5.4 Subgroup Analyses

The TICI will be compared between the baloxavir marboxil plus SOC NAI and matching placebo plus SOC NAI arms for the following subgroups:

- region
 - North America (United States, Canada);
 - Europe, Middle East, and Africa [EMEA] (Belgium, Bulgaria, Czech Republic, Estonia, France, Germany, Hungary, Israel, Netherlands, Romania, Serbia, Spain, Sweden, Turkey, Ukraine);
 - Rest of world [ROW] (Mexico, Japan, South Korea, Brazil, Argentina, Peru, Australia, New Zealand, Hong Kong, Singapore, China)
- baseline age (<65, ≥65 years)
- baseline age (<80, ≥80 years)
- baseline NEWS2 score (≤7, >7)
- time from symptom onset to study treatment (≤48 hours, >48 hours)
- ICU or mechanical (invasive/non-invasive mechanical or ECMO) intervention at baseline or any point during the study prior to clinical improvement (Yes, No)
- Patients who received anti-influenza drug within 48 hours prior to screening (including Oseltamivir, Zanamivir, Peramivir, Laninamivir, Arbidol, Favipiravir, Amantadine, Rimantadine) (Yes, No)
- On-treatment NAI (Oseltamivir, Zanamivir, Peramivir)
- Immunocompromised patients (Yes, No) – see [Appendix 6](#)
- Patients with ongoing comorbidities at baseline
 - Respiratory comorbidities:
 - Pneumonia (Yes, No). Including any event preferred term with “pneumonia”.
 - Respiratory thoracic and mediastinal disorders System Organ Class and/or pneumonia (Yes/ No)
 - Respiratory influenza complications that required or extended hospitalization, defined as required ventilation or supplemental oxygen and/or complications of ‘respiratory’ class as assessed by the investigator
 - Cardiac comorbidities
 - Cardiac disorders System Organ Class

- Cardiac influenza complications that required or extended hospitalization, defined as complications of ‘Cardiac’ class as assessed by the investigator
- Patients contracting nosocomial influenza (e.g. prolonged hospitalization)
- influenza subtype (A, B) at baseline– will be conducted if >10% patients in B
- virus subtype (H1, H3) at baseline
- presence of co-respiratory infection at baseline (identified via the non-influenza respiratory bacterial and virus co-infection panel) (Yes, No)
- high and low baseline viral titre e.g. 2 groups split at the median
- high and low viral titre AUC e.g. 2 groups split at the median

Subgroups will be analyzed descriptively. The median TTCl for each subgroup and a 95% CI will be presented.

4.6 VIROLOGY ENDPOINTS

The following virology endpoints will be analyzed for the mITTI population:

Time to cessation of viral shedding by virus titer

Time to cessation of viral shedding by virus titer is defined as the time, in hours, between the initiation of study treatment and first time when the influenza virus titer is below the limit of detection (0.75 log₁₀ TCID₅₀/mL) and will be analyzed using similar methods as specified for the primary endpoint (see Section 4.5.1).

Patients who are lost to follow-up, whose virus titers have not reached the limit by the last observation time point, or who die will be censored at their last observation time point or date of death, whichever is applicable, as per Table 12 below.

Table 12 Time to Viral Shedding and Censoring

Event	Censor	Date and Time
Death prior to cessation of viral shedding	Yes	last observation prior to death
Discontinuation for any reason prior to cessation of viral shedding	Yes	last observation prior to discontinuation
Lost to follow-up prior cessation of viral shedding	Yes	last observation
Virus titers have not reached the limit by the last observation time point	Yes	last observation

One day is converted into 24 hours. Patients with a positive virus titer on Day 1 will be included in this analysis.

Time to cessation of viral shedding by RT-PCR

Time to cessation of viral shedding by RT-PCR, in hours, is defined as the time between the initiation of study treatment and first time when the virus RNA by RT-PCR is below the limit of detection (2.05 for flu A and 2.83 for flu B \log_{10} virus particles/mL) and will be analysed using similar methods as specified for the primary endpoint (see Section 4.5.1).

Patients who are lost to follow-up, whose virus titers have not reached the limit by the last observation time point, or who die will be censored at their last observation time point or date of death, whichever is applicable, as per Table 12 above. For the patients with multiple virus types, this endpoint is defined as the time between the initiation of the study treatment and first time when the virus RNA by RT-PCR is below the limit of detection for all virus types. One day is converted into 24 hours.

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

Change from baseline in influenza virus titer at each timepoint

Change from baseline in influenza virus titer (\log_{10} TCID₅₀/mL) is defined as the change from baseline in influenza virus titer on Days 2, 3, 4, 5, 7, and 10 and 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 as a covariate. If influenza virus titer is less than the lower limit of quantification, the virus titer will be imputed as 0.749 (\log_{10} TCID₅₀/mL).

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

Change from baseline in the amount of virus RNA (RT-PCR) at each timepoint

Change from baseline in the amount of virus RNA (unit: \log_{10} virus particles/mL) is defined as the change from baseline in the amount of virus RNA on Days 2, 3, 4, 5, 7, and 10 and will be analyzed using an 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 as a covariate.

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

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

Proportion of patients with positive influenza virus titer

Proportion of patients positive for influenza virus titer will be presented by treatment at each visit and is defined as the percentage of patients whose influenza virus titer is not less than the lower limit of quantification (0.75 \log_{10} TCID₅₀/mL) or positive among those

assessed for influenza virus titer on Days 2, 3, 4, 5, 7, and 10. The Cochran-Mantel-Haenszel test with region (North America, EMEA, ROW), NEWS2 at baseline (≤ 7 , > 7), and time from symptom onset to study treatment (≤ 48 hours, > 48 hours) as stratification variables, and the baseline value as a covariate will be used to compare proportion of patients positive for influenza virus titer between treatments at each scheduled time point.

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

Proportion of patients positive by RT-PCR at each time-point

Proportion of patients positive by RT-PCR will be presented by treatment at each visit is defined as the percentage of patients with detectable virus RNA (2.05 for flu A and 2.83 for flu B log₁₀ virus particles/mL) among those assessed by RT-PCR on Days 2, 3, 4, 5, 7, and 10. The Cochran-Mantel-Haenszel test with region (North America, EMEA, ROW), NEWS2 at baseline (≤ 7 , > 7), and time from symptom onset to study treatment (≤ 48 hours, > 48 hours) as stratification variables, and the baseline value as a covariate will be used to compare proportion of patients positive by RT-PCR between treatments at each scheduled time point.

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

Area under the curve in virus titer

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

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

where t_k (hours) represents the date of the k th viral titer assessment ($k = 0, \dots, K$) and y_k represents the log₁₀ value of the k th viral titer assessment (TCID₅₀/mL). 24-hours of time will be converted into one day. Patients with a positive virus titer on Day 1 will be subjected to this analysis. The lower limit of quantification and lower limit of detection is defined as 0.75 log₁₀ TCID₅₀/mL for flu A and 0.75 log₁₀ TCID₅₀/mL for flu B (TCID₅₀/mL). If a patient is infected with multiple virus types, the sum of those virus titers will be used for analysis.

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

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

where t_k (hours) represents the date of the k^{th} viral titer assessment ($k = 0, \dots, K$) and y_k represents the \log_{10} value of the k^{th} viral titer assessment (TCID₅₀/mL). 24-hours of time will be converted into one day. Patients with a positive virus titer on Day 1 will be subjected to this analysis. The lower limit of quantification and lower limit of detection is defined as $0.75 \log_{10}$ TCID₅₀/mL for flu A and $0.75 \log_{10}$ TCID₅₀/mL for flu B (TCID₅₀/mL). If a patient is infected with multiple virus types, the sum of those virus titers will be used for analysis.

Area under the curve in the amount of virus RNA (RT-PCR)

AUC in virus RNA (RT-PCR) will be presented by treatment group and is defined as AUC of change from baseline in the amount of virus RNA (RT-PCR) from Day 1 to Day 10. AUC is calculated using the trapezoidal method similar to AUC in virus titer.

Patients with a positive RT-PCR result on Day 1 will be subjected to this analysis. The lower limit of quantification is defined as 2.18 for flu A and 2.93 for flu B (\log_{10} virus particles/mL). If a patient is infected with multiple virus types, the sum of those the amount of virus RNA will be used for analysis.

Exposure and virology will be included in the pop PK report.

4.6.1 Exploratory Endpoints

Polymorphic and treatment-emergent amino acid substitutions in the PA, PB1, PB2, and NA genes

Sanger sequencing of PA and NA will be performed for all or neuraminidase treated patients, respectively, and with paired (pre and post dose) samples available, at baseline and at the last evaluable timepoint (last sample with $> 4 \log_{10}$ viral particles/ml). For patients with amino acid substitutions in the PA gene, additional sequencing will be performed for all earlier timepoint samples to evaluate the timepoint of emergence of the amino acid substitution. In addition, sequencing of PB1 and PB2 genes will be performed on samples selected based on the criteria below. The number and proportion of patients with the detected amino acid substitutions will be reported for all investigated genes.

Sequencing of PB1 and PB2 will be done for:

- baseline viruses with reduced susceptibility to baloxavir (fold-change in $EC_{50} > 10$ for type A viruses and > 5 for type B viruses compared to reference virus in phenotypic assay).
- viruses (baseline and last evaluable time-point) without amino acid substitution in PA, but with reduced response to treatment or with virus rebound.

These will be defined according to the following criteria below in [Table 13](#). If an amino acid substitution is detected, an additional intermediate time point sample will be sequenced.

Table 13 PB1 and PB2 Sequencing

	Criteria
1) Subjects who exhibit viral titer rebound:	Viral titer at [(a certain time point) – (just before time point)] \geq 2 x SD value of viral titer of control virus in assay * * [REDACTED]
2) Subjects who continue to shed virus at Day 6 and beyond:	Viral titer (log ₁₀ TCID ₅₀ /mL) at Day 6 and beyond > 1.5
3) Subjects who do not show a reduction in virus titer:	Viral titer (log ₁₀ TCID ₅₀ /mL) at a certain time point: A > 1.5 Viral titer (log ₁₀ TCID ₅₀ /mL) at just before time point: B > 1.5 AND Viral titer (log ₁₀ TCID ₅₀ /mL) at [(a certain time point: A) - (just before time point: B)] \geq 0

Drug susceptibility in patients with evaluable virus

As assessments of the drug susceptibility of the influenza virus, the 50% effective concentration (EC₅₀) of baloxavir or the 50% inhibitory concentration (IC₅₀) of neuraminidase inhibitor # (will be measured by the ViroSpot™ or NA-Star® assay, respectively, using baseline swab samples.

#The neuraminidase inhibitor (oseltamivir acid or zanamivir or peramivir) selected for drug susceptibility testing in the NA-Star® assay will be based on the neuraminidase inhibitor received by the patient on study Day 1

Values (EC₅₀ or IC₅₀) will be compared with values of reference strains and respective ratio (EC₅₀ / EC₅₀ reference or IC₅₀ / IC₅₀ reference) will be reported.

The following influenza virus vaccine strains from 2018-2019 season will be used as reference for the ViroSpot™ assay: A/Michigan/45/2015 (H1N1)pdm09 for A/H1N1 samples, A/Singapore/INFIMH-16-0019/2016 for A/H3N2 samples from Northern hemisphere, A/Switzerland/8060/2017 for A/H3N2 samples from Southern hemisphere, and B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage) and B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage) for influenza type B samples. Mean EC₅₀ value of the two B reference strain EC₅₀ values will be used to calculate EC₅₀ ratio.

Reference viruses used for the NA-Star® assay are A/Puerto Rico/8/34 (H1N1) and B/Lee/1940.

Respiratory coinfections (Biofire)

All baseline samples will be tested for respiratory pathogens using the qualitative PCR-based FDA cleared BioFire FilmArray® Respiratory Panel 2 assay. This assay detects 17 respiratory viral or bacterial pathogens in addition to influenza A and B. Frequency and proportions for each co-infection will be presented.

Influenza antibody titer

A hemagglutination inhibition assay for the detection of influenza virus A and B specific antibodies will be performed from blood samples at baseline and at end of the study and the antibody titer will be determined. The lower limit of quantification is defined as a hemagglutination inhibition titer of 10. Summaries of findings will be presented.

4.6.2 Subgroup Analyses

Subgroup analysis of the following virology endpoints, based on virus type and subtype, will be conducted by treatment group:

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

For the baloxavir treatment group only, an additional subgroup analysis comparing the patients with or without the presence of virus with an I38x substitution will be conducted for the following:

- Time to cessation of viral shedding by RT-PCR
- Time to cessation of viral shedding by virus titer
- Number and % of patients having 2 doses of baloxavir; number of patients having 3 doses of baloxavir

Subgroup analyses will be produced where appropriate and where the number of patients in each subgroup is sufficient.

4.7 SAFETY ANALYSES

The safety analysis population will be used for all safety analyses. Patients will be analyzed according to the treatment they actually received.

4.7.1 Adverse Events

AEs will be classified by system organ class and preferred term using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and adverse event severity will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. Of reported AEs on the eCRF, AEs reported after the initial dose of study drug will be used for safety analyses.

In summaries by SOC and PT, AEs will be sorted by overall decreasing frequency within each SOC and PT.

All Adverse Events

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

All Adverse events will be coded and tabulated by system organ class and/or preferred term. In tabulations, preferred terms and their associated system organ class will be presented in order of descending frequency summed across the treatment arms. Adverse events will also be tabulated by severity and relationship to study medication as indicated by the investigator.

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

- Serious AEs
- AEs leading to withdrawal from study
- AEs leading to death
- AEs leading to a withdrawal of study drug
- AEs occurring in $\geq 5\%$ of patients in at least one treatment group
- AEs occurring in $\geq 1\%$ of patients in at least one treatment group
- AEs by background NAI treatment
- AEs by outcome
- AEs by time of onset
- AEs by CTCAE Grade
- AE related to Study Medication or SOC NAI
- AE related to Study Medication

Adverse Events of Special Interest

All adverse events of special interest (AESI) will be presented by treatment group. AESI include but are not limited to the following:

- Case of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in protocol
- Suspected transmission of an infectious agent by the study drug

Adverse Events by Dosage

Overall summary of adverse event will be presented by baloxavir dosage (2 dose, 3 dose)

4.7.2 Deaths

Details of any deaths will be presented in the form of an individual patient listing, as well as a frequency table by treatment.

4.7.3 Laboratory Data

All laboratory data will be converted to SI units. The International Standard for the Handling and Reporting of Laboratory Data COG 3007 (Version 4.0) will be used to implement reference ranges and marked abnormalities for laboratory data where possible.

For each of the haematological and biochemical test parameters, summary statistics of observed and change from baseline values at Day 10 will be presented by treatment group. Baseline is defined as the last assessment prior to treatment on Day 1.

A listing will present all lab assessments data for patients who had any significant change from baseline.

Summaries of the number of patients by CTC grade at each assessment will also be presented. For laboratory parameters, observations on Day 1 will be classed as baseline.

Additionally, summary statistics of observed and change from baseline values of liver function tests (Total Bilirubin, Alkaline phosphatase [ALP], Alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), which are collected on Day 1, Day 4, Day 7 (if 3rd dose of baloxavir received) and Day 10, will be presented by treatment group for each scheduled time point, as well as box and whisker plots at each time point.

The number and proportion of patients who meet the pre-specified criteria shown in [Table 14](#) will be presented by treatment group during the study.

Table 14 Pre-specified Abnormal Laboratory Criteria

AST (U/L) or ALT (U/L) and Total bilirubin (mg/dL)
AST(U/L) or ALT (U/L) > 3 × ULN
AST(U/L) or ALT (U/L) > 5 × ULN
AST (U/L) or ALT (U/L) > 3 × ULN and Total bilirubin (mg/dL) > 2 × ULN

ALT= Alanine aminotransferase; AST= aspartate aminotransferase; ULN = upper limit of normal.

A listing of all pregnancies will be presented.

4.7.4 Vital Signs

Summary statistics for all observed vital signs (diastolic blood pressures, systolic blood pressures, peripheral oxygen saturation, respiratory rate, pulse rate and body temperature) and the change from baseline to last observation on Day 10, and to patients last observation, will be presented by treatment group.

Baseline is defined as the last assessment prior to treatment.

Additionally, a graphical representation of vital signs data over time will be presented.

4.7.5 ECG

The number and proportion of patients having ECG, as well as the result (Normal, Abnormal, Abnormal, not clinically significant, Abnormal, clinically significant, Unable to evaluate), will be presented by treatment group.

4.7.6 Exposure to Study Medication

The duration of treatment exposure will be summarized with descriptive statistics by treatment group for the safety population.

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

$$\{(final\ dose\ date) - (initial\ dose\ date) + 1\}$$

Compliance will be calculated based on the actual and expected doses, as recorded on the eCRF, as follows:

$$\{(actual\ dose\ of\ treatment / expected\ dose\ of\ treatment)*100\}$$

The treatment compliance rate will be summarized with descriptive statistics by the treatment group for the safety population. The frequency and percentage of patients with compliance <80% and ≥80% will be presented.

The number of patients with a missed or incorrect dose will be presented by treatment group.

In addition, the patients who did not receive the expected dose, together with reason for this, will be listed.

4.7.7 Exposure to SOC NAI Medication

The duration of exposure, number of doses received and compliance with expected dosing will be presented for each SOC NAI of Oseltamivir, Peramivir and Zanamivir.

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

$$\{(final\ NAI\ dose\ date) - (initial\ NAI\ dose\ date) + 1\}$$

Compliance will be calculated based on the actual and expected doses as follows:

$$\{(actual\ treatment\ received / expected\ treatment)*100\}$$

The treatment compliance rate for both treatments will be summarized with descriptive statistics by the treatment group for the safety population. The frequency and percentage of patients with compliance <80% and ≥80% will be presented.

4.8 PHARMACOKINETIC ANALYSES

4.8.1 Standard PK Analyses

The PK population, as described in section 4.1.3, will be used for all analyses.

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 post dose. 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 3) 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_{0-72h} , C_{max} , C24, 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 AUC_{0-72h} 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 3) will be presented separately (i.e., not pooled with data from patients who underwent sparse PK sampling).

4.8.2 Population PK Modelling

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 be 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.

4.9 EXPLORATORY ANALYSES

4.9.1 Palatability and Acceptability

The palatability and acceptability endpoint for patients who receive the study treatment (baloxavir marboxil or matching placebo) as 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.

4.9.2 Adolescent Population

The following endpoints will be presented descriptively, including only patients <18 years of age:

- Time to Clinical Improvement
- Response Rate of 6-point ordinal scale at Day 7
- Time to clinical response
- Time to cessation of viral shedding by virus titer
- Time to cessation of viral shedding by RNA-PCR

4.10 MISSING DATA

In safety analyses, all deaths are included, from all sources, regardless of completeness of death date; patients who died with only a partial death date available will be included.

Partial dates for AEs, concomitant medications, laboratory assessments, and medical history will be imputed following a conservative approach.

In efficacy analyses, missing data will be handled according to rules in [Table 15](#) below:

Table 15 Handling for Missing Data

Endpoint	Imputation Rules
Time to Clinical Improvement (TTCI)	No imputation of missing data in calculation of NEWS2 for the following reasons: TTCI endpoint can be met through hospital discharge. The physiological components of the NEWS2 can be highly heterogeneous in the study patient population and therefore the

Endpoint	Imputation Rules
	<p>process of imputation would not be relevant.</p> <p>Missing data due to death, discontinuation or lost to follow up will be censored based on rules in Table 3.</p>
6-Point Ordinal Scale Measured at Day 7	<p>No imputation of missing data for patients who 'Discontinued' or are 'Lost to follow-up' (prior to Day 7), with the exception of patients whose last assessment was 'Death' or 'Discharge', in which case the last assessment will be used.</p> <p>For patients who are ongoing with missing data at Day 7 this will be imputed to the higher scale score of the prior and subsequent assessment</p>
Time to Clinical Response (TTCR)	<p>No imputation of missing data in calculation of Clinical Response for same reason as TTCl.</p> <p>Missing data due to death, discontinuation or lost to follow up will be censored based on rules in Table 5.</p>
Incidence of Mechanical Ventilation	<p>This will also be the case for each subsequent event. If there is a missing mechanical ventilation status, and the prior and subsequent status are the same, it can be assumed this is the one continuous incidence of mechanical ventilation.</p> <p>Alternatively, these will be counted as separate incidences.</p>
Duration of Mechanical Ventilation	<p>For patient who Discontinued or Lost to follow-up duration of last incidence uses date of discontinuation or date lost to follow up as the end date</p> <p>For patient who died duration of last incidence uses date of death as the end date</p>
Time to clinical failure	There will be no imputation for this endpoint.
Mortality rate at Day 7	If date of death is not recorded for any patient who has died, the last known date where the patient was alive will be used to ascertain if they were alive at Day 7
Mortality rate at Day 28	If date of death is not recorded for any patient who has died, the last known date where the patient was alive will be used to ascertain if they were alive at Day 28
Time to NEWS2 of ≤ 2 maintained for 24 hours	Patients who are lost to follow-up, die or discontinue for any reason prior to achieving NEWS2 of ≤ 2 for 24 hours will be censored at the time of their last assessment or date of death, whichever is applicable, as per rules presented in Table 11

5. REFERENCES

Marty FM, Vidal-Puigserver J, Clark C, et al. Intravenous zanamivir or oral oseltamivir for hospitalised patients with influenza: an international, randomised, double-blind, double-dummy, phase 3 trial. *The Lancet Respiratory Medicine*. 2017;5(2):135-46.

Appendix 1 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

PROTOCOL NUMBER: CP40617

VERSION NUMBER: 2

EUDRACT NUMBER: 2018-001416-30

IND NUMBER: 126653

TEST PRODUCT: Baloxavir marboxil (RO7191686)

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
<ul style="list-style-type: none"> • To evaluate the clinical efficacy of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI 	<ul style="list-style-type: none"> • TTCI defined as: <ul style="list-style-type: none"> – Time to hospital discharge OR – Time to NEWS2 of ≤ 2 maintained for 24 hours
Efficacy Objectives	Corresponding Endpoints
<ul style="list-style-type: none"> • To evaluate the clinical efficacy of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI 	<p>Key Secondary Endpoints:</p> <ul style="list-style-type: none"> • Response rates of the 6-point ordinal scale at Day 7 • <i>Time to clinical response based on temperature ranges, oxygen saturation, respiratory status, heart rate, and hospitalization status^a</i> <p>Other Secondary Endpoints:</p> <ul style="list-style-type: none"> • Incidence of mechanical ventilation • Duration of mechanical ventilation • Incidence of ICU stay

	<ul style="list-style-type: none"> •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
<ul style="list-style-type: none"> •To evaluate the virological activity of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI 	<ul style="list-style-type: none"> •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)
<ul style="list-style-type: none"> •To evaluate the polymorphic and treatment-emergent amino acid substitutions in the <i>PA</i>, <i>PB1</i>, <i>PB2</i>, and <i>NA</i> genes and drug susceptibility in patients with evaluable virus 	<ul style="list-style-type: none"> •Polymorphic and treatment-emergent amino acid substitutions in the <i>PA</i>, <i>PB1</i>, <i>PB2</i>, and <i>NA</i> genes •Drug susceptibility in patients with evaluable virus
Safety Objective (cont.)	Corresponding Endpoints (cont.)
<ul style="list-style-type: none"> •To evaluate the safety of baloxavir marboxil plus a SOC NAI compared with matching placebo plus a SOC NAI in hospitalized patients with influenza 	<ul style="list-style-type: none"> •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 $>3 \times \text{ULN}$, $>5 \times \text{ULN}$, $>10 \times \text{ULN}$
Pharmacokinetic Objective	Corresponding Endpoints
<ul style="list-style-type: none"> •To evaluate the single- and multiple-dose pharmacokinetics of baloxavir 	<ul style="list-style-type: none"> •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
<ul style="list-style-type: none"> • <i>To describe the palatability and acceptability of the oral suspension in hospitalized patients with influenza</i> 	<ul style="list-style-type: none"> • <i>Number and proportion of patients reporting each palatability and acceptability response at each timepoint</i>

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*; TICI = 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 (≥ 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 m²) 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 (*mITTI*) 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 *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 TTCl in the placebo plus NAI group to 94 hours was selected after consideration of the response rates observed in a blinded review of TTCl 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 TTCl events, a formal unblinded non-binding futility interim analysis based on the TTCl 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.

Appendix 2 Schedule of Activities

		Treatment Period ^a										Follow-Up Period			Unsched Visit
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		
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	
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, aa}		
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 ^h
Blood liver chemistry ^l					x ^m				x ^m						
Electrocardiogram ⁿ	x		x												
Chest X-ray/CT Scan ^o	x	(x)													

Appendix 2 Schedule of Activities (cont.)

	Treatment Period ^a											Follow-Up Period			Unscheduled Visit
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		
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 ^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 2 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 Protocol 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 Protocol 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 Protocol 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 Protocol Appendix 3 for calculation instructions.
- l. See Protocol 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 2 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 Protocol 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 Protocol Appendix 3.
- y. Sequential PK samples: See Protocol Appendix 3. 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.
- aa. Bodyweight measurement in the 'Follow-Up Period: Discharged D11-30' column was a medical editing error. Bodyweight is only measured at Screening and not at any other timepoint during the study.

Appendix 3 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 4 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 SpO₂ Scale 1 or 2 presented in the table above. The SpO₂ 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 SpO₂ Scale 2 should be made by the treating physician and should be recorded in the eCRF. In all other circumstances, the SpO₂ Scale 1 should be used.

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 (°C)	39	1
	Total NEWS2 Score	6

Appendix 5 Palatability and Acceptability Assessment of Study Drug Questionnaire

Questionnaire A: Adolescent (Age 12 to 15 Years) 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 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.

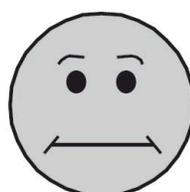
How was the taste of the medicine?



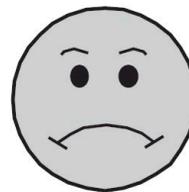
Like very much



Like a little



Not sure



Dislike a little



Dislike very much

Would you be happy to take the medicine again?

yes

no

not sure/no answer

Appendix 5 Palatability and Acceptability Assessment of Study Drug Questionnaire (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

Appendix 6 Immunocompromised Patient Population

An immunocompromised patient population has been previously defined from the Roche NV20234 study evaluating conventional and double dose oseltamivir in the treatment of immunocompromised patients with influenza (ClinicalTrials.gov Identifier: NCT00545532). Similar criteria will be used to define the immunocompromised subgroup analysis of the TICI primary endpoint in the current study, which is detailed below:

1. Primary Immunodeficiency

OR

2. Secondary immunodeficiency, defined as:

- a. Solid Organ Transplant with ongoing immunosuppression* OR
- b. Allogenic haematological stem cell transplant with ongoing immunosuppression* OR
- c. HIV with a most recent CD4 <500/mm³ within the last 6 months (if available) and considered to be immunocompromised in the investigator's opinion OR
- d. Haematological malignancy that is ongoing OR
- e. Investigator confirmed OR
- f. Systemic (e.g., enteric, subcutaneous, intramuscular or intravenous) immunosuppressive therapy*, irrespective of medical indication, that were started at least 12 weeks prior to[#], and ongoing at the first time of study drug.

*Ongoing immunosuppression and immunosuppressive therapy will be assessed via the following drug classes:

- Steroids
- Cytotoxic agents e.g. alkylating agents, anti-metabolites, anti-tumour antibiotics, anti-mitotic agents, molecularly targeted agents
- Proteasome inhibitors
- Calcineurin inhibitors
- mTOR inhibitors
- Immunosuppressive antibodies
- Monoclonal antibodies e.g. inhibitors of pro inflammatory cytokines, T-cell inhibitors, B-cell inhibitors
- Immunosuppressants

[#]If the start date of immunosuppressive therapy is unknown, the medication has been assumed to be greater than 12 weeks prior to study drug. For cyclical immunosuppressive therapy, any treatment course initiated within 12 weeks prior to study drug will also be included.

Clinical Science will complete a manual review of patient level data to ensure that all patients that meet the immunocompromised criteria are included in the characterization of the immunocompromised subgroup.