PROTOCOL

TITLE:	**A PHASE IIIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CLINICAL EFFICACY STUDY OF BALOXAVIR MARBOXIL FOR THE REDUCTION OF DIRECT TRANSMISSION OF INFLUENZA FROM OTHERWISE HEALTHY PATIENTS TO HOUSEHOLD CONTACTS**
PROTOCOL NUMBER:	MV40618
VERSION NUMBER:	4
EUDRACT NUMBER:	2018-004056-37
IND NUMBER:	126653
NCT NUMBER:	*NCT03969212*
TEST PRODUCT:	Baloxavir marboxil (RO7191686)
MEDICAL MONITOR:	[redacted] *B.M., B.Ch.*
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
29-Mar-2022 17:24:41	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
4	See electronic date stamp on title page.
3	10 August 2020
2	11 June 2019
1	14 March 2019

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol MV40618 has been amended to reduce the requirement from 2 or more household contacts (HHCs) to 1 or more HHCs to participate in the entire duration of the study (referred to herein as "full study" HHCs) and who have not received the influenza vaccine within 6 months prior to screening. In addition, index patients (IPs) who are $<$12 years old who have received the oral suspension will be asked to answer a questionnaire regarding the palatability and acceptability of the study drug.

Changes to the protocol along with a rationale for each change are summarized below:

- The name of the Medical Monitor has been changed (title page and Protocol Amendment Acceptance Form).
- The background on clinical experience with baloxavir marboxil (BXM) has been updated to align with the recent data in Baloxavir Marboxil Investigator's Brochure, Version 9 (Sections 1.2.2, 1.2.2.1, 1.2.2.4, and 1.2.2.5). Results of a new pediatric study (1813T0835) and a study (CP40617) in adult patients who are hospitalized with severe influenza have been added.
- The description and background information on the cobas® Liat® system and assay tubes have been updated to remove reference to the use of the single assay cobas Influenza A/B nucleic acid test as this is no longer in production. Sites will only be provided with the combination assay, cobas severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) & Influenza A/B nucleic acid test for use on the cobas Liat System (cobas SARS-CoV-2 & Influenza A/B test) (Sections 1.3, 3.4.6.1, 4.1.1, and 4.5.5.2). The description of the test has been revised to align with the most recent literature (Section 1.3). As a result, Table 1 has been removed and subsequent tables have been re-numbered.
- For completeness, the benefit–risk assessment has been revised to include an assessment of SARS-CoV-2 infection (Section 1.4.2).
- The secondary efficacy objective has been clarified to indicate the transmission of influenza A/B as virological or symptomatic to align with wording in the secondary efficacy endpoints (Section 2.1.2).
- It has been clarified that HHCs bearing an amino acid substitution of isoleucine for another amino acid at position 38 (I38X) or other identified substitution in the polymerase acidic (PA) protein require a matched PA substitution with their IP (Section 2.1.3.1).
- The assessment of infectious viral titer assays has been expanded and will be conducted on samples collected from IPs on Days 0, 3, 5, and 9, and not on Day 0 only (Sections 2.1.3.1, 3.4.6.3, and 4.5.5.3). Such titer samples will be used to maximize the chance of identifying a relationship between viral titer load in IPs and the ability of BXM to prevent transmission to HHCs. No additional samples are required from IPs for this additional testing.

- Clarification has been made that the EQ-5D-5L questionnaire and Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions are to be completed by IPs aged ≥12 years old because the questionnaires are not age appropriate for IPs <12 years old (Sections 2.3.1, 3.1, and 4.5.7, and Appendix 1a).
- A palatability and acceptability endpoint has been added to address a request from the European Medicines Agency's Paediatric Committee to assess the acceptability of the BXM granules for the oral suspension for the treatment of pediatric patients (Section 2.4).

  As a result, the following changes have also been made:

  – A description of the questionnaire has been added (Sections 3.1 and 4.5.8).
  – The questionnaire has been added at the screening study site visit in the schedule of activities for IPs <12 years of age (Appendix 1a).
  – An appendix describing the questionnaire has been added (Appendix 5).
- The number of sites has been updated in the description of the study to reflect the current number of sites participating in the study (Sections 3.1 and 9.5).
- The reduction in the required number of eligible unvaccinated HHCs per household from 2 or more HHCs to 1 or more HHCs has been incorporated to broaden potential households that may be eligible for enrollment (Sections 3.1, 3.3, 3.4.2, 4.1.1, and 4.5.9). The change allows households with two occupants or those households from regions where the number of influenza vaccinations may have increased during the coronavirus disease 2019 (COVID-19) pandemic to participate in the study.
- The total length of the study has been extended from 2.5 years to 3.5 years. Sites recruited fewer patients than expected due to a combination of weak 2020–2021 and 2021–2022 influenza seasons at many sites and the impact of the COVID-19 pandemic (Section 3.2).
- Additional treatment-emergent amino acid substitutions in the polymerase acidic protein that have been associated with reduced susceptibility to BXM for influenza A/H1N1 have been added to align with recent data (Section 3.4.6.4).
- The COVID-19 statistic has been removed as it does not reflect the impact of COVID-19 in 2022 following vaccination programs and the approval of targeted therapeutic agents (Section 3.4.6.7).
- Favipiravir has been added as an exclusion criterion for IPs and HHCs and as a prohibited therapy for IPs and HHCs (Sections 4.1.1, 4.1.2, 4.4.1, and 4.4.2).
- The potential risk factor "m" of the exclusion criterion 2 for IPs has been revised to align with the updated definition of "People at Higher Risk of Flu Complications" provided by the Centers for Disease Control and Prevention (Section 4.1.2).
- The regional stratification has been revised and replaced southern hemisphere with "rest of world" as several new countries, including Mexico and India, are participating in the trial and do not strictly fit into the original three regions for stratification (United States or Europe, Asia, and southern hemisphere). An

adjustment has also been made to the stratification for household size to account for the reduction in the required number of eligible unvaccinated HHCs per household (Section 4.2).

- The responsibilities of the investigator and the role of the Medical Monitor during study conduct have been clarified (Section 4.2).
- Language has been added to indicate that sites can confirm that appropriate temperature conditions have been maintained during investigational medicinal product transit either by time monitoring (shipment arrival date and time) or temperature monitoring (Section 4.3.4).
- Examples have been provided to help determine if a traditional Chinese medicine or other herbal remedies should be prohibited for IPs and HHCs (Sections 4.4.1 and 4.4.2).
- The description of the local analysis of respiratory samples has been updated as the single assay cobas Influenza A/B nucleic acid test is no longer in production and the preferred system for local influenza analysis for respiratory samples will be the cobas SARS-CoV-2 & Influenza A/B test. As both influenza and SARS-CoV-2 results are being generated, sites are expected to supply both results, including when SARS-CoV-2 testing is not mandated by the protocol (Section 4.5.5.2).
- Sequencing to evaluate reduced-susceptibility substitutions, additional genome sequencing (selected sites only), and phenotypic resistance assays for selected samples for central laboratory analysis have been added for IPs on the Day 3 visit to ensure all incidences of reduced susceptibility substitutions and related phenotypic resistance are identified (Section 4.5.5.3, Table 3).
- HHCs will measure their temperature daily at bedtime and any time they feel feverish. It has been clarified that on the Day 9 (end of study) visit, body temperature must be measured during the visit either at the study site or at home as it would not be possible to take the bedtime measurement as HHCs would likely complete the Day 9 (end of study) visit earlier in the day (Section 4.5.6 and Appendix 1b).
- Guidance has been added to clarify that adverse events associated with a special situation that also qualify as adverse events of special interest should be reported within 24 hours (Section 5.3.5.10).
- Language has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1).
- Language regarding investigator reporting of pregnancies has been clarified (Section 5.4.3.2).
- Depending on the exact timing of the group-sequential interim analysis, it has been clarified that other acceptable boundaries may be preferable for efficiency reasons (Section 6.9.2).
- A new section has been added to describe the implementation of a system to manage the quality of the study (Section 9.3).

- Language has been modified to clarify that Roche's global policy on data sharing does not have requirements that must be met before study results can be made available (Section 9.6).
- The name of a Roche policy on data sharing has been corrected (Section 9.6).
- References have been revised based on changes made to the body of the protocol (Section 10).

Additional minor changes have been made to improve clarity and consistency throughout the protocol. Substantive new information appears in italics. The Synopsis and appendices have been updated accordingly.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IIIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CLINICAL EFFICACY STUDY OF BALOXAVIR MARBOXIL FOR THE REDUCTION OF DIRECT TRANSMISSION OF INFLUENZA FROM OTHERWISE HEALTHY PATIENTS TO HOUSEHOLD CONTACTS**
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MEDICAL MONITOR:	[redacted] *B.M., B.Ch.*
SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IIIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CLINICAL EFFICACY STUDY OF BALOXAVIR MARBOXIL FOR THE REDUCTION OF DIRECT TRANSMISSION OF INFLUENZA FROM OTHERWISE HEALTHY PATIENTS TO HOUSEHOLD CONTACTS**
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TEST PRODUCT:	Baloxavir marboxil (RO7191686)
PHASE:	Phase IIIb
INDICATION:	Influenza
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy of a single, oral dose of baloxavir marboxil (BXM) compared with placebo for the reduction of the direct transmission rate of influenza A/B from otherwise healthy (OwH) index patients (IPs) to household contacts (HHCs). Specific objectives and corresponding endpoints for the study are outlined below.

Objectives and their associated Endpoints

Primary Efficacy Objective: To evaluate the efficacy of a single, oral dose of BXM compared with placebo to prevent secondary within-household transmission of influenza A/B.

Primary Efficacy Endpoint

- **Virological transmission by Day 5:** Proportion of HHCs who become PCR (+) [confirmed at central laboratory] for influenza by Day 5 visit, with virus subtype consistent with IP.

Secondary Efficacy Objective: To evaluate the efficacy of a single, oral dose of BXM compared with placebo to prevent *virological or symptomatic* transmission of influenza A/B *and effects* beyond secondary within-household transmission.

Secondary Efficacy Endpoints

- **Symptomatic transmission by Day 5:** Proportion of HHCs who become PCR (+) [confirmed at central laboratory] for influenza by Day 5 visit, with virus subtype consistent with IP, **AND**:
  - For HHC aged ≥ 12 years:
    - Temperature ≥ 38.0°C* and one respiratory symptom, **OR**
    - One respiratory symptom and one general systemic symptom (with or without fever).
  - For HHC aged ≥ 2 to < 12 years:
    - Temperature ≥ 38.0°C* **AND** signs or symptoms of an upper respiratory tract infection.

  - Symptoms must be either new, or have worsened versus baseline in HHC with baseline symptoms due to a preexisting comorbidity.
  - * Temperature obtained from tympanic thermometers provided to households (or exceptionally from other thermometers/locations in case of tympanic thermometer failure for any reason).
- **Virological transmission at the household level by Day 5:** Proportion of households with at least one HHC who meets the primary endpoint.
- **Symptomatic transmission at the household level by Day 5**: Proportion of households with at least one HHC who meets the "Symptomatic transmission by Day 5" endpoint.
- **Virological transmission by Day 9:** Proportion of HHCs who become PCR (+) (confirmed at central laboratory) for influenza by Day 9 visit, with virus subtype consistent with IP, including:
  - (1) all HHC meeting primary endpoint, **AND**
  - (2) all HHC cases detected after Day 5 visit meeting the following criteria:
    - Included HHC case is in a household where another HHC has already met the primary endpoint, **OR**
    - Included HHC case is PCR (+) [confirmed at central laboratory] for influenza bearing *an amino acid substitution of isoleucine for another amino acid at position 38 (I38X) in the polymerase acidic (PA) protein (*PA/I38X substitution*)* (or other identified substitutions).
- **Symptomatic transmission by Day 9:** Proportion of HHCs who meet the "Virological transmission by Day 9" endpoint **AND** are symptomatic per the definition for symptoms in the "Symptomatic transmission by Day 5" endpoint.
- **Any virological infection by Day 9:** Proportion of HHCs who become PCR (+) for influenza (confirmed at central laboratory) by Day 9.
- **Any virological infection at the household level by Day 9:** Proportion of households with at least one HHC who meets the "Any virological infection by Day 9" endpoint.
- **Any symptomatic infection by Day 9:** Proportion of HHCs who meet the "Any virological infection by Day 9" endpoint **AND** are symptomatic per the definition for symptoms in the "Symptomatic transmission by Day 5" endpoint.
- **Any symptomatic infection at the household level by Day 9:** Proportion of households with at least one HHC who meets the "Any symptomatic infection by Day 9" endpoint.

Other Efficacy Objective: To further evaluate the efficacy of a single, oral dose of BXM compared with placebo to prevent transmission of influenza A/B.

Other Efficacy Endpoints

- The effect of IP baseline viral titer on the rate of direct transmission of influenza A or influenza B to HHCs.
- **BXM arm only:** Proportion of IPs who are PCR (+) [confirmed at central laboratory] for influenza bearing a PA/I38X substitution (or other identified substitution) post randomization.
- **BXM arm only:** Proportion of HHCs who become PCR (+) [confirmed at central laboratory] for influenza bearing a PA/I38X substitution (or other identified substitution) *with matched PA substitution with their IP* by Day 9 visit.
- **BXM arm only:** Proportion of symptomatic cases among HHCs who become PCR (+) [confirmed at central laboratory] for influenza bearing a PA/I38X substitution (or other identified substitution) *with matched PA substitution with their IP* by Day 9 visit (utilizing same symptoms definition as used for secondary symptomatic transmission endpoint).
- Proportion of HHC who become PCR (+) [confirmed at central laboratory] for influenza by Day 9 visit, with virus subtype consistent with IP.
- Measurement of viral titer *by* PCR *and TCID50* in IPs over *the* Day 0, 3, 5, and 9 visits.
- **Subgroup analysis:** endpoints requiring a subtype match will be assessed with a match based on sequencing in a subset of households (sequencing will be performed for samples from selected sites and countries based on feasibility, including availability of adequate number of IP sequences for specific community).

Safety Objective: To evaluate the safety and tolerability of a single, oral dose of BXM compared with placebo.

Safety Endpoints

- **IP only:** The incidence, severity, and timing of adverse events, and serious adverse events.

Health Status Utility Objective: To evaluate IPs treated with BXM compared with those receiving placebo.

Health Status Utility Endpoints

- **IP *≥12 years old* only:** Change from baseline in health-related quality of life according to EQ-5D-5L questionnaire at Day 3 and Day 9 visits.
- **IP *≥12 years old* only:** Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: SHP, Version 2 (WPAI+CIQ:SHP, V2) to measure lost work or school days assessed at Day 9 visit.

Additional Objective: *To describe the palatability and acceptability of BXM oral suspension in IPs <12 years old*

Additional Endpoint

- *Proportion of IPs reporting each palatability and acceptability response*

STUDY DESIGN

DESCRIPTION OF THE STUDY

This is a randomized, double-blind, multicenter, parallel-group, placebo-controlled study designed to evaluate the clinical efficacy of BXM for the reduction of direct transmission of influenza A/B from OwH IPs to their HHCs. For this household study, IPs with influenza will be randomized to receive BXM or placebo, and their HHCs will be repeatedly tested for influenza virus and assessed for influenza symptoms during the next 9 days. The total number of new HHC infections (symptomatic and asymptomatic) and total number of new HHC infections associated with symptoms will be key measures *used* to evaluate the "virological transmission" and "symptomatic transmission" endpoints.

Approximately 1,130 IPs with influenza and approximately 2,030 evaluable HHCs will participate in the study.

Index Patient: Screening and Randomization

Eligible IPs must be aged from ≥5 to ≤64 years old, have influenza symptom onset within 48 hours, test positive for influenza A/B, and be OwH (i.e., not at high risk for complications of influenza). Screening assessments informing IP eligibility include physical examination, vital signs, height and weight, medical history and concomitant therapies, urine pregnancy testing, and respiratory sampling for influenza testing.

With regard to the household, IPs should be determined at screening to live with *1 or more* HHCs who have not received an influenza vaccine in the past 6 months ("unvaccinated HHCs"), are likely to fulfill all HHC eligibility criteria, and are expected to participate in the "full study" (i.e., participate in all study assessments).

IPs who meet the eligibility criteria will be randomized in a 1:1 ratio to receive a single dose of either BXM or placebo within 2 hours of randomization. The dose and formulation of BXM is based on weight and age.

Index Patient: Post-Randomization

Respiratory samples and AEs will be collected. IPs *who are ≥12 years old* will also complete questionnaires describing their health status and absence from work or school. *IPs who are <12 years old will be asked to complete a questionnaire on the palatability and acceptability of the study drug oral suspension.*

Household Contacts: Screening and Enrollment

All HHCs present in the home must have their screening visit start within 24 hours of IP randomization. If any HHC tests positive for influenza A/B, then all HHCs fail screening. If *1 or more* unvaccinated HHCs meet all HHC eligibility criteria and agree to participate in the full study, it is allowable for additional HHCs to not participate beyond the screening visit (even if

they meet all HHC eligibility criteria). There is no maximum number of vaccinated and unvaccinated HHCs that can participate in the full study.

HHCs who agree to participate in the full study ("full study HHCs") must meet the full study criteria (HHC inclusion criteria 7 to 14), including that they must reside in the household for 7 of the 9 study days, and must not have any influenza symptoms at screening (mild symptoms determined by the investigator to be due to a preexisting condition are allowed).

Screening assessments informing HHC eligibility include influenza symptoms, medical history, concomitant medications, and respiratory sampling for influenza testing.

Full Study Household Contacts: Post-Screening

Only full study HHCs participate in visits and assessments post-screening. Full study HHCs are monitored for new or worsening influenza symptoms, and will also maintain a daily temperature diary. HHCs will be instructed to telephone the site if they develop influenza symptoms or fever so that a scheduled or unscheduled visit occurring within 24 hours can be arranged. Respiratory samples, adverse events due to study procedures, and concomitant medications will be collected.

Study Visits

The IP screening visit must occur at the study site. All other visits for IPs and HHCs may be conducted at home or at the *study site*. Home visits may be performed by home nurses or by site staff (if local practices are in place). All assessments except respiratory swab collection may be conducted remotely (e.g., via telephone or computer).

SARS-CoV-2 Testing

Given overlapping influenza and coronavirus disease 2019 symptoms, *severe acute respiratory syndrome coronavirus 2 (*SARS-CoV-2*)* testing will be conducted at screening and as needed during study conduct. If any subject (IP or HHC) tests positive for SARS-CoV-2, then all subjects in the household should be discontinued.

Independent Data Monitoring Committee

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

NUMBER OF PATIENTS

The proposed sample size for this study is 2,030 evaluable HHCs. Assuming a 15% drop-out for inclusion of HHCs into the primary analysis population, an average of 2.5 HHCs per IP and a 15% exclusion rate on the household level, this equates to an approximate number of IPs of 1,130.

Target Population

Inclusion Criteria

Inclusion Criteria: Index Patients

Each IP must meet the following criteria for study entry:

1. Signed Informed Consent Form (ICF). In the case of minors, a parent or authorized adult will be required to sign the ICF on behalf of the patient. The informed consent/assent of voluntary participation should be obtained in accordance with local requirements.
2. Age ≥ 5 and ≤ 64 years at time of signing ICF.
3. Able to comply with the study protocol per investigator judgment.
4. Diagnosed with acute influenza infection by investigator.
5. PCR (+) or RIDT (+) for influenza A/B based on cobas® *SARS-CoV-2 &* Influenza A/B *test* or other point-of-care/local laboratory results.
6. PCR (–) or antigen test (–) for SARS-CoV-2 based on cobas SARS-CoV-2 *& Influenza A/B test* or other point-of-care/local laboratory result.
7. Presence of (a) fever (≥ 38.0°C per tympanic or rectal thermometer; ≥ 37.5°C per axillary, oral or forehead/temporal thermometer) or (b) any influenza symptoms (cough, sore throat, nasal congestion, headache, feverishness or chills, muscle or joint pain, fatigue).
8. The time interval between the onset of fever or influenza symptoms and the pre-dose examinations is 48 hours or less.

9. IP lives in a household where:
    a. No HHC is known to have been diagnosed with influenza or SARS-CoV-2 infection by a healthcare professional in the past 4 weeks.
    b. All HHCs are expected to meet the key HHC inclusion criteria (criteria 1, 2, 3, 4, 5, and 6).
    c. *1 or more* HHCs are expected to participate in the full study who have not received the influenza vaccine within 6 months prior to screening.
10. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures as defined below:

    Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 21 days after the final dose of *study treatment*.

    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 is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

    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.

    Hormonal contraceptive methods must be supplemented by a barrier method.

    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. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Inclusion Criteria: All Household Contacts

Each HHC living in the home at any time during the study must meet criteria 1–6 below. The screening visit should start within 24 hours after IP randomization unless the HHC is a late-arrival HHC.

1. Signed ICF. In the case of minors, a parent or authorized adult will be required to sign the ICF on behalf of the HHC. The informed consent/assent of voluntary participation should be obtained in accordance with local requirements. All late-arrival HHCs must be willing to be consented for screening as soon as possible after their arrival.
2. PCR (–) or RIDT (–) based on cobas *SARS-CoV-2 & Influenza A/B test* or other local point-of-care/local laboratory result.
3. PCR (–) or antigen test (–) for SARS-CoV-2 based on cobas SARS-CoV-2 *& Influenza A/B test* or other POC/local laboratory result.
4. HHC lives with no HHC who will be present in the home at any time during the study and who meets any HHC exclusion criteria.
5. HHC lives with no HHC (except late-arrival HHCs) who does not meet HHC inclusion criteria 1–6.
6. HHC lives in a household where *1 or more* HHCs meet all of the following:
    a. Start screening within 24 hours *after* IP randomization.
    b. Have NOT received the influenza vaccine within 6 months prior to screening.
    c. Fulfill full study HHC inclusion criteria 7–14.

Inclusion Criteria: Full Study Household Contacts

*Each HHC intended for **full study** must meet the following additional criteria:*

7. Agree to participate in the full study (i.e., participate in all assessments after screening).
8. Able to comply with the study protocol per investigator judgment.

9. No influenza symptoms within 7 days prior to screening. Alternatively, mild symptoms (at worst) are permissible if determined by the investigator to be due to a preexisting condition (e.g., mild nasal congestion due to seasonal allergies).
    a. Symptoms for HHC ≥ 12 years old: cough, sore throat, nasal congestion, headache, feverishness or chills, muscle or joint pain, fatigue.
    b. Symptoms for HHC ≥ 2 to < 12 years old: cough, nasal congestion or rhinorrhea.
10. Temperature < 38.0°C (tympanic).
11. Will reside in the IP's house for at least 7 of the next 9 days and will be present for scheduled study visits.
12. Willing and able to measure and record temperature, or have another household member perform the task on his or her behalf. Furthermore, a responsible adult will assume responsibility to oversee or perform this task on behalf of minors.
13. In the 6 months prior to screening:
    a. Has not been diagnosed with influenza by a healthcare professional
    b. Has not received BXM, peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir, amantadine*, or favipiravir*
14. Does not have a moderate or worse active infections **OR** infections requiring systemic (e.g., oral or intravenous) or otherwise internally administered (e.g., inhaled, intrathecal) antibiotic/antiviral/antifungal therapy, (topical therapies for mild external infections allowed).

Exclusion Criteria

Exclusion Criteria: Index Patients

An IP meeting any of the following criteria will be excluded from the study:

1. IP with severe influenza virus infection requiring inpatient treatment.
2. IP judged by the investigator to be at high risk for complications of influenza, after consideration of the following* or other potential risk factors:
    a. Women who are pregnant or within 2 weeks post-partum;
    b. Chronic respiratory diseases including chronic obstructive pulmonary disease, current asthma, and cystic fibrosis;
    c. Neurological and neurodevelopmental disorders including disorders of the brain, spinal cord, peripheral nerve, and muscle (e.g., cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury);
    d. Heart disease (such as congenital heart disease, congestive heart failure, or coronary artery disease);
    e. Blood disorders (such as sickle cell disease);
    f. Endocrine disorders (such as diabetes mellitus);
    g. Kidney disorders;
    h. Liver disorders;
    i. Metabolic disorders (such as inherited metabolic disorder and mitochondrial disorders);
    j. Compromised immune system due to disease (such as people with HIV or AIDS, or some cancers such as leukemia) or medications (such as those receiving chemotherapy or radiation treatment for cancer, or persons with chronic conditions requiring chronic corticosteroids or other drugs that suppress the immune system);
    k. Morbid obesity (body mass index [BMI] ≥ 40);
    l. People younger than 19 years of age on long-term aspirin- or salicylate-containing medications;
    m. *People from certain racial and ethnic minority groups are at increased risk for hospitalization with influenza, including non-Hispanic Black persons, Hispanic or Latino persons, and* American Indian or Alaska Native *persons. The investigator should consider the overall risk of the individual.;*

n. People who live in nursing homes and other long-term care facilities.

** Adapted from the definition of "People at Higher Risk of Flu Complications" provided by the Centers for Disease Control and Prevention*

3. IP is ≥ 12 years old and unable to swallow tablets (not applicable to IPs 5 to <12 year olds who will receive oral suspension).
4. Women who are breastfeeding or have a positive pregnancy test in the pre-dose examinations. Female patients with documentation of at least one of the following items are exempt from pregnancy testing:
    a. Postmenopausal women (defined as cessation of regular menstrual periods for ≥ 12 continuous months).
    b. Women who are surgically sterile by hysterectomy, bilateral oophorectomy, or tubal ligation.
    c. Females < 12 years old and pre-menarcheal.
5. IP with concurrent (non-influenza) infections requiring systemic antimicrobial and/or antiviral therapy at the pre-dose examinations.
6. IP who has received BXM, peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir, amantadine, or favipiravir within 30 days prior to screening.
7. IP who has received an investigational monoclonal antibody for a viral disease in the last year.
8. IP who has received an investigational therapy within 30 days or 5 drug-elimination half-lives, whichever is longer, prior to screening.
9. IP lives with an HHC who, based on available information, is:
    a. Pregnant or within 2 weeks post-partum.
    b. Immunocompromised (including patients receiving immunosuppressant therapy, or those with cancer or HIV infection).
    c. < 2 years old.
    d. Unwilling to sign informed consent.
    e. Diagnosed with influenza or SARS-CoV-2 infection by a healthcare professional in the past 4 weeks.
    f. Previously included in the study.
    g. Plan to arrive home from after 24 hours post IP randomization to Day 9 and (late-arrival HHC defined in Section 4.5.9 of the protocol) is not willing to be consented as soon as possible upon arrival.
10. Known hypersensitivity to BXM or the drug product excipients.
11. Any other contraindication for treatment with BXM as deemed by the treating physician or Principal Investigator.
12. IP previously included in the study.

Exclusion Criteria: All Household Contacts

An HHC (living in the home at any time during the study) meeting any of the following criteria will be excluded from study entry:

1. Pregnant or within 2 weeks post-partum at screening.
2. Immunocompromised (including patients receiving immunosuppressant therapy, or those with cancer or HIV infection).
3. < 2 years old.
4. Received an investigational therapy within 30 days or 5 drug-elimination half-lives, whichever is longer, prior to screening.
5. Diagnosed with influenza or SARS-CoV-2 infection by a healthcare professional in the past 4 weeks.
6. HHC previously included in the study.

7. HHC who plans to arrive home after 24 hours post IP randomization to Day 9 and is not willing to be consented as soon as possible upon arrival.

END OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs. The end of the study for all patients (except IPs < 12 years old) is expected to occur 9 days after the last IP is enrolled. For IPs < 12 years old, the last visit will be Day 21.

LENGTH OF STUDY

The expected study duration for both IPs and $full\ study$ HHCs is 9 days, and study duration for IPs < 12 years old is 21 days. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3.5 years.

INVESTIGATIONAL MEDICINAL PRODUCTS

BALOXAVIR MARBOXIL AND PLACEBO

IPs will receive the initial and only dose of study drug (BXM or matching placebo) to be taken in tablet or oral suspension form at the study center within 2 hours of randomization. IPs will be dosed according to age and body weight as listed below.

STUDY DRUG ADMINISTRATION AND DOSE FOR INDEX PATIENTS < 12 YEARS OLD

Weight	Dose, Formulation
< 20 kg	2 mg/kg, oral suspension
≥ 20 kg	40 mg, oral suspension

STUDY DRUG ADMINISTRATION AND DOSE FOR INDEX PATIENTS ≥ 12 YEARS OLD

Weight	Dose, Formulation
< 80 kg	40 mg, (two 20 mg tablets)
≥ 80 kg	80 mg, (four 20 mg tablets)

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

During the study, influenza antiviral drugs are among the prohibited concomitant medications for IPs and full study HHCs. Symptomatic therapies without antiviral properties are permitted for all subjects. Antivirals are only permitted for full study HHCs as soon as they are diagnosed with influenza A/B, and their further treatment will be determined by the investigator according to local standards. The study sponsor will not provide treatment beyond the investigational medicinal products.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary efficacy analysis population will consist of all unvaccinated full study HHCs in households where all HHCs were confirmed at screening to be PCR negative and the IP was confirmed at screening to be PCR positive for influenza A/B. Supportive analyses including all full study HHCs of all randomized IPs will be performed. Treatment groups will be defined based on the arm to which the respective IP was randomized.

The primary analysis will compare the transmission rate for the primary endpoint between the two arms and express the effect by an adjusted odds ratio. The comparison will be based on a model providing population-averaged estimates using a generalized estimating equations approach and accounting for the stratification factors used at randomization. The primary test for the treatment effect will be two-sided and the significance level will be 5%. For this analysis, missing values will not be imputed. The Statistical Analysis Plan will specify sensitivity analyses performed with different imputation methods and alternative definitions of the analysis population.

A hierarchical testing strategy will be used for secondary endpoints.

DETERMINATION OF SAMPLE SIZE

A transmission rate in the placebo arm of approximately 20% is assumed based on *data from* the literature, including work by Welliver et al. (2001). For a 30% relative risk reduction with BXM, which is considered clinically meaningful, the transmission rate in the active treatment group is expected to be 14%. Under these assumptions and for a two-sided test *for binary proportions* at the 5% significance level, the power for the between-arm comparison based on the primary endpoint *will be* approximately *>90%. For the secondary "Symptomatic transmission endpoint" (*symptomatic influenza*) the power* will be *80% for an assumed 65% proportion of* symptomatic *cases among infected HHCs, and not considering the hierarchical testing procedure.*

INTERIM ANALYSES

There are no planned interim efficacy analyses for this study. Safety interim analyses will be performed regularly by an iDMC. Efficacy data will only be provided if requested by the iDMC. Further details on the function and logistics (e.g., frequency of the meetings) of the iDMC will be provided in the iDMC Charter.

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one or more interim efficacy analyses. Possible goals of these interim analyses include assessing the futility of study continuation or reassessing the sample size in case the overall transmission rates (calculated in a blinded manner) are smaller than anticipated. If recruitment projections indicate that a large proportion of the currently planned sample can be recruited by the end of the 2020/2021 or subsequent Northern hemisphere influenza seasons (e.g., >70%), the Sponsor will determine whether to perform an interim analysis with stopping rules based on efficacy endpoints in accordance to a group-sequential design.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
$AUC_{0\text{-}inf}$	area under the concentration–time curve from time 0 extrapolated to infinity
BID	twice daily
BMI	body mass index
BXM	baloxavir marboxil
C_{24}	concentration 24 hours post dose
C_{72}	concentration 72 hours post dose
CDC	Center for Disease Control and Prevention
CEN	cap-dependent endonuclease
CLIA	Clinical Laboratory Improvement Amendments
COVID-19	coronavirus disease 2019
CRO	contract research organization
C_T	threshold cycle
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic Case Report Form
EDC	electronic data capture
EC	Ethics Committee
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
HHC	household contact
HIPAA	Health Insurance Portability and Accountability Act
I38X	substitution of isoleucine for another amino acid at position 38 (of the polymerase acidic protein)
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug
IP	index patient
IRB	Institutional Review Board
ITTI	intent-to-treat-influenza-infected
IxRS	interactive voice or web-based response system

Abbreviation	Definition
MDCK	Madin-Darby Canine Kidney
NAI	*neuraminidase inhibitor*
NCI	National Cancer Institute
NPA	negative percent agreement
OwH	otherwise healthy
PA	polymerase acidic (protein)
PB1/2	polymerase basic (protein) 1/2
PCR	polymerase chain reaction
PK	pharmacokinetic
POC	point of care
PPA	positive percent agreement
PRO	patient-reported outcome
RIDT	Rapid Influenza Diagnostic Test
RSV	respiratory syncytial virus
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	*severe acute respiratory syndrome coronavirus 2*
SOC	*standard of care*
$t_{1/2}$	half-life
TCID50	50% tissue culture infectious dose
TTAS	time to alleviation of symptoms
TTCVS	time to cessation of viral shedding
TTIIS	time to improvement of influenza symptoms
ULN	upper limit of normal
WPAI+CIQ	Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions

1. BACKGROUND

1.1 BACKGROUND ON INFLUENZA VIRUS INFECTION

Influenza virus infection is an acute respiratory infectious disease caused by the influenza viruses and is spread mainly by droplet infection. Following an incubation period of 1–4 days, clinical symptoms such as sudden onset of fever, chills, headache and myalgia occur. Within 24 hours from the onset, body temperature reaches 38°C to 40°C (Wright et al. 2007; Monto et al. 2000). Other symptoms include cough (often highly frequent and persistent), sore throat and nasal congestion (Pringle 2014). Based on these symptoms, influenza virus infection tends to be a severe illness and should be discriminated from the common cold. There are four types of influenza viruses, A, B, C, and D; A and B viruses show a seasonal spread of infection.

Anti-influenza virus drugs have been approved (with geographic variability): M2 channel inhibitors - amantadine hydrochloride and rimantadine hydrochloride; NA inhibitors - oseltamivir phosphate, zanamivir hydrate, peramivir hydrate and laninamivir octanoate hydrate; RNA polymerase inhibitor - favipiravir. The U.S. Centers for Disease Control and Prevention (CDC) advised that use of current M2 channel inhibitors (amantadine hydrochloride and rimantadine hydrochloride) be restricted for the treatment of influenza virus infection (CDC 2006). Use of amantadine hydrochloride is also restricted in Japan and rimantadine hydrochloride has not been approved in Japan.

1.2 BACKGROUND ON BALOXAVIR MARBOXIL

Baloxavir marboxil (BXM; S-033188/RO7191686) is an anti-influenza virus drug with a novel mechanism of action. It was discovered and is being developed by Shionogi & Co., Ltd. and F. Hoffman-La Roche, Ltd. BXM is a prodrug that is metabolized to an active form (S-033447) through hydrolysis. The active form selectively inhibits cap-dependent endonuclease (CEN) activity necessary for replication of influenza viruses (Omoto et al. 2018). A broad spectrum of activity against seasonal influenza viruses and on alleviating effects of influenza symptoms were shown in nonclinical efficacy studies and clinical studies in patients with influenza, including the Phase 2 proof of concept and dose-finding study, the Phase 3 double-blind study in otherwise healthy (OwH) patients (Hayden et al. 2018), and the Phase 3 open-label study in OwH pediatric patients *(Baker et al. 2020)*. Clinical studies also showed that with a single oral administration, BXM led to more rapid reduction of influenza viruses than oseltamivir phosphate. Due to its novel mechanism of action, BXM is anticipated to be effective against influenza virus strains resistant to currently marketed drugs.

1.2.1 Previous Non-Clinical Studies

In in vivo nonclinical studies, S-033447 inhibited transcription of influenza virus by selective inhibition of CEN activity. The 50% inhibitory concentration values of S-033447 against CEN activity for influenza A and B viruses ranged from 1.4 to 3.1 nmol/L and from 4.5 to 8.9 nmol/L, respectively; determined by using Madin-Darby Canine Kidney

(MDCK) cells infected with influenza A virus. The 90% effective concentration values of S-033447 against replication of influenza A and B viruses in MDCK cells ranged from 0.46 to 0.98 nmol/L and from 2.21 to 6.48 nmol/L, respectively. S-033447 exhibited more potent inhibition on virus replication compared with anti-influenza virus drugs such as the active form of oseltamivir phosphate. In vivo studies with S-033447 using mouse-adapted influenza A and B viruses (A/Osaka/129/2009, A/Hong Kong/8/68, B/Hong Kong/5/72) found that the EC_{50} values of S-033447 for A/Osaka/129/2009, A/Hong Kong/8/86, and B/Hong Kong/5/72 were 0.75, 0.58, and 8.37 nmol/L, respectively, indicating that the susceptibility to S-033447 of the mouse-adapted viruses was comparable to that of the parent viruses. In mouse models infected with influenza A, B or NA inhibitor-resistant virus with NA/H274Y, BXM showed inhibitory effects on viral titers in the lung 24 hours after twice daily (BID) oral administration for 1 day and these results reflected the in vitro antiviral effects. A dose of 5 mg/kg BID BXM for 1 day, 5 days post-infection, exhibited significantly lower viral titers in the lung than oseltamivir phosphate at the clinically equivalent dose (5 mg/kg BID). In the mouse model infected with influenza A virus, BXM given orally 5 days post-infection, at 0.5 mg/kg BID for 1 day, exhibited significantly lower viral titers in the lung over 3 days after one BID administration compared with oseltamivir phosphate at the clinically equivalent dose given for 3 days.

In ferrets infected with influenza A(H1N1)pdm09 virus, BXM treatment (4 × injections, 4 mg/mL/kg total, subcutaneously) at 24 or 48 hours post-infection significantly reduced the duration of viral shedding and reduced viral transmission to co-housed treatment-naive ferrets (direct transmission) by 75% and 50%, respectively, compared with both oseltamivir and placebo (Study 1102424).

In ferrets infected with a recombinant influenza A(H1N1)2009 virus, BXM treatment (4 × injections, 4 mg/mL/kg total, subcutaneously) at 24 hours post-infection led to decreased viral shedding and reduced the transmission to treatment-naive ferrets in adjacent cages (indirect transmission) by 66% compared with both oseltamivir and placebo (Study 1100893).

1.2.1.1 Toxicology and Safety Pharmacology

No single-dose toxicity study of BXM has been conducted. Acute toxicity was evaluated in a 2-week repeated oral toxicity study of BXM in rats (up to 2,000 mg/kg/day), a 2-week repeated oral toxicity study of BXM in monkeys (up to 200 mg/kg/day), and a safety pharmacology study of BXM for cardiovascular system in monkeys (up to 400 mg/kg/day). There were no deaths or acute toxicity symptoms in these studies.

In an oral fertility and early development study of BXM (0 [control], 20, 200, and 1,000 mg/kg/day) in rats, there were no test substance-related deaths throughout the study period. There were no adverse effects of BXM on any parameter in parent animals. No effects of BXM were observed in embryos. In an oral embryo-fetal development study of BXM (0 [control], 20, 200, and 1000 mg/kg/day) in rats, no death

occurred in any animals. Slight decreases in body weight gain and food consumption were observed in the 200-mg/kg/day or higher dosing groups. These changes were not considered to be adverse since they were slight and temporary. There were no adverse effects on fetal viability, intrauterine growth, or external, visceral and skeletal morphologies of live fetuses. In an oral embryo-fetal development study of BXM (0 [control], 30, 100, and 1000 mg/kg/day) in rabbits, 2/19 dams in the 1,000-mg/kg/day group aborted their litters. No death was observed in any dams. Maternal toxicities such as decreases in food consumption and body weight gain were observed in the 1,000-mg/kg/day group. There were no adverse effects on fetal viability and intrauterine growth. The incidence of cervical rib was high in the 1,000-mg/kg/day group, and the finding was considered to be fetal toxicity but not teratogenicity. There were no adverse effects on external, placental or visceral morphologies of live fetuses up to 1,000 mg/kg/day.

1.2.2 Previous Clinical Experience

To date, BXM has been investigated in $twelve$ Phase 1 studies, one Phase 2 study, and $eight$ Phase 3 studies as part of its global development program. A total of 2944 subjects have been exposed to at least one dose of BXM in the completed studies. The completed Phase 3 studies are summarized below; please see the Baloxavir Marboxil Investigator's Brochure for details regarding all completed and ongoing studies.

1.2.2.1 Completed Phase 3 Studies in Otherwise Healthy Influenza Patients

Study 1601T0831 (Adults and Adolescents)

Study 1601T0831 (CAPSTONE-1; Hayden et al. 2018) was a double-blind, randomized study that compared single dose BXM (40 mg for patients <80 kg; 80 mg for patients ≥ 80 kg) versus placebo in adolescent and adult patients aged 12–64 years old with influenza-like illness in Japan and the United States. The study also compared single dose BXM (with same weight-based dosing) versus repeated dose oseltamivir (75 mg BID for 5 days) in adult patients aged 20–64 years old. A total of 1,432 patients received study drug (610 in the BXM group, 309 in the placebo group, and 513 in the oseltamivir group). Of these, 456, 231, and 377 patients, respectively, were included in the intent-to-treat-influenza-infected (ITTI) population for the efficacy analyses.

Efficacy: The median time to alleviation of symptoms (TTAS) was significantly shorter in the BXM group (53.7 hours) compared with the placebo group (80.2 hours; delta –26.5 hours; two-sided $p<0.0001$). In adults, the median TTAS was 53.5 hours in the BXM group compared with 53.8 hours in the oseltamivir group (difference not statistically significant). Of the secondary endpoints, significant decreases in virus titer and the amount of virus RNA were found in the BXM group compared with the placebo group. Rapid reduction in virus titer and amount of viral RNA results in a significantly shortened time to cessation of viral shedding (TTCVS), which is analogous to a shortened infectivity period. The median TTCVS determined by virus titer was 24 hours in the BXM group compared with 96 hours in the placebo group—a significant difference of

72 hours. A significant difference was also found between the BXM group and the oseltamivir group. BXM rapidly and significantly reduced the proportion of patients with positive influenza virus titer from Days 2 through 5 compared with that in the placebo group. In addition, when compared to the oseltamivir group, the proportion of patients with positive influenza virus titer decreased significantly in the BXM group. Beneficial effects on fever were also shown with BXM, with significantly fewer patients reporting fever compared with the placebo group. The median time to the resolution of fever was shorter for patients who received BXM than with placebo (24.5 hours vs. 42.0 hours, respectively; $p < 0.001$) and a significant improvement was found in the proportion of patients reporting a normal temperature in the BXM group compared with the placebo group.

Safety: No deaths were reported in all the three groups (BXM, oseltamivir, and placebo). Two serious adverse events (SAEs) (1 each of meningitis viral and incarcerated inguinal hernia) were reported in 2 of 610 (0.3%) patients in the BXM group. The events resolved and were considered not related to the study drug. Nine adverse events (AEs) that led to withdrawal of study drug were reported: 3 AEs in 2 of 610 (0.3%) patients in the BXM group, 4 AEs in 1 of 309 (0.3%) patients in the placebo group, and 2 AEs in 2 of 513 (0.4%) patients in the oseltamivir group. All AEs that led to withdrawal of study drug in the BXM group were considered not related to the study drug. AEs were reported in 126 of 610 patients (20.7%) in the BXM group, 76 of 309 patients (24.6%) in the placebo group, and 127 of 513 patients (24.8%) in the oseltamivir group. No statistically significant difference was found in the incidence between the BXM group and the placebo group (the Fisher's exact test, two-sided $p = 0.1781$) or between the BXM group and the oseltamivir group ($p = 0.1146$). Treatment-related AEs were reported in 27 of 610 patients (4.4%) in the BXM group, 12 of 309 patients (3.9%) in the placebo group, and 43 of 513 patients (8.4%) in the oseltamivir group. No statistically significant difference was found in the incidence between the BXM group and the placebo group (the Fisher's exact test, two-sided $p = 0.8627$). However, the incidence was significantly lower in the BXM group than in the oseltamivir group (the Fisher's exact test, two-sided $p = 0.0088$). Except for bronchitis in the placebo group, there were no common AEs (incidence, $\geq 5\%$) among any of the treatment groups. Relatively common AEs (incidence, $\geq 2\%$) in any of the groups were bronchitis, sinusitis, diarrhea, and nausea; however, for each AE, the incidence in the BXM group was lower than or equal to that in the placebo group. In all the three groups, the majority of the AEs were categorized as Grade 1 or 2 and resolved.

Study CP40563 (Children Aged 1 to <12 Years Old)

Study CP40563 (MINISTONE-2; Baker et al. 2020) was a multicenter, randomized, double-blind, active (oseltamivir)-controlled study in non-Asian OwH pediatric patients aged from 1 to < 12 years old with influenza-like symptoms. Patients received either a single dose of BXM (granules for oral suspension [2 mg/mL]) based on body weight (< 20 kg [2 mg/kg] and ≥ 20 kg [40 mg]) or oseltamivir (body weight-adjusted dosing

ranging from 30 mg to 75 mg twice a day) for 5 days with a 24-day safety follow-up period after treatment. The total study duration for each patient was 29 days. A total of 176 patients were randomized, and of these 173 patients received the study drug (115 in the BXM group and 58 in the oseltamivir group). Of these, 81 patients in the BXM group and 43 patients in the oseltamivir group were included in the ITTI population for the efficacy analyses.

Efficacy: Overall, the efficacy analysis results were comparable between the two treatment groups including time to influenza signs and symptoms, fever, duration of symptoms, complications, and the proportion of patients requiring antibiotics. The median TTCVS as determined by virus titer was 24.2 hours in the BXM group compared with 75.8 hours in the oseltamivir group.

Safety: The overall incidence of AEs was similar between the BXM (46.1%) and oseltamivir group (53.4%). No SAEs or deaths were reported. The incidence of AEs related to study drug was 2.6% (3 of 115 patients) in the BXM group and 8.6% (5 of 58 patients) in the oseltamivir group. The most commonly reported AEs were vomiting, diarrhea, and otitis media in either treatment group. All AEs were Grade 1–2 in severity in both treatment groups, with the exception of 3 Grade 3 AEs, one in the BXM group (abdominal pain on Day 8) and two in the oseltamivir group (both undiagnosed preexisting condition of severe vitamin D deficiency on Day 1). The vast majority of AEs (95.1%) were resolving by study end, with the exception of 6 AEs that had not resolved by study end (Day 29). No clinically meaningful changes from baseline were observed for any laboratory parameters in this study, and no clinically meaningful differences were observed between treatment groups for vital signs.

Study 1618T0822 (Children Aged from 6 Months to <12 Years Old in Japan)

Study 1618T0822 (Hirotsu et al. 2019) was an open-label study that investigated a single dose of BXM (tablet formulation) in OwH patients aged 6 months–11 years old in Japan. Dosages studied were 5, 10, 20, and 40 mg for patients weighing from 5 to <10 kg, from 10 to <20 kg, from 20 to <40 kg and ≥40 kg, respectively. A total of 108 pediatric patients were enrolled, of whom 107 received study drug, and of whom 104 were included in the ITTI population for efficacy analyses.

Efficacy: The median time to alleviation of influenza illness (i.e., alleviation of cough, nasal discharge/nasal congestion and fever, the primary endpoint) was 44.6 hours. The median time to resolution of fever (a secondary endpoint) was 21.4 hours. For selected virological endpoints, the mean change from baseline in the virus titer was −4.20 $\log^{10}$ (*50% tissue culture infectious dose* [TCID50]/mL) and the mean change from baseline in the amount of viral RNA was −1.75 $\log^{10}$ (virus particles/mL) on Day 2.

Safety: No deaths, SAEs, or discontinuations due to AEs were reported in the study. AEs were reported in 37 of 107 patients (34.6%). Treatment-related AEs were reported in 4 of 107 patients (3.7%). All AEs were classified as Grade 1 or 2. Most of the AEs

resolved except for 3 AEs in 3 patients: 1 event each of dental caries, dry skin, and ligament sprain; all 3 events were judged by the investigator as not requiring further follow-up. AEs occurring at an incidence of at least 5% were vomiting in 8 patients (7.5%). All cases of vomiting were classified as Grade 1, resolved, and considered not related to the study drug.

Study 1705T0833 (Children Aged <12 Years Old and Weighing <20 kg in Japan)

Study 1705T0833 (Yokoyama et al. 2020) was an open-label, multicenter, non-controlled study investigating BXM 2% granules in OwH patients aged <12 years old and whose body weight was <20 kg in Japan. Patients received a single oral dose of BXM (2% granules) on Day 1 within 48 hours of the onset of influenza symptoms based on body weight at screening. All 33 pediatric patients enrolled received BXM (1 mg/kg for 12 children weighing <10 kg, 10 mg for 21 children weighing from 10 to <20 kg), completed the study, and were included in the ITTI population for efficacy.

Efficacy: The median time to alleviation of influenza illness was 45.3 hours. The median time to resolution of fever (a secondary endpoint) was 34.0 hours. The median TTCVS evaluated by virus titer was 48.0 hours, and the median TTCVS evaluated by reverse transcription polymerase chain reaction (RT-PCR) was 240.0 hours.

Safety: No deaths, SAEs, or discontinuations due to AEs were reported in the study. AEs were reported in 18 of 33 patients (54.5%). Most common AEs reported were vomiting, diarrhea, and pharyngitis. Treatment-related AEs (as assessed by the investigator) were reported in 1 of 33 patients (3.0%, 1 event of platelet count increased). All AEs were classified as Grade 1 or 2. All AEs were resolved or were resolving at the end of the study.

Study 1813T0835 (Children Aged <12 Years Old and Weighing <20 kg in Japan)

Study 1813T0835 (Sonoyama et al. 2021) was an open-label, multicenter, non-controlled study investigating BXM 2% granules in OwH patients aged <12 years old and whose body weight was <20 kg in Japan. Patients received a single oral dose of BXM on Day 1 within 48 hours of the onset of influenza symptoms based on age and body weight at screening (1 mg/kg: <10 kg and <3 months old, 2 mg/kg: <10 kg and ≥3 months old, 20 mg: ≥10 to <20 kg). A total of 45 pediatric patients were enrolled (0 were <3 months and <10 kg, 9 were <10 kg and 36 were 10 to <20 kg). Of the 45 patients, 43 pediatric patients were included in the ITTI population.

Efficacy: The median time to alleviation of influenza illness was 37.8 hours. The median time to resolution of fever (a secondary endpoint) was 22.0 hours. The mean change from baseline in the virus titer was −4.40 log^{10} (TCID50/mL) and the mean change from baseline in the amount of viral RNA was −1.28 log^{10} (virus particles/mL) on Day 2.

Safety: No deaths, SAEs, or discontinuations due to AEs were reported in the study. AEs were reported in 24 of 45 patients (53.3%). Most common AEs reported were nasopharyngitis and diarrhea. Treatment-related AEs were reported in 3 of 45 patients (6.7%; 3 events of diarrhea). All AEs were classified as Grade 1 or 2 in severity. All AEs were resolved or were resolving at the end of the study.

1.2.2.2 Completed Phase 3 Study in High-Risk Influenza Patients Study 11602T0832 (Adults and Adolescents)

Study 11602T0832 (CAPSTONE-2; Ison et al. 2020) was a double-blind, randomized study that compared a single oral dose of BXM (40 mg for patients <80 kg; 80 mg for patients ≥ 80 kg) with placebo or 75 mg of oseltamivir BID for 5 days in patients with influenza-like illness who were ≥ 12 years old and at high risk of complications from influenza. The study was conducted in 17 countries and territories. Overall, a total of 730, 729, and 725 patients were randomized to receive BXM, placebo, and oseltamivir, respectively, and of these, 388, 386, and 389 patients, respectively, were included in the ITTI population for the efficacy analyses.

Efficacy: The time to improvement of influenza symptoms (TTIIS) was significantly shorter in patients treated with BXM than placebo (median 73.2 vs. 102.3 hours, $p<0.0001$) and numerically shorter than oseltamivir (81.0 hours, $p=0.8347$). TTIIS in patients with A/H3N2 virus treated with BXM was shorter than those treated with placebo (median: 75.4 vs. 100.4 hours; $p=0.0141$). TTIIS in patients with influenza B treated with BXM was also significantly shorter (74.6 hours) than those treated with either placebo (100.6 hours; $p=0.0138$) or oseltamivir (101.6 hours; $p=0.0251$). Median TTCVS in BXM-treated patients was 48 hours, which was significantly less than the 96 hours seen with both placebo and oseltamivir. Systemic antibiotic use and influenza-related complications were significantly fewer in the BXM versus the placebo group (3.4% vs. 7.5%, $p=0.0112$; and 2.8% vs. 10.4%, $p<0.0001$; respectively).

Safety: The incidence of any AE (25.1%–29.7%) or any SAE (0.7%–1.2%) did not differ significantly between the groups treated with a single oral dose of BXM, placebo, or oseltamivir.

1.2.2.3 Completed Phase 3 Post-Exposure Prophylaxis Study Study 1719T0834 (Adults and Children Aged ≥ 1 Years Old)

Study 1719T0834 (BLOCKSTONE; Ikematsu et al. 2020) was a randomized, double-blind, multicenter, parallel-group, placebo-controlled, comparative post-exposure prophylaxis study that evaluated a single dose of BXM in the prevention of influenza virus infection in Japanese subjects (adults and children ≥ 1 years old) who were household members of influenza-infected index patients (IPs). Eligible subjects were randomly assigned with the stochastic minimization method in a 1:1 ratio to receive BXM or placebo. BXM was administered based on the subjects' age and body weight (adults and adolescents: 40 mg for patients <80 kg; 80 mg for patients ≥ 80 kg and pediatrics: <10 kg [1 mg/kg], from 10 to <20 kg [10 mg], from 20 to <40 kg [20 mg],

≥40 kg [40 mg]). Study drug was orally administered at the study site on Day 1. Subjects visited the study site a maximum of 5 times during the 15-day period for 11 days of efficacy evaluations and 15 days of safety evaluations. A total of 752 household participants underwent randomization, 749 of whom constituted the modified intention-to-treat population for efficacy analyses.

Efficacy: The proportion of subjects who were infected with influenza virus (RT-PCR positive) and presented with fever and at least one respiratory symptom from Day 1 to Day 10 (primary efficacy endpoint) in the modified intent-to-treat population was significantly lower in the BXM group (7 of 374 subjects; 1.9%) compared with the placebo group (51 of 375 subjects; 13.6%); the adjusted risk ratio was 0.14 [95% CI: 0.06, 0.30], $p < 0.0001$).

Safety: One SAE (psychotic disorder in the placebo group) was reported in a patient who had a medical history of acute psychosis. The event was the only AE that lead to withdrawal from the study. The event was considered related to the study drug. No deaths were reported. The incidences of AEs and treatment-related AEs were similar between the treatment groups. All AEs were Grade 1 or 2 in severity except for 1 (0.3%) patient with Grade 3 psychotic disorder in the placebo group. The majority of AEs resolved or were resolving *at the end of the study*. No clinically relevant differences were found in the changes from baseline in laboratory values between the treatment groups.

1.2.2.4 *Completed Phase 3 Study in Hospitalized Patients with Severe Influenza (Aged ≥12 Years Old)*

Study CP40617 (FLAGSTONE; Kumar et al. 2022) was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy, safety, and pharmacokinetics of BXM 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 adult and adolescent patients (aged ≥12 years old) with severe influenza. BXM was administered as a body 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 on Day 7 if clinical improvement had not occurred on Day 5 per protocol-defined criteria. Treatment with a SOC NAI was administered to patients in accordance with local clinical practice. A total of 366 patients were randomized to receive BXM plus SOC NAI or matching placebo plus SOC NAI. Of the 366 patients, 322 patients constituted the modified intent-to-treat infected population.

Efficacy: There was no statistically significant difference in the time to clinical improvement observed between the BXM plus SOC NAI and placebo plus SOC NAI treatment groups (the primary efficacy endpoint). The median time to clinical improvement was 97.5 hours (95% CI: 75.9 to 117.2 hours) in the BXM group compared with 100.2 hours (95% CI: 75.9 to 144.4 hours) in the control group, with a

median difference of −2.7 hours (95% CI: −53.4 to 25.9 hours). The results of the key secondary and other secondary efficacy endpoints were consistent with the results of the primary endpoint, although the results generally showed numerical improvements in favor of the BXM plus SOC NAI group.

Safety: Study CP40617 was the first study evaluating the efficacy and safety of repeat dosing with BXM and it was also the first study of BXM used in combination with an NAI. The incidence of AEs and SAEs were similar between the two treatment groups and neither repeat dosing nor use in combination with NAI identified any new safety signal. Overall, BXM was well tolerated in combination with a NAI with no change in safety profile observed.

1.2.2.5 Pharmacokinetics

Baloxavir (S-033447) pharmacokinetic *(PK)* results are provided below for OwH patients and post-exposure prophylaxis subjects enrolled in the studies described in Sections 1.2.2.1 and 1.2.2.3. Please see the Baloxavir Marboxil Investigator's Brochure for further details (or results from other studies).

Results for OwH Patients and Post-Exposure Prophylaxis Subjects Aged ≥12 Years Old

Study 1601T0831 (CAPSTONE-1; Hayden et al. 2018): The geometric mean concentration 24 hours post dose (C_{24}) of S-033447 was similar between the patients weighing ≥40 to <80 kg and those weighing ≥80 kg, and between the patients 12 to 19 years *old* and 20 to 64 years *old*. The geometric mean C_{24} was 34% and 39% lower in Caucasians and others than that in Asians, respectively. The geometric mean C_{24} was slightly lower (7.2% to 10.8%) in the fed condition (dosing <2 hours before or <2 hours after food intake) compared with the fasted condition (dosing ≥4 hours before and ≥4 hours after food intake). The geometric mean C_{24} in the intermediate fed state (dosing between 2 to 4 hours before or between 2 to 4 hours after food intake) was similar to that in the fasted state.

Study 1719T0834 (BLOCKSTONE; Ikematsu et al. 2020): *Baloxavir* concentration values in subjects aged ≥12 years old were comparable with those observed in Study 1601T0831.

Results for OwH Patients and Post-Exposure Prophylaxis Subjects Aged <12 Years Old

The pharmacokinetics of *baloxavir* was investigated in non-Asian pediatric patients (1 to <12 years old; Study CP40563) and in Japanese pediatric patients (Studies 1618T0822, 1705T0833, 1719T0834*, and 1813T0835*).

Study CP40563 (MINISTONE-2; Baker et al. 2020): Similar plasma C_{24} (derived from the population *PK* model) was observed at 2 mg/kg (55.7 ng/mL, 28.1 CV%) and 40 mg (53.2 ng/mL, 22.4 CV%). Overall, the Bayesian estimates of the *PK* parameters from the pediatric patients in Study CP40563 were comparable with *PK* parameters in non-Asian

adult and adolescent patients from the OwH and high-risk studies (1601T0831 and 1602T0832). The mean area under the concentration–time curve from time 0 extrapolated to infinity ($AUC_{0\text{-inf}}$) in pediatric patients was between the mean $AUC_{0\text{-inf}}$ values observed with the 40 mg and 80 mg dose in adults/adolescents. The mean maximum concentration and C_{24} in pediatric patients were similar to the mean of the 80 mg dose group, and the mean concentration 72 hours post dose (C_{72}) matched the 40 mg dose group in adults, indicating an apparent shorter half-life ($t_{1/2}$) in patients $<$12 years *old* relative to adults and adolescents.

Study 1618T0822 (Hirotsu et al. 2019): The C_{24} values of patients treated with BXM ranged between 11.2–146 ng/mL, with a trend toward lower C_{24} with decreasing bodyweight. All values were within the range of the overall mean C_{24} (55.1 ng/mL [0.322–209 ng/mL]) observed in Study 1601T0831.

Study 1705T0833 (Yokoyama et al, 2020): The C_{24} values were comparable with those observed in Study 1618T0822.

Study 1813T0835 (Sonoyama et al. 2021): The observed C_{24} (as Geometric Mean [CV% Geometric Mean]) for all patients of 90.2 ng/mL (43.5%) was 1.7 times higher than in Study 1705T0833 (52.7 ng/mL [51.5%]), in accordance with the dose differences between the two studies. The mean (range) of the estimated plasma C_{72} was 31.2 ng/mL (13.5–64.9 ng/mL), which was similar to the estimated C_{72} for adults following a single oral dose of 40 mg or 80 mg of BXM in Study 1601T0831 (23.9 ng/mL [4.42–70.6 ng/mL]).

Study 1719T0834 (BLOCKSTONE; Ikematsu et al. 2020): *Baloxavir* concentration values were comparable with those observed in Studies 1618T0822 and 1705T0833.

As evidenced by a population *PK* model, both race and body weight influenced the PK of *baloxavir*. The effect of race (Asian/non-Asian) on *baloxavir pharmacokinetics* was similar across age groups. On an equal body weight basis, exposures were approximately 2-fold higher in Asians compared with non-Asians regardless of age (adult, adolescent, and pediatric patients). The impact of body weight was the same for both ethnic groups. Overall, an apparent shorter *baloxavir* $t_{1/2}$ was observed in both the Japanese and non-Asian patients aged $<$12 years old relative to adults and adolescents. Consequently, because the $t_{1/2}$ tends to be shorter in patients with lower bodyweight, the higher dose expressed in mg/kg body weight used in pediatrics in Study CP40563 results in matching *baloxavir* exposures (e.g., $AUC_{0\text{-inf}}$, C_{72}) to those observed in adults (Study 1601T0831).

1.2.3 Postmarketing Safety Data

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

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

1.3 BACKGROUND ON THE COBAS® SARS-COV-2 & INFLUENZA A/B NUCLEIC ACID TEST FOR USE ON THE COBAS LIAT® SYSTEM

The cobas *severe acute respiratory syndrome coronavirus 2 (*SARS-CoV-2*)* & Influenza A/B nucleic acid test for use on the cobas Liat System *(cobas SARS-CoV-2 & Influenza A/B test)* is an automated multiplex real-time RT-PCR assay for the rapid in vitro qualitative detection and discrimination of SARS-CoV-2, influenza A virus, and influenza B virus RNA in nasopharyngeal *and nasal* swabs from individuals suspected of a respiratory *viral* infection. *The* cobas SARS-CoV-2 & Influenza A/B *test* is intended for use as an aid in the differential diagnosis of SARS-CoV-2, influenza A, and influenza B *virus nucleic acids in clinical specimens and is not intended to detect influenza C virus*. This test is *CE-IVD marked and* authorized for use *at the point of care (POC) or in a clinical lab setting* under the *Food and Drug Administration (*FDA*)* Emergency Use Authorization ([EUA] *201779*).

This assay targets *both the ORF1 a/b non-structural region and nucleocapsid protein gene that are unique to SARS-CoV-2,* a well-conserved region of the matrix gene of influenza A, and the non-structural protein gene of influenza B. The cobas SARS-CoV-2 & Influenza A/B *test* was developed by mainly replacing the respiratory syncytial virus (RSV) primers and probes with those required to detect the SARS-CoV-2 targets in the existing *FDA-cleared* cobas Influenza A/B & RSV assay *(K153544)*. Previous studies of the cobas Influenza A/B & RSV assay remain relevant for the performance of influenza A/B targets in the cobas SARS-CoV-2 & Influenza A/B *test* (Gibson et al. 2017; Banerjee et al. 2018*, 2019; Gosert et al. 2019; Schmidt et al. 2019; Vos et al. 2019*).

For influenza A/B targets, clinical performance of the assay was evaluated at 12 CLIA-waived healthcare facilities using nasopharyngeal specimens prospectively collected from patients with signs and symptoms of respiratory infection in the United States during the 2013–2014 and 2014–2015 flu seasons (N = 1350). Additionally, retrospective nasopharyngeal specimens were obtained from two reference laboratories and tested at healthcare sites (N = 292). A total of 38 untrained operators representative of CLIA waived site intended operators participated in the study. Results for Influenza A/B were compared against the results from an FDA-cleared laboratory-based RT-PCR test (ProFlu+™, Prodesse, Waukesha, WI, USA).

For prospective specimens, the assay demonstrated positive percent agreement (PPA) of 98.3% and 95.2% for influenza A and influenza B, respectively; and negative percent agreement (NPA) of 96.0% and 99.4% for influenza A and influenza B, respectively. For retrospective specimens, the assay demonstrated PPA of 98.7% and 99.0% for influenza A and influenza B, respectively; and NPA of 99.1% and 99.5% for influenza A and influenza B, respectively. Overall, the cobas Liat System showed sensitivities of

98.4% and 97.9% for influenza A and influenza B, respectively, with specificities of 96.5% and 99.4% for influenza A and influenza B, respectively, as determined from PPA and NPA with reference test results (cobas SARS-CoV-2 & Influenza A/B Package Insert).

The accuracy of the cobas SARS-CoV-2 & Influenza A/B test for the detection of SARS-CoV-2 was *established* using *remnant* clinical *specimens* collected from patients with a suspected respiratory infection. Testing of *remnant* clinical samples was performed with the cobas SARS-CoV-2 & Influenza A/B test and *confirmed with a highly sensitive* FDA EUA-*authorized RT-PCR SARS-CoV-2 assay*, cobas SARS-CoV-2 test for use on the cobas 6800/8800 systems (Poljak et al. 2020). Results of *this* clinical performance evaluation demonstrated 100% PPA and 100% NPA compared with the *comparator assay (*cobas SARS-CoV-2 & Influenza A/B Package Insert*). Clinical performance of the cobas SARS-CoV-2 & Influenza A/B test relative to the cobas SARS-CoV-2 test for use on the cobas 6800/8800 systems was also evaluated in a multisite study using fresh clinical specimens from symptomatic and asymptomatic patients, which yielded 100% PPA and 97.4% NPA for SARS-CoV-2 targets (Hansen et al. 2021).*

Additionally, paired clinical nasopharyngeal and nasal swab specimens prospectively collected from patients with a suspected respiratory infection were tested with the cobas SARS-CoV-2 & Influenza A/B test and compared with another highly sensitive FDA EUA-authorized multiplexed RT-PCR EUA assay. For nasopharyngeal specimens, the cobas SARS-CoV-2 & Influenza A/B test demonstrated 95.2% PPA and 99.6% NPA for SARS-CoV-2 detection compared to the reference test. For nasal specimens (either healthcare provider-collected or self-collected swabs), cobas SARS-CoV-2 & Influenza A/B test demonstrated 96.4% PPA and 99.5% NPA for SARS-CoV-2 detection compared to paired nasopharyngeal specimen results from the reference test (cobas SARS-CoV-2 & Influenza A/B Package Insert). Since EUA was granted in September 2020, independent studies have also evaluated the sensitivity and specificity of the cobas SARS-CoV-2 & Influenza A/B test and found its clinical performance equivalent to routine laboratory-based RT-PCR methods (Er et al. 2021; Jian et al. 2021; Tsang et al. 2021).

These data demonstrate that the cobas SARS-CoV-2 & Influenza A/B *test* will provide accurate diagnosis of influenza A/B *and SARS-CoV-2 infections*.

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.4.1 Study Rationale

Seasonal influenza is a major burden to global health. There are an estimated 3–5 million cases of severe disease worldwide and approximately 290–650 thousand people die from influenza annually (Baxter 2016; WHO 2018a). Influenza also places significant demands on healthcare services each season, and impacts society through

lost workforce productivity (WHO 2018). Annual vaccination programs are the cornerstone of attempts to prevent influenza infections, but the effectiveness of these programs is variable due to both suboptimal uptake of vaccinations and mismatches between the vaccine and circulating influenza strains (CDC 2017). Consequently, the need for antiviral agents remains high.

Influenza A and B viruses are highly contagious (Vanderlinden and Naesens 2014). Most individuals with influenza infection are advised to stay at home until they have been afebrile for at least 24 hours, which puts other household members at risk of infection (CDC 2018a). Once one household member is infected with influenza, the risk of transmission to a household contact (HHC) can be up to 38%, with a delay between onset in the IP and infection of the HHC of around 3 days (Tsang et al. 2016). There is currently no agent for infected patients proven to reduce influenza transmission, and this is an important unmet medical need.

BXM is a first-in-class influenza antiviral that blocks RNA replication by inhibiting cap-dependent endonuclease activity (Omoto et al. 2018). BXM is administered by a convenient and unique one-dose, one-time regimen. In the Phase III (1601T0831/CAPSTONE-1) double-blind randomized study in OwH patients (Hayden et al. 2018), a single treatment of BXM (40 mg for patients $<$80 kg and 80 mg for patients $\geq$80 kg) significantly reduced the TTAS compared with placebo and also effectively reduced viral load, as shown by a significant reduction compared with placebo in:

- The proportion of patients with positive influenza titer between Days 2 and 5
- The proportion with positive influenza virus RNA determined by PCR on Day 5
- The median TTCVS

Study MV40618 was therefore designed to $assess$ if the ability of BXM to rapidly reduce viral load would translate into a reduction in onward transmission of influenza virus from infected individuals. The study will randomize patients with locally diagnosed influenza A/B infection to receive a single treatment $with$ BXM (40 mg for patients $<$80 kg and 80 mg for patients $\geq$80 kg) or matching placebo. The primary objective will be to assess the rate of onwards transmission to HHCs of the IPs who are PCR-negative (central laboratory confirmed) for influenza infection at baseline.

1.4.2 Benefit–Risk Assessment

The HHCs of the IPs with confirmed influenza infection may benefit in this study if treatment of the IP with BXM prevents transmission of the influenza virus to their HHCs. The IPs may also directly benefit from a therapeutic effect of treatment with BXM (see Section 1.2.2.1).

The risks posed to the IPs recruited to this study are believed to be minimal, as treatment with BXM has been shown to be well tolerated (see Sections 1.2.2.3 and

1.2.3). The numerous inclusion and exclusion criteria related to comorbidities associated with a high risk of influenza complications are designed to limit the IP study population to OwH individuals. These criteria will also limit the risk that IPs experience influenza complications. HHCs will not receive treatment with BXM.

With overlapping clinical symptoms between influenza and coronavirus disease 2019 (COVID-19), POC testing for the detection of influenza and SARS-CoV-2 infection is required for entry into the study to reduce the risk of enrolling IP and HHCs infected with SARS-CoV-2. During the study, IPs and HHCs will be tested for SARS-CoV-2 infection and if any household member tests positive, the household will be discontinued from the study given that self-quarantine remains as an advised or mandated requirement in many countries for the management of the COVID-19 pandemic. With the incorporation of the above measures, the benefit–risk profile of participants in this study is considered unchanged compared with study conduct pre-COVID-19 pandemic.

The protocol will permit enrollment of pediatric IPs aged 5–11 years old. Study CP40563 provides the necessary safety and *PK* data to support the dose rationale described in Section 3.4.1. This dose schedule was shown to be well tolerated with comparable efficacy to oseltamivir (see Section 1.2.2.1). The risks posed for OwH IPs aged 5–11 years old are believed to be minimal (no SAEs or deaths were reported in pediatric Studies CP40563, 1618T0822, and 1705T0833; see Section 1.2.2.3). Investigators must exclude IPs 5–11 years old judged to be at high risk for complications of influenza. In addition, IPs aged <5 years old will be excluded, given that this age range is considered to be at high risk of developing influenza-related complications (see Section 3.4.5).

No blood samples will be taken during the study, minimizing the risk of adverse events related to study procedures. The only invasive study-specific procedure that IPs and HHCs will undergo is a respiratory swab, which is generally considered to be a safe and routine medical procedure. The nasopharyngeal swab can be replaced with less invasive swabs such as midturbinate or nasal swabs as decided by the healthcare professional taking into account the tolerability of the procedure from the IP or HHC (e.g., for very young children). The location of the swab will be recorded each time.

It is possible that neither the HHCs nor the IPs will benefit in this study. However, HHCs who participate in this study will benefit from free, convenient monitoring and early/rapid diagnosis. HHCs who develop influenza will be allowed to be treated according to the local *SOC* for influenza management by their physician.

The data generated in this study will also enable further development of BXM.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy of a single, oral dose of BXM compared with placebo for the reduction of the direct transmission rate of influenza A/B from OwH IPs to HHCs. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of a single, oral dose of BXM compared with placebo to prevent secondary within-household transmission of influenza A/B.

2.1.1.1 Primary Efficacy Endpoint

- **Virological transmission by Day 5:** Proportion of HHCs who become PCR (+) [confirmed at central laboratory] for influenza by Day 5 visit, with virus subtype consistent with IP.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of a single, oral dose of BXM compared with placebo to prevent *virological or symptomatic* transmission of influenza A/B *and effects* beyond secondary within-household transmission according to the measures below.

Secondary endpoints will be submitted to a confirmatory statistical analysis with control for multiplicity based on a hierarchical testing procedure in accordance with the order described in Section 6.4.2.

2.1.2.1 Secondary Efficacy Endpoints

- **Symptomatic transmission by Day 5:** Proportion of HHCs who become PCR (+) [confirmed at central laboratory] for influenza by Day 5 visit, with virus subtype consistent with IP, **AND**:
  - For HHC aged ≥ 12 years:
    - Temperature ≥ 38.0°C* and one respiratory symptom, **OR**
    - One respiratory symptom and one general systemic symptom (with or without fever).
  - For HHC aged ≥ 2 to < 12 years:
    - Temperature ≥ 38.0°C* **AND** signs or symptoms of an upper respiratory tract infection.
  - Symptoms must be either new, or have worsened versus baseline in HHC with baseline symptoms due to a preexisting comorbidity.
  - * Temperature obtained from tympanic thermometers provided to households (or exceptionally from other thermometers/locations in case of tympanic thermometer failure for any reason).

- **Virological transmission at the household level by Day 5:** Proportion of households with at least one HHC who meets the primary endpoint.
- **Symptomatic transmission at the household level by Day 5**: Proportion of households with at least one HHC who meets the "Symptomatic transmission by Day 5" endpoint.
- **Virological transmission by Day 9:** Proportion of HHCs who become PCR (+) (confirmed at central laboratory) for influenza by Day 9 visit, with virus subtype consistent with IP, including:
  - (1) all HHC meeting primary endpoint, **AND**
  - (2) all HHC cases detected after Day 5 visit meeting the following criteria:
    a) Included HHC case is in a household where another HHC has already met the primary endpoint, **OR**
    b) Included HHC case is PCR (+) [confirmed at central laboratory] for influenza bearing *an amino acid substitution of isoleucine for another amino acid at position 38 (I38X) in the polymerase acidic (PA) protein (*PA/I38X substitution*)* (or other identified substitutions listed in Section 3.4.6.4).
- **Symptomatic transmission by Day 9:** Proportion of HHCs who meet the "Virological transmission by Day 9" endpoint **AND** are symptomatic per the definition for symptoms in the "Symptomatic transmission by Day 5" endpoint.
- **Any virological infection by Day 9:** Proportion of HHCs who become PCR (+) for influenza (confirmed at central laboratory) by Day 9.
- **Any virological infection at the household level by Day 9:** Proportion of households with at least one HHC who meets the "Any virological infection by Day 9" endpoint.
- **Any symptomatic infection by Day 9:** Proportion of HHCs who meet the "Any virological infection by Day 9" endpoint **AND** are symptomatic per the definition for symptoms in the "Symptomatic transmission by Day 5" endpoint.
- **Any symptomatic infection at the household level by Day 9:** Proportion of households with at least one HHC who meets the "Any symptomatic infection by Day 9" endpoint.

2.1.3 Other Efficacy Objective

The other efficacy objective for this study is to further evaluate the efficacy of a single, oral dose of BXM compared with placebo to prevent transmission of influenza A/B according to the measures below.

2.1.3.1 Other Efficacy Endpoints

- The effect of IP baseline viral titer on the rate of direct transmission of influenza A or influenza B to HHCs.

- **BXM arm only:** Proportion of IPs who are PCR (+) [confirmed at central laboratory] for influenza bearing a PA/I38X substitution (or other identified substitution) post randomization.
- **BXM arm only:** Proportion of HHCs who become PCR (+) [confirmed at central laboratory] for influenza bearing a PA/I38X substitution (or other identified substitution) *with matched PA substitution with their IP* by Day 9 visit.
- **BXM arm only:** Proportion of symptomatic cases among HHCs who become PCR (+) [confirmed at central laboratory] for influenza bearing a PA/I38X substitution (or other identified substitution) *with matched PA substitution with their IP* by Day 9 visit (utilizing same symptoms definition as used for secondary symptomatic transmission endpoint).
- Proportion of HHC who become PCR (+) [confirmed at central laboratory] for influenza by Day 9 visit, with virus subtype consistent with IP.
- Measurement of viral titer *by* PCR *and TCID50* in IPs over *the* Day 0, 3, 5, and 9 visits.
- **Subgroup analysis:** endpoints requiring a subtype match will be assessed with a match based on sequencing in a subset of households (sequencing will be performed for samples from selected sites and countries based on feasibility, including availability of adequate number of IP sequences for specific community).

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of a single, oral dose of BXM compared with placebo according to the measures below.

2.2.1 Safety Endpoints

- ***IP* only:** The incidence, severity, and timing of adverse events, and serious adverse events.

2.3 HEALTH STATUS UTILITY OBJECTIVE

The health status utility objective for this study is to evaluate IPs treated with BXM compared with those receiving placebo according to the measures below.

2.3.1 Health Status Utility Endpoints

- ***IP ≥12 years old* only:** Change from baseline in health-related quality of life according to EQ-5D-5L questionnaire (Appendix 3) at Day 3 and Day 9 visits.
- ***IP ≥12 years old* only:** Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: SHP, Version 2 (WPAI+CIQ:SHP, V2) to measure lost work or school days (Appendix 4) assessed at Day 9 visit.

2.4 *ADDITIONAL OBJECTIVE*

An additional objective for this study is to describe the palatability and acceptability of BXM oral suspension in IPs <12 years old on the basis of the following endpoint:

- *Proportion of IPs reporting each palatability and acceptability response (Appendix 5)*

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a randomized, double-blind, multicenter, parallel-group, placebo-controlled study designed to evaluate the clinical efficacy of BXM for the reduction of direct transmission of influenza A/B from OwH IPs to their HHCs. For this household study, IPs with influenza will be randomized to receive BXM or placebo, and their HHCs will be repeatedly tested for influenza virus and assessed for influenza symptoms during the next 9 days. The total number of new HHC infections (symptomatic and asymptomatic) and total number of new HHC infections associated with symptoms will be key measures used to evaluate the "virological transmission" and "symptomatic transmission" endpoints (see Section 2).

Approximately 1,130 IPs with influenza and approximately 2,030 evaluable HHCs will participate (assuming an average of 2.5 HHCs per IP, a 15% exclusion rate at the household level, and a 15% drop-out rate) in the study. The total study duration for each household will be up to 9 (±1) days (IPs aged 5–11 years old will have a safety follow-up visit at 21 [+2] days). This study will be conducted at approximately *200* sites globally in the Northern and Southern hemispheres.

Index Patient: Screening and Randomization

Eligible IPs must be aged from ≥5 to ≤64 years old, have influenza symptom onset within 48 hours, test positive for influenza A/B, and be OwH (i.e., not at high risk for complications of influenza). Screening assessments informing IP eligibility include physical examination, vital signs, height and weight, medical history and concomitant therapies, urine pregnancy testing, and respiratory sampling for influenza testing (see Appendix 1a for details).

With regard to the household, IPs should be determined at screening to live with *1 or more* HHCs who have not received an influenza vaccine in the past 6 months ("unvaccinated HHCs"), are likely to fulfill all HHC eligibility criteria, and are expected to participate in the "full study" (i.e., participate in all study assessments in Appendix 1b).

IPs who meet the eligibility criteria (see Section 4.1) will be randomized in a 1:1 ratio to receive a single dose of either BXM or placebo within 2 hours of randomization. The dose and formulation of BXM is based on weight and age (see Section 4.3.2).

Index Patient: Post-Randomization

Respiratory samples and AEs will be collected. IPs *who are ≥12 years old* will also complete questionnaires describing their health status and absence from work or school (see Appendix 3 and Appendix 4). *IPs who are <12 years old will be asked to complete a questionnaire on the palatability and acceptability of the study drug oral suspension (see Appendix 5).* See Appendix 1a for details and timing of study assessments.

Household Contacts: Screening and Enrollment

All HHCs present in the home must have their screening visit start within 24 hours of IP randomization (see Section 4.5.9 for details). If any HHC tests positive for influenza A/B, then all HHCs fail screening. If *1 or more* unvaccinated HHCs meet all HHC eligibility criteria and agree to participate in the full study, it is allowable for additional HHCs to not participate beyond the screening visit (even if they meet all HHC eligibility criteria). There is no maximum number of vaccinated and unvaccinated HHCs that can participate in the full study.

HHCs who agree to participate in the full study ("full study HHCs") must meet the full study criteria (HHC inclusion criteria 7 to 14; see Section 4.1.1), including that they must reside in the household for 7 of the 9 study days, and must not have any influenza symptoms at screening (mild symptoms determined by the investigator to be due to a preexisting condition are allowed).

Screening assessments informing HHC eligibility include influenza symptoms (see Appendix 2), medical history, concomitant medications, and respiratory sampling for influenza testing (see Appendix 1b for details).

Full Study Household Contacts: Post-Screening

Only full study HHCs participate in visits and assessments post-screening. Full study HHCs are monitored for new or worsening influenza symptoms (see Appendix 2), and will also maintain a daily temperature diary (see Section 4.5.6). HHCs will be instructed to telephone the site if they develop influenza symptoms or fever so that a scheduled or unscheduled visit occurring within 24 hours can be arranged (see Section 4.5.6). Respiratory samples, adverse events due to study procedures, and concomitant medications will be collected (see Appendix 1b for details).

Study Visits

The IP screening visit must occur at the study site. All other visits for IPs and HHCs may be conducted at home or at the *study site*. Home visits may be performed by home nurses or by site staff (if local practices are in place). All assessments except respiratory swab collection may be conducted remotely (e.g., via telephone or computer).

SARS-CoV-2 Testing

Given overlapping influenza and COVID-19 symptoms, SARS-CoV-2 testing will be conducted at screening and as needed during study conduct (see Section 4.5.5.2). If any

subject (IP or HHC) tests positive for SARS-CoV-2, then all subjects in the household should be discontinued (see Section 4.6.2).

Independent Data Monitoring Committee

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

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs. The end of the study for all patients (except IPs $<$12 years old) is expected to occur 9 days after the last IP is enrolled. For IPs $<$12 years old, the last visit will be Day 21.

The expected study duration for both IPs and $full\ study$ HHCs is 9 days, and study duration for IPs $<$12 years old is 21 days.

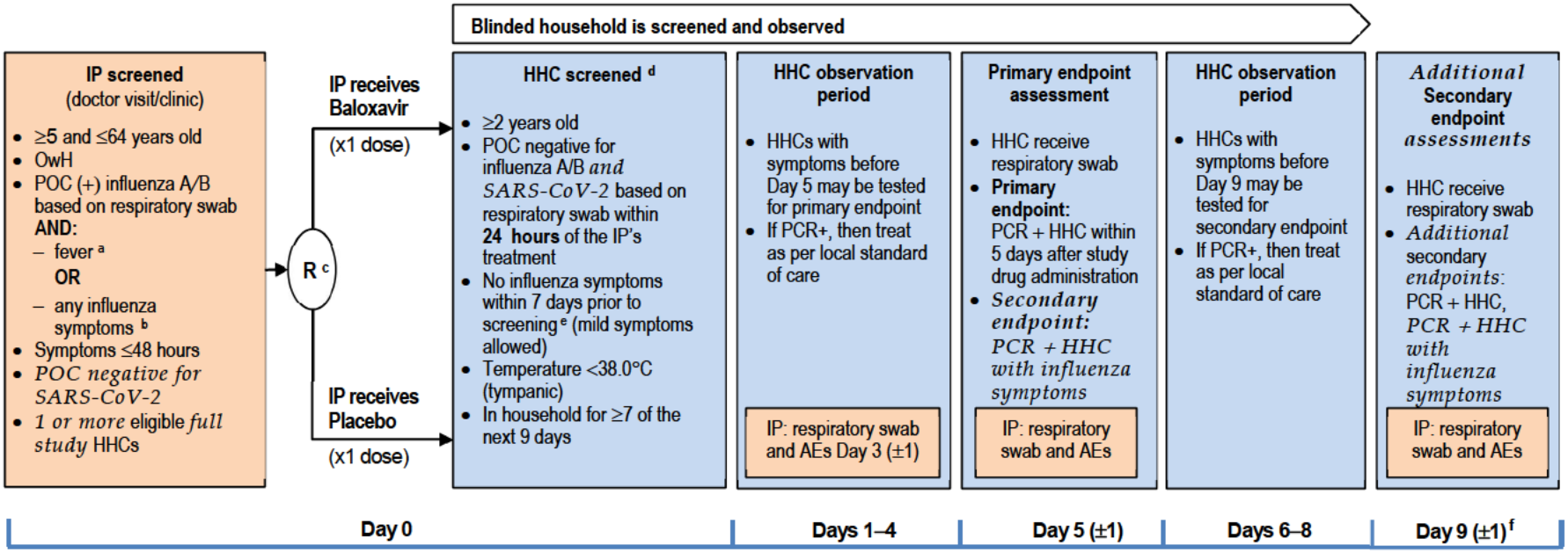
The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3.5 years.

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

3.3 STUDY SCHEMA

Figure 1 presents an overview of the study design. A schedule of activities for the IPs is provided in Appendix 1a and a schedule of activities for HHCs is provided in Appendix 1b.

Figure 1 Study Schema



AEs = adverse events; HHC = household contact; IP = index patient; OwH = otherwise healthy; PCR = polymerase chain reaction; POC = point of care.

[a] ≥38.0°C per tympanic or rectal thermometer; ≥37.5°C per axillary, oral or forehead/temporal thermometer.

[b] Cough, sore throat, nasal congestion, headache, feverishness or chills, muscle or joint pain, fatigue.

[c] Stratification factors: age; household size; region; time since symptom onset.

[d] HHC screening must start within 24 hours of IP randomization, and may occur on IP study Day 0 or 1.

[e] Symptoms for HHC ≥12 years old: cough, sore throat, nasal congestion, headache, feverishness or chills, muscle or joint pain, fatigue; Symptoms for HHC ≥2 to <12 years old: cough, nasal congestion or rhinorrhea.

[f] IPs <12 years old will have a safety follow-up visit on Day 21 (+2 days).

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Baloxavir Marboxil Dose and Schedule

The doses and schedules selected for this study (see Section 4.3.2.1) have been demonstrated to be safe and effective in previous large randomized controlled studies in patients aged ≥12 years old and <12 years old.

Dose and Schedule for Patients ≥12 Years Old based on Study 1601T0831

Study 1601T0831 (CAPSTONE-1; Hayden et al. 2018) compared the effects of a single dose of BXM (40 mg for patients <80 kg and 80 mg for patients ≥80 kg administered as 20 mg tablets) with placebo or oseltamivir in OwH patients with influenza aged from ≥12 to ≤64 years of old. Study 1601T0831 demonstrated that a single 40 mg/80 mg dose on Day 1 was well tolerated and significantly reduced the TTAS (the primary efficacy endpoint; see Section 1.2.2 for further details). This dose and regimen were also effective at reducing viral load (see Section 1.4.1).

Dose and Schedule for Patients *5 to* <12 Years Old based on Study CP40563

Study CP40563 (miniSTONE-2; Baker et al. 2020) compared the effects of a body weight-adjusted dose of BXM (<20 kg [2 mg/kg] and ≥20 kg [40 mg] administered as an oral suspension) with oseltamivir administered twice daily on Days 1–5 in OwH patients with influenza aged from ≥1 to <12 years old. Study CP40563 demonstrated that both BXM and oseltamivir groups had a similar incidence of AEs and median TTAS of influenza. There were no deaths, SAEs, or hospitalizations reported (see Section 1.2.2). The antiviral activity of BXM was shown to be favorable compared with oseltamivir. This regimen enables BXM exposures in patients <12 years old that are similar to the exposures observed in Study 1601T0831.

3.4.2 Rationale for Patient Population and Analysis Groups

As described above, treatment with BXM has been shown to reduce viral load and symptoms in patients with influenza A/B. Therefore, this study was designed to see if this translated into a reduction in viral transmission. HHCs of patients with confirmed influenza A/B infection were selected to test this hypothesis, as these individuals will be in close contact with the infected individual. As stated in Section 1.4.1, the estimated risk of transmission from an IP to HHCs is up to 38% (Tsang et al. 2016).

The inclusion criteria limit IPs to those with symptom onset within 48 hours. This is because it is believed that BXM will be most effective at preventing viral transmission if given early in the course of infection. (This 48-hour period is also consistent with the labels approved to date for BXM in countries including the *United States*, Hong Kong, and Japan).

The study eligibility criteria allow for the inclusion of IPs who are minors. This is also consistent with the labels approved to date for BXM, which include approved for use in individuals aged ≥12 years old in some countries and any age in Japan ≥10 kg. As this

is a household study, and intended to reflect a real-world population, child HHCs aged ≥2 years old are also included. Children have an important role in the transmission of influenza and have higher attack rates than adults (Longini et al. 1982).

The primary efficacy analysis population will consist of all unvaccinated full study HHCs of the randomized IPs. HHCs vaccinated against the current season's influenza are expected to be protected from influenza transmission. However, to enhance the feasibility of the trial, and to reflect how BXM would be used for the prevention of influenza within households in the real-world setting, the protocol allows enrollment of vaccinated HHCs, as long as there is a minimum of one otherwise eligible non-vaccinated HHC.

Similarly, HHCs who will not be present in the IP's home during the majority of the study due to travel commitments may be less likely to become infected than those present throughout the study period. Again, to enhance the study feasibility, the protocol allows enrollment of households with an unlimited number of HHCs who are not present for the minimum 7- of the 9-day study period, as long as there is at least one otherwise eligible non-travelling (and non-vaccinated) HHC.

3.4.3 Rationale for Study Duration

The focus of the study is to assess the effect of BXM on reduction of transmission. It is expected that by Day 5 most secondary transmission will have occurred, since at randomization (patients are randomized within 48 hours of onset of symptoms) IPs will be at or near their peak viral shedding, which subsequently decreases rapidly due to natural course of influenza in OwH patients.

Furthermore, by Day 9, many tertiary transmissions will have occurred, since HHCs infected via secondary infection by Day 5 will achieve maximal viral shedding at least a few days before Day 9.

Finally, transmissions of virus with reduced susceptibility will have occurred by Day 9, based on maximum viral shedding of I38X mutants observed at approximately 4 days post BXM administration in previous studies.

Extension of the time window beyond Day 9 may increase the risk of externally acquired infections being counted in the assessment of the endpoints.

The 9-day study duration for IPs and $full\ study$ HHCs was also designed with feasibility in mind. A short study duration will limit the burden on study participants. Furthermore, it would be difficult to ensure that study participants will be available for repeat visits over an extended period due to school and work obligations.

IPs aged 5 $to < 12$ years old will have their study duration extended to facilitate a safety follow-up visit on Day 21. This last visit corresponds to $at\ least$ five half-lives for

baloxavir, and safety data generated in this study will complement safety data generated in other pediatric studies.

3.4.4 Rationale for Selection of Symptoms Assessed in Household Contacts and the Definition of Clinical Influenza

The secondary "Symptomatic transmission endpoint" (see Section 2.1.2.1) is designed to measure the clinical burden resulting from transmission of influenza, i.e. measure the number of cases of symptomatic influenza.

Separate definitions for symptomatic influenza are applied to HHC ≥ 12 years versus < 12 years *old*. Both definitions assess constitutional and respiratory signs and symptoms which characterize uncomplicated influenza, namely fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis (Fiore et al. 2008). Key elements of both definitions have precedence in previous trials, including the Fluzone® vaccine trials (Fluzone® Quadrivalent Prescribing Information) and previous BXM studies (Hayden et al. 2018).

For HHCs ≥ 12 years old, the following defines symptomatic influenza:

- PCR+ (confirmed at central laboratory), **AND** one of the following:
  - Temperature ≥ 38.0°C **AND** one respiratory symptom (cough, sore throat, nasal congestion), **OR**
  - One respiratory symptom (cough, sore throat, nasal congestion) **AND** one general systemic symptom (headache, feverishness or chills, muscle or joint pain, fatigue) (with or without fever)

For HHCs ≥ 2 to < 12 years old, the symptom assessment will be conducted by the responsible adult, and therefore a simplified list of objectively observable yet very frequently occurring signs and symptoms will be used. The following defines symptomatic influenza for this age range:

- PCR+ (confirmed at central laboratory), **AND**
- Temperature ≥ 38.0°C **AND** signs or symptoms of an upper respiratory tract infection (cough, nasal congestion or rhinorrhea).

The study may enroll some HHCs who may have comorbidities with symptoms overlapping with influenza-like symptoms (e.g., respiratory allergies, autoimmune or musculoskeletal conditions). In order to strike a compromise between encouraging real world representation while simultaneously ensuring an adequately evaluable symptoms endpoint, HHCs with influenza-like symptoms at baseline will be allowed into the study **IF** their influenza-like symptoms are no worse than "mild" (per contact's assessment) and considered by the investigator to be due to their underlying condition and not indicative of influenza. HHCs with fever ≥ 38.0°C or PCR+/Rapid Influenza Diagnostic Test (RIDT)+ will not be enrolled. For HHCs with baseline symptoms, their influenza will

be considered to be symptomatic if the HHCs consider their baseline symptoms to have *worsened* (versus baseline), in addition to meeting the other symptom definition criteria.

An HHC will be determined to have 'symptomatic influenza' (i.e., the secondary "Symptomatic transmission endpoint" will be met) even if symptom onset occurs after the sample collection yielding influenza virus (the Day 5 visit or an unscheduled visit before the Day 5 visit). Therefore, symptoms will continue to be assessed throughout the study.

HHCs will measure their own temperatures at bedtime and whenever they feel feverish (or have their temperature measured by a responsible adult) (see Section 4.5.6). To promote consistency, households will be provided with tympanic thermometers, however other anatomical sites may be measured (axillary, oral, forehead/temporal, rectal temperatures) on an exceptional basis (in case of tympanic thermometer breakage, etc.) and the anatomical site will be documented by the contact.

To further promote consistency and capture of symptoms, study healthcare providers will query HHCs about new or worsening influenza-like symptoms at all screening, Day 5, Day 9, and unscheduled visits (see Appendix 2), and HHCs will be instructed to contact the site/study nurse at any time in case of not feeling well.

A note regarding fever: The presence of fever is not always required to meet the endpoint for HHCs 12 and older. Although fever is included in commonly accepted case definitions for influenza-like illness (CDC 2018b; WHO 2018b), fever is not always present in patients with confirmed influenza. In a retrospective, pooled analysis involving eight Phase II and Phase III clinical trials, 32% of 2,470 patients with laboratory-confirmed influenza did not have fever ($\geq$37.8°C) (Monto et al. 2000). Furthermore, fever may present less commonly in the elderly compared with younger adults (Norman 2000).

3.4.5 Rationale for Control Group

This is a placebo-controlled study. Placebo was selected for the control group, as opposed to oseltamivir (Tamiflu®), because oseltamivir is not a SOC treatment for preventing influenza virus transmission. The effect of oseltamivir on transmission from an IP to an HHC has not been studied in an adequately powered placebo-controlled randomized trial. Comparison with placebo will enable analysis of the true effect of BXM on preventing influenza virus transmission.

Given that IPs randomized to the control group will receive placebo as the only treatment for influenza, this study is restricted to OwH patients (i.e., patients who are not at increased risk for complications of influenza). The U.S. Centers for Disease Control and World Health Organization provide guidance that IPs aged $<$5 and $>$64 years old are at high risk. Furthermore, certain medical conditions (e.g., emphysema or asthma) regardless of age predispose a person as high risk. Therefore, only patients aged from

≥5 to ≤64 years old and judged by the investigator not to be at high risk for complications will be eligible.

3.4.6 Rationale for Virology Assessments

All virology assessments in this study will be based on respiratory swabs.

3.4.6.1 Diagnosis of Influenza A/B Infection

This study will preferentially use the cobas $SARS\text{-}CoV\text{-}2$ & Influenza A/B test at study visits to provide information on influenza A/B infection for the enrollment of IPs and HHCs. This system has high sensitivity and specificity for detecting influenza A/B infections (see Section 1.3). The use of this POC system will facilitate the timely diagnosis of influenza infection and enrollment of IPs, and the rule-out of infection in HHCs at screening.

This cobas Liat System will also be used for POC assessment of influenza A/B infection for HHCs throughout the study.

If PCR-based POC testing using the cobas $SARS\text{-}CoV\text{-}2$ & Influenza A/B test is not available at the study site, other POC tests or local laboratory results can be used instead (see Section 4.5.5.2).

All respiratory samples will also be analyzed in the central laboratory (see Section 4.5.5.3). Central laboratory PCR will be used to determine whether HHCs meet the eligibility criteria for purposes of the primary analysis population (all HHCs within a household were PCR-negative for influenza at screening), and to determine if primary and secondary efficacy endpoints have been met (HHCs become PCR-positive for influenza).

3.4.6.2 Viral Type and Subtype Assessment

Respiratory samples collected from IPs on Day 0 and HHCs who become PCR positive (confirmed at central laboratory) for influenza during the study will be analyzed in a central laboratory. Only HHCs with an influenza type (A or B) and influenza A subtype (H1N1 and H3N2) subtype that is consistent with that of the IP (i.e., consistent with within-household transmission) will be considered for the primary efficacy endpoint and secondary efficacy endpoints as indicated in Section 2.1.

Viral genome sequencing will not be used to confirm infection origin in HHCs (i.e., consistency with the IP) for the purpose of the primary and secondary endpoints. This is because sequencing and subsequent phylogenetic analysis cannot reliably determine infection origin at study sites with low IP numbers (see Section 3.4.6.5).

Several studies indicate that levels of co-incident transmission (i.e., transmission of infection originating outside the household) are likely low. One study estimated that 97% of secondary cases were acquired within the household (Tsang et al. 2015). In another

study, sequence analysis of 52 epidemiologically linked putative household transmission events (symptom onset within a 7-day window) showed that 47 (91%) were likely to be true household transmission pairs and five were suspicious for co-incident community acquired infection (McCrone et al. 2018).

Based on this low level of co-incident community-acquired infection, and the limitations of the sequencing approach, all infections in households will be assumed to be due to within-household transmission as long as the virus subtype is consistent with the IP.

3.4.6.3 Viral Titer Assessment

Respiratory samples collected from IPs at the timepoints indicated in Appendix 1a will also be used to measure influenza viral titer to determine if viral titer impacts on the ability of BXM to prevent transmission of influenza from OwH patients to HHCs (other efficacy endpoint).

To maximize the chances of identifying a relationship between viral titer in the IP and the ability of BXM to prevent transmission to HHCs, viral titer will be assessed using two techniques: quantitative PCR (using C_T [threshold cycle] values on Days 0, 3, 5, and 9) and infectivity (using the TCID50 *on Days 0, 3, 5, and 9*).

3.4.6.4 Analysis of Viruses with Reduced Susceptibility to Baloxavir Marboxil

Amino acid substitutions in the polymerase acidic (PA) protein have been linked with reduced susceptibility to BXM (Omoto et al. 2018). In particular, the isoleucine to threonine substitution at position 38 (I38T substitution). Treatment-emergent amino acid substitutions in the PA protein that have been associated with reduced susceptibility to BXM to date include:

- Influenza A/H1N1: E23K/R, I38F/*N/S/*T
- Influenza A/H3N2: E23G/K, A37T, I38M/T, E199G
- Influenza B: I38T

Viral RNA sequencing of samples collected from patients treated with BXM will be conducted to identify treatment-emergent amino acid substitutions to evaluate whether the efficacy of BXM for preventing viral transmission is affected by the viral genotype (selected secondary and other endpoints).

Samples from IPs who experience a rebound in viral titers and/or show treatment-emergent amino acid substitutions in PA identified by sequencing analysis will be assayed for phenotypic reduced susceptibility (as per Table 3).

3.4.6.5 Viral Genome Sequencing

Whole genome next-generation sequencing will be conducted on respiratory samples from HHCs and IPs at a central laboratory from selected sites. This will be done as a supportive analysis in a subset of study subjects to assess the accuracy of using viral

type/subtype assessment (see Section 3.4.6.2) to match IP to HHC transmission for the primary/secondary endpoints. The feasibility of this sequencing analysis will depend on sufficient samples being obtained. Sites will be selected on the basis that they can provide adequate numbers of IPs with unique sequences, or if sequences from databases for the same season are available for this community.

3.4.6.6 Other Viral Parameters

No blood-based assessments will be conducted in this study. The rationale for this is to reduce the burden on the study participants and to increase the feasibility of the study. Consequently, parameters such as the serum influenza antibody titer cannot be assessed in this study.

Serum antibody titer in patients treated with BXM has been studied previously. The CAPSTONE 1 study (Study 1601T0831; Hayden et al. 2018) measured serum influenza antibody titer on Day 1 and Day 22 in OwH adult and adolescent patients with uncomplicated influenza randomized to a single dose of BXM (40 mg for patients who weigh $<$80 kg and 80 mg for patients who weigh $\geq$80 kg), oseltamivir 75 mg twice daily for 5 days, or placebo (see Section 1.2.2.1). Apparent increases in serum influenza antibody titer were found on Day 22 in all three treatment groups, regardless of the infected virus type/subtype, with no statistically significant differences between groups.

3.4.6.7 Diagnosis of SARS-CoV-2 Infection

COVID-19 is an infectious disease caused by the coronavirus SARS-CoV-2. This virus and disease became known in December 2019 and has since become a global pandemic. Common symptoms are fever, dry cough, *loss of taste or smell,* and tiredness. Less common symptoms include aches and pains, nasal congestion, headache, conjunctivitis, sore throat, diarrhea, a rash on skin, or discoloration of fingers or toes. Some of these symptoms overlap with those for influenza.

Many communities worldwide recommend or require that people with suspected or confirmed SARS-CoV-2 infection self-isolate and only visit designated healthcare facilities. There is limited data concerning outcomes in patients with influenza and SARS-CoV-2 coinfection.

All IPs will be screened for SARS-CoV-2 infection. Those found to be infected will be excluded from the study.

All HHCs will also be screened for SARS-CoV-2 infection. If any HHC is found to be infected, no HHCs from the same household may be enrolled and the IP will be withdrawn from the study. Excluding households with SARS-CoV-2 infection will allow households to better comply with community requirements regarding isolation and avoid further unnecessary contact with healthcare providers and non-designated healthcare facilities (i.e., the study site).

See Section 4.5.5.2 for SARS-CoV-2 testing post-enrollment.

4. MATERIALS AND METHODS

4.1 INDEX PATIENTS AND HOUSEHOLD CONTACTS

The proposed sample size for this study is 2,030 evaluable HHCs. Assuming a 15% drop-out for inclusion of HHCs into the primary analysis population, an average of 2.5 HHCs per IP and a 15% exclusion rate on the household level, this equates to an approximate number of IPs of 1,130.

4.1.1 Inclusion Criteria

Inclusion Criteria: Index Patients

Each IP must meet the following criteria for study entry:

1. Signed Informed Consent Form (ICF). In the case of minors, a parent or authorized adult will be required to sign the ICF on behalf of the patient. The informed consent/assent of voluntary participation should be obtained in accordance with local requirements.
2. Age ≥5 and ≤64 years at time of signing ICF.
3. Able to comply with the study protocol per investigator judgment.
4. Diagnosed with acute influenza infection by investigator.
5. PCR (+) or RIDT (+) for influenza A/B based on cobas *SARS-CoV-2 & Influenza A/B test* or other point-of-care/local laboratory results.
6. PCR (–) or antigen test (–) for SARS-CoV-2 based on cobas SARS-CoV-2 *& Influenza A/B test* or other point-of-care/local laboratory result.
7. Presence of (a) fever (≥38.0°C per tympanic or rectal thermometer; ≥37.5°C per axillary, oral or forehead/temporal thermometer) or (b) any influenza symptoms (cough, sore throat, nasal congestion, headache, feverishness or chills, muscle or joint pain, fatigue).
8. The time interval between the onset of fever or influenza symptoms and the pre-dose examinations is 48 hours or less.
9. IP lives in a household where:
    a) No HHC is known to have been diagnosed with influenza or SARS-CoV-2 infection by a healthcare professional in the past 4 weeks.
    b) All HHCs are expected to meet the key HHC inclusion criteria (criteria 1, 2, 3, 4, 5, and 6).
    c) *1 or more* HHCs are expected to participate in the full study who have not received the influenza vaccine within 6 months prior to screening.

10. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures as defined below:

    Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 21 days after the final dose of $study\ treatment$.

    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 is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

    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.

    Hormonal contraceptive methods must be supplemented by a barrier method.

    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. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Inclusion Criteria: All Household Contacts

Each HHC living in the home at any time during the study must meet criteria 1–6 below. The screening visit should start within 24 hours $after$ IP randomization unless the HHC is a late-arrival HHC (see Section 4.5.9):

1. Signed ICF. In the case of minors, a parent or authorized adult will be required to sign the ICF on behalf of the HHC. The informed consent/assent of voluntary participation should be obtained in accordance with local requirements. All late-arrival HHCs (as defined in Section 4.5.9) must be willing to be consented for screening as soon as possible after their arrival.
2. PCR (–) or RIDT (–) based on cobas $SARS\text{-}CoV\text{-}2\ \&$ Influenza A/B $test$ or other local point-of-care/local laboratory result.
3. PCR (–) or antigen test (–) for SARS-CoV-2 based on cobas SARS-CoV-2 $\&$ $Influenza\ A/B\ test$ or other POC/local laboratory result.
4. HHC lives with no HHC who will be present in the home at any time during the study and who meets any HHC exclusion criteria.
5. HHC lives with no HHC (except late-arrival HHCs) who does not meet HHC inclusion criteria 1–6.

6. HHC lives in a household where *1 or more* HHCs meet all of the following:
    a) Start screening within 24 hours *after* IP randomization.
    b) Have NOT received the influenza vaccine within 6 months prior to screening.
    c) Fulfill full study HHC inclusion criteria 7–14.

Inclusion Criteria: Full Study Household Contacts

Each HHC intended for **full study** must meet the following additional criteria:

7. Agree to participate in the full study (i.e., participate in all assessments after screening).
8. Able to comply with the study protocol per investigator judgment.
9. No influenza symptoms within 7 days prior to screening. Alternatively, mild symptoms (at worst) are permissible if determined by the investigator to be due to a preexisting condition (e.g., mild nasal congestion due to seasonal allergies).
    a) Symptoms for HHC $\geq$12 years old: cough, sore throat, nasal congestion, headache, feverishness or chills, muscle or joint pain, fatigue.
    b) Symptoms for HHC $\geq$2 to $<$12 years old: cough, nasal congestion or rhinorrhea.
10. Temperature $<$38.0°C (tympanic).
11. Will reside in the IP's house for at least 7 of the next 9 days and will be present for scheduled study visits.
12. Willing and able to measure and record temperature, or have another household member perform the task on his or her behalf. Furthermore, a responsible adult will assume responsibility to oversee or perform this task on behalf of minors.
13. In the 6 months prior to screening:
    a) Has not been diagnosed with influenza by a healthcare professional
    b) Has not received BXM, peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir, amantadine*, or favipiravir*
14. Does not have a moderate or worse active infections **OR** infections requiring systemic (e.g., oral or intravenous) or otherwise internally administered (e.g., inhaled, intrathecal) antibiotic/antiviral/antifungal therapy, (topical therapies for mild external infections allowed).

4.1.2 Exclusion Criteria

Exclusion Criteria: Index Patients

An IP meeting any of the following criteria will be excluded from the study:

1. IP with severe influenza virus infection requiring inpatient treatment.
2. IP judged by the investigator to be at high risk for complications of influenza, after consideration of the following* or other potential risk factors:
    a) Women who are pregnant or within 2 weeks post-partum;

b) Chronic respiratory diseases including chronic obstructive pulmonary disease, current asthma, and cystic fibrosis;

c) Neurological and neurodevelopmental disorders including disorders of the brain, spinal cord, peripheral nerve, and muscle (e.g., cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury);

d) Heart disease (such as congenital heart disease, congestive heart failure, or coronary artery disease);

e) Blood disorders (such as sickle cell disease);

f) Endocrine disorders (such as diabetes mellitus);

g) Kidney disorders;

h) Liver disorders;

i) Metabolic disorders (such as inherited metabolic disorder and mitochondrial disorders);

j) Compromised immune system due to disease (such as people with HIV or AIDS, or some cancers such as leukemia) or medications (such as those receiving chemotherapy or radiation treatment for cancer, or persons with chronic conditions requiring chronic corticosteroids or other drugs that suppress the immune system);

k) Morbid obesity (body mass index [BMI] ≥ 40);

l) People younger than 19 years of age on long-term aspirin- or salicylate-containing medications;

m) *People from certain racial and ethnic minority groups are at increased risk for hospitalization with influenza, including non-Hispanic Black persons, Hispanic or Latino persons, and* American Indian or Alaska Native *persons. The investigator should consider the overall risk of the individual.;*

n) People who live in nursing homes and other long-term care facilities.

**** Adapted from the definition of "People at Higher Risk of Flu Complications" provided by the Centers for Disease Control and Prevention (CDC 2021)***

3. IP is ≥ 12 years old and unable to swallow tablets (not applicable to IPs 5 *to* <12 year olds who will receive oral suspension).
4. Women who are breastfeeding or have a positive pregnancy test in the pre-dose examinations. Female patients with documentation of at least one of the following items are exempt from pregnancy testing:

    a) Postmenopausal women (defined as cessation of regular menstrual periods for ≥ 12 continuous months).

    b) Women who are surgically sterile by hysterectomy, bilateral oophorectomy, or tubal ligation.

    c) Females < 12 years old and pre-menarcheal.

5. IP with concurrent (non-influenza) infections requiring systemic antimicrobial and/or antiviral therapy at the pre-dose examinations.
6. IP who has received BXM, peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir, amantadine*, or favipiravir* within 30 days prior to screening.
7. IP who has received an investigational monoclonal antibody for a viral disease in the last year.
8. IP who has received an investigational therapy within 30 days or 5 drug-elimination half-lives, whichever is longer, prior to screening.
9. IP lives with an HHC who, based on available information, is:
    a) Pregnant or within 2 weeks post-partum.
    b) Immunocompromised (including patients receiving immunosuppressant therapy, or those with cancer or HIV infection).
    c) $<$2 years old.
    d) Unwilling to sign informed consent.
    e) Diagnosed with influenza or SARS-CoV-2 infection by a healthcare professional in the past 4 weeks.
    f) Previously included in the study.
    g) Plan to arrive home from after 24 hours post IP randomization to Day 9 and (late-arrival HHC defined in Section 4.5.9) is not willing to be consented as soon as possible upon arrival.
10. Known hypersensitivity to BXM or the drug product excipients.
11. Any other contraindication for treatment with BXM as deemed by the treating physician or Principal Investigator.
12. IP previously included in the study.

Exclusion Criteria: *All* Household Contacts

An HHC (living in the home at any time during the study) meeting any of the following criteria will be excluded from study entry:

1. Pregnant or within 2 weeks post-partum at screening.
2. Immunocompromised (including patients receiving immunosuppressant therapy, or those with cancer or HIV infection).
3. $<$2 years old.
4. Received an investigational therapy within 30 days or 5 drug-elimination half-lives, whichever is longer, prior to screening.
5. Diagnosed with influenza or SARS-CoV-2 infection by a healthcare professional in the past 4 weeks.
6. HHC previously included in the study.

7. HHC who plans to arrive home after 24 hours post IP randomization to Day 9 and (late-arrival HHC defined in Section 4.5.9) is not willing to be consented as soon as possible upon arrival.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Study site personnel and patients will be blinded to treatment assignment (active drug or placebo) during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the clinical supply chain managers, the interactive voice or web-based response system (IxRS) service provider, the iDMC, and central laboratory staff responsible for assessments conducted in BXM-treated patients only.

Allocation to one of the two treatment arms will be randomized in a 1:1 proportion and will consider the following stratification factors:

- Region: *United States* or Europe; Asia; *and rest of world*
- Number of HHCs: ≤ 2; > 3
- Age: ≥ 5 to < 12 years; ≥ 12 to ≤ 30 years; > 30 years
- Duration of symptoms: ≤ 24; > 24 to ≤ 48 hours

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

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. Unblinding may be permitted if an investigator is deciding whether a patient should withdraw from the study and initiate treatment with a proven therapy. However, unblinding will not be permitted if an investigator is deciding whether a patient should withdraw from the study and initiate treatment with an unproven therapy. The investigator should document and provide an explanation for any non-emergency unblinding. The investigator will be able to break the treatment code by contacting the IxRS.

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

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is BXM/matching placebo.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Baloxavir Marboxil and Placebo

BXM and placebo for IPs will be supplied by the Sponsor as tablets or granules for oral suspension.

To maximize the study blind, each site must delegate the constitution of BXM and placebo oral suspensions (from the supplied granule) to dedicated site personnel who are not involved in any other study-related assessments or procedures. The administration of the oral suspension can be performed by study personnel.

For information on the formulation, packaging and handling of BXM and placebo, see the pharmacy manual.

4.3.2 Study Treatment Dosage, Administration, and Compliance

IPs will receive either a single dose of BXM or matching placebo.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.10.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.

4.3.2.1 Baloxavir Marboxil and Placebo

This is a single, oral dose study.

IPs will receive the initial and only dose of study drug (BXM or matching placebo) to be taken in tablet or oral suspension form at the study center within 2 hours of randomization.

See Table 1 and Table 2 for study drug (BXM or matching placebo) administration.

Table 1 Study Drug Administration and Dose for Index Patients <12 Years Old

Weight	Dose, Formulation
<20 kg	2 mg/kg, oral suspension
≥20 kg	40 mg, oral suspension

Table 2 Study Drug Administration and Dose for Index Patients ≥12 Years Old

Weight	Dose, Formulation
<80 kg	40 mg, (two 20 mg tablets)
≥80 kg	80 mg, (four 20 mg tablets)

IPs who are morbidly obese are not eligible for the study (see Section 4.1.2).

4.3.3 Additional Medication

The further treatment of HHCs diagnosed with influenza A/B during the study will be determined by the investigator according to local standards (see Section 4.4.2). The study sponsor will not provide further treatment.

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (BXM and placebo) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. *The investigator or his or her designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.*

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

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

4.3.5 Continued Access to Baloxavir Marboxil

Currently, the Sponsor does not have any plans to provide the Roche IMP (BXM) or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing BXM in accordance with the Roche

Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

4.4 CONCOMITANT THERAPY

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

4.4.1 Permitted and Prohibited Therapy for the Index Patient

All medications (including symptomatic therapy for their influenza, oral contraceptives, and hormone replacement therapy) are permitted in the IPs during the study except for:

- Investigational therapy (other than protocol-mandated study treatment)
- Traditional Chinese medicine or other herbal remedies with antiviral properties for the treatment or prevention of influenza *(e.g., the product's label clearly states that the product is for the treatment or prevention of influenza or there exists at least two scientific studies [in vitro or in vivo] published in peer-reviewed medical journals demonstrating a specific antiviral effect against influenza for the product or for one of the main ingredients)*
- Influenza antiviral drugs (BXM, [other than protocol-mandated study treatment], peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir, amantadine*, or favipiravir*)
- Immunosuppressants (including biologics)

4.4.2 Permitted and Prohibited Therapy for the Full Study HHCs

All medications are permitted in HHCs except for:

- Investigational therapy
- Traditional Chinese medicine or other herbal remedies with antiviral properties for the treatment or prevention of influenza *(e.g., the product's label clearly states that the product is for the treatment or prevention of influenza or there exists at least two scientific studies [in vitro or in vivo] published in peer-reviewed medical journals demonstrating a specific antiviral effect against influenza for the product or for one of the main ingredients)*
- Influenza antiviral drugs (BXM, peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir, amantadine*, or favipiravir*)
- Immunosuppressants (including biologics)

Local SOC (including antivirals) are only permitted in HHCs, **IF** the HHC is diagnosed with influenza as confirmed by local testing or the investigator diagnoses influenza despite negative test results, **AND** one of the below:

1) HHC is symptomatic as per the secondary "Symptomatic transmission endpoint" (see Section 2.1.2.1), or
2) HHC is asymptomatic but considered by the investigator to be at high risk for complications of influenza.

4.4.3 Cautionary Therapy and Foods for Index Patients

BXM is not expected to affect the PK of co-administered drugs, nor are co-administered drugs expected to affect the PK of $baloxavir$. See the $Baloxavir\ Marboxil$ Investigator's Brochure for more information.

No specific food is prohibited in this study.

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

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed for IPs during the study is provided in Appendix 1a. The schedule of activities to be performed for HHCs during the study is provided in Appendix 1b.

All activities should be performed and documented for each IP and HHC.

Study assessments indicated in Appendix 1a (IPs) and Appendix 1b (HHCs) will be performed at the $study\ site$, at the home, or via remote visit (e.g., via telephone or computer). The IP screening visit must be conducted at the $study\ site$. All respiratory swabs must be obtained by a healthcare professional. Home and remote visits may improve access and convenience for all subjects participating in the study. Applicable study assessments may be performed by staff from study site (if local processes are in place) at the patient's home or another suitable location, to improve access and convenience.

The Sponsor will select a healthcare company that will be responsible for providing home nurse services for participating sites (the home nurse vendor). Alternatively, investigators may delegate a professional home nurse affiliated with a home nurse vendor (approved by the Sponsor). The home nurse vendor is responsible for ensuring that all home nurse professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed.

Study visits (at the *study site*, home, or remote) will occur on scheduled and unscheduled visit days, as defined in Appendix 1a and Appendix 1b.

All information collected at home or remote visits will be reviewed by the investigator. All respiratory samples collected offsite will be returned to the site for local analysis and/or for preparation for shipment to the central laboratory.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. In addition, Informed Consent Forms for enrolled HHCs and for HHCs who are not subsequently enrolled will be maintained at the study site.

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

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history for the IP will be obtained in the *study site* at screening to confirm inclusion and exclusion criteria. Medical history will include clinically significant diseases, history of influenza symptoms, reproductive status, influenza vaccination status, history of local laboratory results. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the IP during the study and within 7 days prior to initiation of study treatment will be recorded.

IPs will also provide, to the best of their knowledge, information on the vaccination status of their HHC, and an assessment of whether any of their HHCs have exhibited influenza like-illness (and the severity of the symptoms) in the last 7 days (see inclusion/exclusion criteria).

Medical history for the HHCs will be obtained at the screening visit to confirm inclusion and exclusion criteria, including establishing influenza vaccination status and to rule out influenza-like illness in the previous 7 days (mild influenza-like symptoms are permitted in HHCs *if determined by the investigator to be due to a preexisting condition*). In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the HHC during the study and within 7 days prior to enrollment will be recorded. Demographic data will include age, sex, self-reported race/ethnicity (where allowed according to local regulations) and size of the household (number of HHCs).

4.5.3 Physical Examinations

A limited physical examination of IPs should be performed at screening to evaluate the patient for symptoms related to complications of influenza comprising assessment of the eyes, ears, nose, throat, and respiratory system. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

4.5.4 Vital Signs

Vital signs will be assessed at screening in IPs and will comprise measurement of temperature, blood pressure, and heart rate. Temperature measurement can be done using tympanic, rectal, axillary, oral or forehead/temporal thermometers. Blood pressure and heart rate should be taken in sitting position after 5 minutes of rest.

Height and weight will also be recorded at screening in IPs only to calculate the BMI for eligibility criteria and to determine the dose of study drug.

4.5.5 Laboratory and Other Biological Samples

The collection and analysis of respiratory and urine samples are described in the sections below.

4.5.5.1 Respiratory Samples

Respiratory samples will be collected at the timepoints indicated in the schedule of activities for IPs (see Appendix 1a) and for HHCs (see Appendix 1b). Detailed instructions for collecting respiratory samples (via “swabbing”) are provided in the laboratory manual and must be followed.

- **IP samples collected at screening**

  Two samples will be collected (one for local and one for central laboratory analysis) by the investigator or site staff. A respiratory sample for local analysis (see Section 4.5.5.2) is not needed if the medical record documents show influenza A/B positive and SARS-CoV-2 negative test results based on respiratory samples collected within 24 hours prior to signed ICF (as part of SOC).

- **HHC samples collected at screening**

  Two samples will be collected (one for local and one for central laboratory analysis) from all HHCs present in the household within 24 hours of the IP's treatment with study medication.

  Late-arrival HHCs (as defined in Section 4.5.9) should be swabbed (to collect 2 samples [one for local and one for central laboratory analysis]) as soon as possible at an unscheduled visit, after signing ICF.

- **IP samples collected post-randomization**

  One sample is collected for central laboratory analysis on Days 3, 5, and 9. Furthermore, the investigator may at any time collect a sample for local analysis of SARS-CoV-2 if the investigator suspects co-infection. If this collection occurs during

an unscheduled visit, an additional sample should be obtained for central laboratory analysis of SARS-CoV-2.

- **Full study HHC samples collected post-screening**

  Post-screening samples will only be obtained from HHCs participating in the full study at Days 5, 9, and any unscheduled visits. Two samples will be collected at each visit (one for local and one for central laboratory analysis). HHCs unable to participate in the full study will not receive any post-screening swabs.

- **Early discontinuation of sample collection for IPs and HHCs**

  Any HHC with a positive influenza A/B result based on local analysis will no longer receive subsequent swabs *(i.e., respiratory sample collection is discontinued)*. However, such HHCs will continue to undergo other assessments as described in Appendix 1b. If any IP or HHC has a positive SARS-CoV-2 result based on local analysis, all swabbing *(i.e., respiratory sample collection)* will stop for all subjects (IP and HHCs) in the same household, and all subjects will be discontinued (see Section 4.6.2).

4.5.5.2 Local Analysis of Respiratory Samples

This study will use the cobas Liat System (preferred system) that consists of the cobas Liat Analyzer together with a disposable assay tube that holds the reagents required to perform a test on the cobas Liat *System*. Sites will be provided with the analyzer and cobas SARS-CoV-2 & Influenza A/B test *(a combination assay)*.

When sites use the cobas *SARS-CoV-2 &* Influenza A/B test*, both influenza and SARS-CoV-2 results are generated from a single respiratory sample. Both results are expected to be recorded on the eCRF, including* when testing for SARS-CoV-2 is not mandated by the protocol.

If the preferred system is not available at the study site, the RIDT or other POC test for influenza A/B or POC test for SARS-CoV-2 can be used instead. If an IP or HHC is tested using an RIDT or other POC test, the site will record the use of the alternative test.

Samples locally analyzed are as follows:

- Screening samples

  Local analysis at screening informs the assessment of IP and HHC inclusion criteria (Section 4.1.1). IPs will be randomized based on the local test results that confirm the IP is influenza A/B positive and SARS-CoV-2 negative.

  All HHCs must be screen failed if local test results confirm that any single HHC is influenza A/B positive. All HHCs must be screen failed and the IP discontinued if any single HHC is SARS-CoV-2 positive (see Section 4.6.2).

- IP samples post-randomization

  No samples will be collected for local analysis except samples collected for SARS-CoV-2 local testing by investigators as needed (see Section 4.5.5.1).

  If any IP or HHC tests positive for SARS-CoV-2, all subjects (IP and HHCs) in the same household must be discontinued (see Section 4.6.2).

- HHC samples post-screening

  HHCs participating in the full study will have all post-screening respiratory samples tested for influenza A/B *using the* cobas *SARS-CoV-2 &* Influenza A/B test*. If the preferred system is not available at the study site, a RIDT or other POC test for influenza A/B can be used.*

  HHCs who test positive for influenza A/B may be treated as per Section 4.4.2.

  HHCs participating in the full study are assessed for symptoms of influenza and fever at all visits (see Section 4.5.6 and Appendix 2). Once an HHC is assessed to have worsened or new influenza symptoms or fever, then all their remaining samples will *be required to* additionally be tested for SARS-CoV-2 *using the* cobas SARS-CoV-2 *&* Influenza A/B test *or other POC test for SARS-CoV-2 if the preferred system is not available at the study site (NB other POC tests for SARS-CoV-2 may need an additional sample if this POC test is not a combination assay)*. No SARS-CoV-2 local testing is required after criteria have been met for early discontinuation of sample collection (*see* Section 4.5.5.1 *for early discontinuation of sample collection for IPs and HHCs*). (Note: if worsened or new influenza symptoms or fever occur after discontinuation of sample collection, no local SARS-CoV-2 testing is conducted).

  If any HHC or IP tests positive for SARS-CoV-2, all subjects (HHCs and IP) in the same household must be discontinued (see Section 4.6.2).

NOTE: All IP and HHC samples collected after signed ICF and used for local analysis will also be sent to the central laboratory.

4.5.5.3 Central Laboratory Analyses

All respiratory samples collected from the IPs and HHCs during the study will be sent to a central laboratory for analysis of the measures below (see Table 3).

The rationales for these central laboratory assessments are described in Section 3.4.6.

Confirmation of influenza infection for *all* enrolled households

Respiratory samples obtained at screening from all IPs and *all* HHCs will be analyzed by quantitative PCR to confirm that the IP was PCR-positive for influenza A/B and all HHCs were PCR-negative for influenza A/B. The central laboratory test result will be used to confirm eligibility to define the analysis populations.

Respiratory samples obtained *post-screening* from HHCs *participating in* the *full* study will be analyzed by quantitative PCR to determine if the HHC has become PCR-positive

for influenza A/B. The central laboratory test result will be used to determine if the primary and secondary efficacy endpoints have been met.

Viral type and subtype assessment

Respiratory samples obtained from IPs on Day 0 and from HHCs who become central laboratory PCR-positive for influenza will be analyzed by PCR in the central laboratory to determine the influenza type (A or B) and influenza A subtype (H1N1 and H3N2).

Only HHCs with a virus type/subtype that is consistent with that of the IP (i.e., consistent with within-household transmission) will be considered for the primary efficacy endpoint and secondary efficacy endpoints.

Viral titer assessment

Samples from IPs only will be assessed in the central laboratory to determine viral titer:

- at all timepoints using C_T (threshold cycle) values from viral RNA PCR (with results reported as particles or copies per mL).
- *at all timepoints* using 50% tissue culture infectious dose (TCID50) values.

Analysis of viruses with reduced susceptibility to BXM

Viral RNA sequencing of the PA protein gene to identify amino acid substitutions conferring reduced susceptibility to BXM (see Section 3.4.6.4) will be done for IPs randomized to BXM and their HHCs if the HHC becomes central laboratory PCR-positive for influenza A/B during the study.

Additional sequencing of polymerase basic (PB) protein 1 (PB1) and PB2 may be conducted in case an I38X substitution (or other identified substitution) is found in the PA protein in the IP and the corresponding HHC (i.e., transmission of a viral variant with reduced susceptibility).

Samples from IPs who experience a rebound in viral titers and/or show treatment-emergent amino acid substitutions in PA identified by sequencing analysis will be assayed for phenotypic reduced susceptibility.

Viral genome sequencing

Viral genome sequencing will be conducted for IPs and HHCs at selected sites which provide adequate numbers of IPs.

The methods for additional sequenced-based transmission identification are currently being developed and will be described in a separate methodological document.

Testing for SARS-CoV-2 infection for *all* enrolled households

Respiratory samples obtained from IPs or HHCs and submitted to the central laboratory will be subsequently analyzed by qualitative or quantitative PCR for SARS-CoV-2, if deemed necessary for accurate assessment of co-infection.

Table 3 Central Laboratory Assessments on Respiratory Samples Obtained From Index Patients and Household Contacts on the Visits Indicated

	Index Patients				Household Contacts			
Visit Day	**0**	**3**	**5**	**9**	**0**	**5**	**9**	**UV**
Confirmatory PCR influenza A/B testing	x				x	x	x	x
Subtype PCR Influenza A	x					x [a]	x [a]	x [a]
Viral titer [b, c]	x	x	x	x				
Sequencing to evaluate reduced-susceptibility substitutions [d]	x	*x*	x	x		x [a]	x [a]	x [a]
Additional genome sequencing (selected sites only)	x	*x*	x	x		x [a]	x [a]	x [a]
Phenotypic resistance assay for selected samples [e]	x	*x*	x	x				
SARS-CoV-2	x [f]			x [f]	x [f]		x [f]	

UV = unscheduled visit.

a. Only for household contacts who are central laboratory PCR positive for influenza A/B.

b. 50% tissue culture infectious dose (TCID50).

c. *Quantitative* viral RNA PCR.

d. Only for index patients randomized to BXM and their household contacts.

e. Only for index patients randomized to BXM who have a rebound in viral titer and/or a treatment-emergent amino acid substitution.

f. SARS-CoV-2 testing will be conducted at screening and Day 9 or last evaluable visit, if deemed necessary for accurate assessment of co-infection.

4.5.5.4 Other Laboratory Samples

A urine sample will be taken from female IPs for pregnancy testing as indicated in Appendix 1a.

The following female IPs are exempt from providing a urinary sample:

- Postmenopausal women (defined as cessation of regular menstrual periods for ≥ 12 continuous months).
- Women who are surgically sterile by hysterectomy, bilateral oophorectomy, or tubal ligation.
- Females < 12 years old and pre-menarcheal.

4.5.5.5 Sample Procedures and Storage

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

Respiratory samples (from IPs and HHCs) collected for analysis of viral parameters will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

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

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

Given the complexity of viral genome sequencing, data derived from these analyses will generally not be provided to study investigators or IPs/HHCs unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.6 Household Contact Symptoms and Temperature

Assessment of symptoms of influenza and temperature measurement will be conducted as part of screening.

Starting at Day 0 through to Day 9, all full study HHCs aged ≥12 years old will be instructed in the symptoms of early influenza (Appendix 2). HHCs will record their temperature every day at bedtime, as well as any time they feel feverish, in a paper diary. For HHC aged <12 years old, the responsible adult will record the child's temperature every day at bedtime, as well as any time the child appears feverish, in a paper diary. *On Day 9, body temperature must be measured during the visit conducted either at the study site or at the HHC's home.*

HHCs will be instructed to contact the site in case of symptoms of influenza, fever ≥38°C, or any other concern. Responsible adults (parents, legal guardians) will be responsible for contacting the site on behalf of HHCs <18 years old. The site will assess the incoming telephone call and may arrange an unscheduled visit within 24 hours.

The nurse or site staff will review the temperature log and assess symptoms of influenza at scheduled and unscheduled visits (see Appendix 2).

Note: Symptom and temperature assessments may be conducted at home or at the *study site*. Home visits may be performed by home nurses or by site staff (if local

practices are in place). Symptom assessment interview and temperature log review may be conducted remotely (e.g., via telephone or computer).

4.5.7 Patient-Reported Outcomes

Patient-reported outcome (PRO) data will be collected via paper questionnaires at the timepoints indicated in Appendix 1a to document the treatment benefit of BXM in IPs *≥12 years old* only. The questionnaires, translated into the local language as appropriate, will be completed in their entirety at specified timepoints during the study.

The EQ-5D-5L (see Appendix 3) is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale that measures health state. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 5 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

The Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ) will be used to measure lost work or school days (adapted from Reilly et al. 1996; see Appendix 4). This validated, self-reported questionnaire quantifies both the amount of absenteeism (work time missed) and presenteeism (reduced on-the-job effectiveness) due to health problems.

4.5.8 *Palatability and Acceptability*

IPs <12 years old who receive study drug (BXM or matching placebo) as an oral suspension will be assessed for perceived palatability and acceptability of the study drug. A two-question palatability and acceptability questionnaire (completed by the IP or with assistance from a responsible adult permitted for children who cannot read) will be used to record palatability and acceptability (see Appendix 5).

4.5.9 Household Contact Screening (including Late-Arrival HHCs)

In line with the eligibility criteria (see Section 4.1), any HHC may only be enrolled for the full study if a total of *1 or more* unvaccinated HHCs agree and are eligible to participate in the full study. These *1 or more* full study HHCs should be identified and screened at the Day 0 visit, and respiratory swabs should be obtained ≤24 hours *after the* IP *receives* study drug. If *a* full study HHC *cannot be* screened at the Day 0 visit, then no HHC can be enrolled (even if potential full study HHCs may arrive home >24 hours after IP randomization [late-arrival HHCs]).

HHCs in the home within 24 hours after IP randomization

All consenting HHCs present at any time in the home during the first 24 hours *after* IP randomization must undergo the Day 0 visit, and respiratory swabs should be obtained ≤24 hours *after* IP study medication administration. HHCs intended for the full study and present within 24 hours after IP randomization should be enrolled together for the full study only after all HHCs (who were present at the Day 0 visit) have completed the Day 0 screening and have tested negative for both influenza and SARS-CoV-2 per local test.

If the investigator identifies during IP screening (i.e., prior to randomization and dosing) that timely Day 0/1 screening of HHCs cannot be achieved (as described above), then the IP should be screen failed. If after IP randomization and dosing the associated household is screen failed, the IP should not be discontinued, and will follow assessments as per Appendix 1a.

HHCs not present in the home at any time within 24 hours after IP randomization (late-arrival HHC)

If an HHC arrives home >24 hours *after* IP randomization where HHCs have already been enrolled in the full study, the late-arrival HHC should be screened as soon as possible at an unscheduled visit. If the late-arrival HHC meets all study eligibility criteria, they can also be enrolled in the full study. If the late-arrival HHC refuses screening or is influenza positive, the IP and HHCs enrolled will remain in the study. Note that all HHCs (including late-arrival HHCs) intended for the full study must reside in the IP's home for at least 7 of the following 9 days and be present for scheduled study visits (i.e., a late-arrival HHC must arrive no later than Day 2 to potentially qualify for the full study).

If an HHC arrives home >24 hours *after* IP randomization where HHCs have already been enrolled and the late-arrival HHC refuses to be screened or is influenza A/B positive at screening, all the enrolled subjects (IP and the existing enrolled HHCs) should **not** be discontinued.

If a late-arrival HHC or any subject is determined to be SARS-CoV-2 positive at any time during the study, all enrolled subjects (IP and HHCs) should be discontinued from the study.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Not applicable – this is a single-dose study.

4.6.2 Subject Discontinuation from Study

HHCs who develop influenza symptoms before the Day 9 visit may be tested for infection at an earlier unscheduled visit (see Appendix 1b for additional details). If an HHC tests positive for influenza A/B before the Day 9 visit they would not undergo any

further respiratory swabbing; however, these HHCs would continue to complete their daily temperature measurement and monitor for symptoms until the end of the study (Day 9 visit) and would not be early discontinued from the study.

As of March 2020 because of the ongoing COVID-19 pandemic, many countries and communities advise or require patients with suspected or confirmed SARS-CoV-2 infection to self-quarantine or to visit only designated healthcare facilities. Therefore, consistent with these public health measures, if any study subject (IPs and full study enrolled HHCs) or other person living in the household is diagnosed with the SARS-CoV-2 infection by a healthcare professional, the entire enrolled household will be discontinued from the study, with cessation of study site and/or home visits. Following discontinuation from the study and if not already assessed that day, an early discontinuation visit should be conducted remotely (e.g., via telephone) for all IPs and full study HHCs. Collection of a respiratory sample will not be required.

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

- IP/HHC withdrawal of consent
- Study termination or site closure
- Any medical condition that the investigator or Sponsor determines may jeopardize the IP's or HHC's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the IP/HHC.

Every effort should be made to obtain information through the end of the safety-reporting period on IPs who withdraw from the study but have not withdrawn consent (see Section 5.3.1). The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If an IP/HHC requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

If an IP/HHC discontinues the study early, they will undergo the assessments shown in Appendix 1a or Appendix 1b, respectively.

IPs/HHCs who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

BXM has been approved in *many* countries*,* including *in* Japan since February 2018, *in* the *United States* since October 2018*, and in the European Union since January 2021*. Clinical development is ongoing. The safety plan for IPs in this study is based on clinical experience with BXM in completed and ongoing studies. The anticipated important safety risks for BXM are outlined below. Please refer to the *Baloxavir Marboxil* Investigator's Brochure for a complete summary of safety information.

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

No blood samples will be taken from IPs/HHCs during the study, minimizing the risk of adverse events related to study procedures. While nasopharyngeal swabs are preferred, the laboratory manual allows that less invasive mid-turbinate or nasal swabs to be used if a nasopharyngeal swab is not possible or the IP/HHC (or responsible adult) refuses a nasopharyngeal swab.

Furthermore, HHCs who participate in this study will benefit from free, convenient home monitoring and early/rapid diagnosis. HHCs who develop influenza will be allowed to be treated with *SOC* by their physician.

5.1.1 Risks Associated with Baloxavir Marboxil

BXM is generally well tolerated and no important identified or potential safety concerns associated with BXM have been identified from clinical studies conducted, to date.

Hypersensitivity reactions have been identified in the post marketing setting. Refer to Postmarketing Safety Data section (Section 1.2.3) for further details.

Exclusion criteria for patients with known hypersensitivity to BXM or the drug product excipients are included in this protocol, as re-exposure must be avoided.

5.1.2 Management of Study Participants Who Experience Adverse Events

5.1.2.1 Dose Modifications

This is a single dose study; therefore, the dose of BXM cannot be reduced.

5.1.2.2 Treatment Interruption

This is a single dose study; therefore, the dose of BXM cannot be interrupted.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments in IPs will consist of recording adverse events, including serious adverse events, at the timepoints indicated in Appendix 1a.

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

For HHCs, only adverse events related to the study procedures indicated in Appendix 1b will be considered.

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.7 and 5.3.5.8 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.9)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the IP's/HHC's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the IP/HHC or may require medical/surgical intervention to prevent one of the outcomes listed above).

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

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

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

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

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.5)

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

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

Adverse events that may occur in the HHCs (relating to the study procedures) should be collected in the eCRF only and not reported to the global safety database.

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained from the IP, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., the respiratory swab) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported for IPs ≥ 12 years old until the Day 9 visit and for IPs < 12 years old (at randomization) until the Day 21 safety visit.

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

5.3.2 Eliciting Adverse Event Information

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

"How have you felt since your last *study site* visit?"

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the IP, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no"

accordingly. The following guidance should be taken into consideration (see also Table 5):

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

Table 5 Causal Attribution Guidance

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

For the HHCs, only those adverse events should be collected in the eCRF which are assessed to be related to any study procedure. These events will not be reported to the global safety database.

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related or Injection Reactions

Not applicable.

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Liver Function Tests

As no blood samples will be taken during this study, liver function tests would only be conducted if an adverse event occurs that warrants further work up.

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.6 Deaths

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

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

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

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

5.3.5.7 Preexisting Medical Conditions

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

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

5.3.5.8 Lack of Efficacy or Worsening of Influenza Virus Infection

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

5.3.5.9 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The IP/HHC has not experienced an adverse event

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

- Hospitalization that was necessary because of IP/HHC requirement for outpatient care outside of normal outpatient *study site* operating hours.

5.3.5.10 Cases of Accidental Overdose or Medication Error

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

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

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

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria *or qualifies as an adverse event of special interest*, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For BXM or matching placebo, adverse events associated with special situations should be recorded as described below for each situation:

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

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

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

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one

entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.11 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements). Grade 4 and 5 events must be reported as serious adverse events
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements).

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

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

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

5.4.1 Emergency Medical Contacts

To ensure the safety of study IPs/HHCs, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help

Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation (Index Patients Only)

After initiation of the single dose of study drug to IPs on Day 0, serious adverse events and adverse events of special interest will be reported in IPs $\geq$ 12 years old until Day 9 and for IPs $<$ 12 years old (at randomization) until the Day 21 safety visit.

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Index Patients

Female IPs of childbearing potential will be instructed *through the Informed Consent Form* to immediately inform the investigator if they become pregnant during the study or within 21 days after the initial and only dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the IP, discussing the risks of the

pregnancy and the possible effects on the fetus. Monitoring of the IP should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Index Patients

Male IPs will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 21 days after the initial and only dose of study drug. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male IP exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male IP or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female IP exposed to study drug (or the female partner of a male IP exposed to study drug) should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

Not applicable.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as Visit Day 9 for IPs $\geq$ 12 years old and Visit Day 21 for IPs $<$ 12 years old), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special *Situations* Form using the fax number or email address provided to investigators.

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

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

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

- *Baloxavir Marboxil* Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The present section outlines the planned statistical analysis of the study. Full details will be specified in a separate Statistical Analysis Plan (SAP), which will be finalized prior to locking of the study database and unblinding at the end of the study. The SAP may include additional analyses not explicitly mentioned in this section.

The primary efficacy analysis population will consist of all unvaccinated in the primary analysis will be defined in a blinded review meeting before database lock and documented in the SAP.

Supportive analyses including all full study HHCs of all randomized IPs will be performed.

Treatment groups will be defined based on the arm to which the respective IP was randomized.

The efficacy analysis based on households will primarily use the set of households with all full study HHCs of the randomized IPs, if all the HHCs were PCR negative at screening.

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

6.1 DETERMINATION OF SAMPLE SIZE

The proposed sample size for this study is 2,030 evaluable HHCs. Assuming a 15% drop-out for inclusion of HHCs into the primary analysis population, an average of 2.5 HHCs per IP and a 15% exclusion rate on the household level, this equates to an approximate number of IPs of 1,130.

A transmission rate in the placebo arm of approximately 20% is assumed based on data from the literature, including work by Welliver et al. (2001). For a 30% relative risk reduction with BXM, which is considered clinically meaningful, the transmission rate in the active treatment group is expected to be 14%. Under these assumptions and for a two-sided test for binary proportions at the 5% significance level, the power for the between-arm comparison based on the primary endpoint will be approximately $>90\%$. For the secondary "Symptomatic transmission endpoint" (symptomatic influenza) the power will be 80% for an assumed 65% proportion of symptomatic cases among infected HHCs, and not considering the hierarchical testing procedure. The literature reports a variety of values for the proportion of influenza cases that are symptomatic. The assumption of 65% was authorized by the study steering committee; however, this assumption has limitations.

The effect of clustering was examined in simulations and using analysis methods accounting for the household effect. The power was largely maintained in simulations that assumed the existence of a random variation of the background transmission rate between households with a standard deviation up to 5% (i.e., with about 95% of the values for the BXM and placebo groups in the [4.2, 23.8] and [10.2, 29.8] range, respectively). This is compatible with the inclusion of a large number of small clusters and a small expected intra-cluster correlation, resulting in a negligible design effect and related reduction in effective sample size.

6.2 SUMMARIES OF CONDUCT OF STUDY

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

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, number of HHCs, and duration of symptoms) will be summarized overall and by treatment group.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is *presented* in Section 2.1.1.1.

The primary analysis will compare the transmission rate for the primary endpoint between the two arms and express the effect by an adjusted odds ratio. The comparison will be based on a model providing population-averaged estimates using a generalized estimating equations approach and accounting for the stratification factors used at randomization (see Section 4.2). The primary test for the treatment effect will be two-sided and the significance level will be 5%. For this analysis, missing values will not be imputed. The SAP will specify sensitivity analyses performed with different imputation methods and alternative definitions of the analysis population.

A supportive analysis for robustness will employ a two-sided Cochran-Mantel-Haenszel test accounting for the stratification factors used at randomization.

The same approach will be used for the secondary endpoints considering the hierarchical testing strategy described in the following section.

6.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are listed in Section 2.1.2.1.

If the primary outcome reaches significance, a hierarchical, sequential testing procedure is planned for the analysis of secondary efficacy endpoints. The secondary efficacy endpoints will be tested at the alpha = 0.05 significance level as part of a confirmatory analysis in hierarchal order as listed in Table 6. A given endpoint will be tested if and only if the all endpoints listed ahead of it have reached significance at the 0.05 level. All tests not part of the confirmatory analysis will be considered non-confirmatory.

Table 6 Confirmatory Hierarchical Order for Secondary Efficacy Endpoints

Order	Secondary Efficacy Analysis
1	Symptomatic transmission by Day 5
2	Virological transmission at the household level by Day 5
3	Symptomatic transmission at the household level by Day 5
4	Virological transmission by Day 9
5	Symptomatic transmission by Day 9
6	Any virological infection by Day 9
7	Any virological infection at the household level by Day 9
8	Any symptomatic infection by Day 9
9	Any symptomatic infection at the household level by Day 9

The rate of direct transmission, as a by-household measure, will be analyzed by means of a Cochran-Mantel-Haenszel test accounting for the stratification factors used at

randomization. The rate of symptomatic influenza in HHCs will be analyzed as described for the primary endpoint.

6.4.3 Other Efficacy Endpoints

Other efficacy endpoints are listed in Section 2.1.3.1.

The analysis of other endpoints will be primarily descriptive *and documented within the SAP*.

The rate of direct transmission of either influenza A/B to HHCs in relation to viral titer for the IP at Day 0 will be analyzed by means of models similar to those used for the primary analysis but including other explanatory variables of interest that will be specified in the SAP.

6.5 SAFETY ANALYSES

A descriptive analysis of safety parameters will be performed in the safety population.

Safety analyses will include the assessment of the incidence, severity, and timing of treatment-emergent adverse events and serious adverse events by treatment group.

Safety data collected from included HHCs will be summarized by treatment group based on the respective IP.

6.6 PHARMACOKINETIC ANALYSES

Not applicable.

6.7 IMMUNOGENICITY ANALYSES

Not applicable.

6.8 ANALYSIS OF SUBGROUPS

A subgroup analysis will be conducted in patients from selected sites to assess the accuracy of matching IP to HHC transmission based on influenza subtype for the primary/secondary endpoints. Sequencing will be performed for samples from selected sites and countries based on feasibility, including availability of reference sequence for *a* specific community.

Other subgroups of interest are defined by:

- The stratification factors used for randomization.
- IPs with influenza A *versus* influenza B.
- Influenza seasons.

Subgroup analyses will be primarily descriptive. Where applicable, the heterogeneity of treatment effects across subgroups will be addressed by testing treatment-by-subgroup effects added to the respective models. Details will be provided in the SAP.

6.9 INTERIM ANALYSES

6.9.1 Planned Interim Analyses

There are no planned interim efficacy analyses for this study. Section 6.9.2 describes optional interim analyses of efficacy.

Safety interim analyses will be performed regularly by an iDMC. Efficacy data will only be provided if requested by the iDMC. Further details on the function and logistics (e.g., frequency of the meetings) of the iDMC will be provided in the iDMC Charter.

6.9.2 Optional Interim Analyses

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one or more interim efficacy analyses. Possible goals of these interim analyses include assessing the futility of study continuation or reassessing the sample size in case the overall transmission rates (calculated in a blinded manner) are smaller than anticipated. If recruitment projections indicate that a large proportion of the currently planned sample can be recruited by the end of the 2020/2021 or subsequent Northern hemisphere influenza seasons (e.g., $>70\%$), the Sponsor will determine whether to perform an interim analysis with stopping rules based on efficacy endpoints in accordance to a group-sequential design. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

Any interim analyses would be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter, and the Sponsor will remain blinded throughout the study. The decision to conduct optional interim analyses, along with the rationale, timing, and statistical details for these analyses, will be documented in a specific interim analysis SAP. The iDMC charter will document potential recommendations the iDMC can make to the Sponsor as a result of the analyses and the iDMC charter will also be made available to relevant health authorities, if applicable.

If a group-sequential interim analysis will be performed, a Lan-DeMets alpha-spending function with O'Brien-Fleming $or\ similar$ boundaries will be used to define the null-hypothesis rejection region for the primary and key secondary endpoints. Tests will be conducted at the one-sided 2.5% significance level (alternative hypothesis: $odds\ ratio < 1$ for the comparison of BXM vs. placebo). The iDMC will review interim analysis results and provide a recommendation concerning the continuation of the study. The hierarchical testing procedure will ensure control of the overall type I error rate at the pre-defined level (Hung et al. 2007; Glimm et al. 2010). A recommendation to stop the

study with rejection of the null-hypothesis should be considered if the rejection boundaries are crossed for both the primary and the first secondary endpoint (symptomatic influenza in HHCs).

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

The Sponsor will perform oversight of the data management of this study. The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and other electronic data will be sent securely directly to the Sponsor (Roche) using the Sponsor's (Roche) standard procedures to handle and process the electronic transfer of these data.

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

HHC data will be recorded in a paper diary, and data collected by the home nurse or site staff will be recorded on worksheets. The data from the diaries and worksheets will be entered into the EDC system by site staff.

PRO data from IPs will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper PRO and HHC data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length

of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

The investigator or authorized designee will explain to each IP/HHC the objectives, methods, and potential risks associated with each optional procedure. IPs/HHCs will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason.

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

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

8.4 CONFIDENTIALITY

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

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

Medical information may be given to an IP's/HHC's personal physician or other appropriate medical personnel responsible for the IP's/HHC's welfare, for treatment purposes.

Given the complexity of viral genome sequencing, data derived from these analyses will generally not be provided to study investigators or IPs/HHCs unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 *MANAGEMENT OF STUDY QUALITY*

The Sponsor has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor identified potential risks associated with critical trial processes and data and implemented plans for evaluating and controlling these risks. Risk evaluation and control included the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits are provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

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

Approximately *200* sites globally will participate to enroll approximately 1,130 IPs and 2,030 HHCs. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study as specified in Section 4.5.

An iDMC will be employed to monitor and evaluate IP/HHC safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

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

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

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

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

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1a
Schedule of Activities for the Index Patient

	Screening *Study Site* **Visit**	**Day 3 Visit** [1]	**Day 5 Visit** [1]	*Unscheduled or* **Early Discontinuation** [1, 2, 3]	**Day 9 Visit (End of Study)** [1]	**Safety Follow-Up Visit (5–11 Year Olds Only)** [1]
Day	0	3 (±1)	5 (±1)	Unscheduled	9 (±1)	Day 21 (+2)
Informed consent	x					
Demographic data	x					
Medical history	x					
Limited physical assessment	x					
Vital signs	x					
Height and weight	x					
Urine pregnancy test (see Section 4.5.5.4)	x					
Respiratory sample (swabbing) [4]	x	x [5]	x [5]	x [6]	x [5]	
Review of inclusion/exclusion criteria	x					
Randomization (performed after all above activities completed) followed by study drug administration (performed latest 2 hours post-randomization)	x					
EQ-5D-5L questionnaire [8]	x	x			x	
WPAI+CIQ questionnaire [8]					x	
Palatability and acceptability questionnaire [9]	*x*					
Concomitant medications	x	x	x	x	x	x
Adverse events [7]	x	x	x	x	x	x

Appendix 1a: Schedule of Activities for the Index Patient (cont.)

AE = adverse event; HHC = household contact; IP = index patient; SAE = serious adverse event; *SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2;* WPAI+CIQ = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions.

1. All assessments (except sample collection) for these visits can be conducted remotely (e.g., via telephone or computer), in *study site* or at home.
2. If the IP is discontinued early because a subject in their household tests positive for SARS-CoV-2 (see Section 4.6.2), then this visit must be conducted remotely, and no swabbing is performed.
3. If the IP is discontinued early, the IP should be followed until the end of their safety reporting period (Day 9 for IPs ≥ 12 years old or Day 21 for IPs < 12 years old) (see Section 5.3.1).
4. Follow instructions in the laboratory manual (see Section 4.5.5).
5. Samples for central laboratory only. If SARS-CoV-2 co-infection suspected, collect additional sample for local testing (see Section 4.5.5.1).
6. If SARS-CoV-2 co-infection suspected, collect a sample for central laboratory testing and a sample for local testing (see Section 4.5.5.1).
7. After informed consent is obtained and prior to study drug administration, only SAEs caused by a protocol-mandated intervention should be reported. After study drug administration, all AEs will be reported until Day 9 for IPs aged ≥ 12 to 64 years old, and until Day 21 for IPs aged < 12 years old at randomization.
8. *Only to be completed by IPs 12 years and older.*
9. *Palatability and acceptability questions are to be completed as soon as possible after swallowing the study drug by IPs who are less than 12 years old and who receive study drug as granules for oral suspension. The questionnaire will be completed by the IP or with the assistance of a responsible adult for IPs who cannot read.*

Appendix 1b
Schedule of Activities for Each Household Contact

	All HHCs	Full Study HHCs Only			
	Screening Visit [1, 2]	Day 5 Visit [1]	HHC Sick Visit [1, 3, 4]	Early Discontinuation [1, 5]	Day 9 Visit [1] (End of Study [4])
Day	0 or 1	5 (±1)	Unscheduled	Unscheduled	9 (±1)
Informed consent	x				
Demographic data	x				
Medical history	x				
Respiratory sample (swabbing) [6]	x [7]	x [8, 9]	x [8, 9]	x [8, 9]	x [8, 9]
Review of inclusion/exclusion criteria	x				
Symptoms assessment	x	x [10]	x [10]	x [10]	x [10]
Body temperature recording [11]	x	x	x	x	x
Concomitant medications	x	x	x	x	x
Enrollment IxRS	x				
Dispensing/reviewing/collecting subject diary	x [12]	x [13]	x [13]	x [13]	x [13]
AEs due to study procedures (e.g., nurse-administered swabs)	x	x	x	x	x

AE = adverse event; HHC = household contact; IP = index patient; *IxRs = interactive voice or web-based response system;* SAE = serious adverse event; *SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2;* WPAI+CIQ = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions.

1. All assessments (except swabbing) can be conducted remotely (e.g., via telephone or computer), at the *study site* or at home.
2. **Visit must be initiated within 24 hours of IP randomization** (see Section 4.5.9 for details regarding late-arrival HHCs).
3. HHC is seen within 24 hours of informing the study site of influenza symptoms or fever (Section 4.5.6).
4. HHC must be discontinued if IP or any HHC tests positive for SARS-CoV-2 (see Section 4.6.2 for subject discontinuation criteria).
5. If HHC is discontinued early because a subject in their household tests positive for SARS-CoV-2, then this visit must be conducted remotely, and no swabbing is performed.

Appendix 1b: Schedule of Activities for Each Household Contact (cont.)

6. Two samples will be collected at each visit (one for local and one for central laboratory). Follow instructions in the laboratory manual (see Section 4.5.5).
7. Swab must be performed within 24 hours *after* IP study drug administration (see Section 4.5.9).
8. Sample collection is discontinued after the HHC's sample locally tests positive for influenza A/B or if any subject's (IP or HHC) sample tests positive for SARS-CoV-2 (see Section 4.5.5.1).
9. If an HHC is determined to have new or worsened symptoms or fever, the local respiratory sample collected at this and future visits should also be tested for SARS-CoV-2 (see Section 4.5.5.2) in addition to influenza A/B (unless sample collection discontinued; see Section 4.5.5.1).
10. Symptoms assessed according to Section 4.5.6 and Appendix 2.
11. HHCs will measure their temperature daily at bedtime, and any time they feel feverish and record values in a paper diary. *At the Day 9 visit, body temperature must be measured during the visit either at the study site or at home.*
12. This assessment *is* for full study HHCs only.
13. Daily temperature diary reviewed at each scheduled/unscheduled visit.

Appendix 2
Symptoms Assessed in the Full Study Household Contacts

Starting at Day 0, full study household contacts (HHCs; or the responsible adult of the children < 12 years of age) will be instructed in the symptoms of early influenza. Qualifying symptoms for household contacts are shown below:

Symptoms assessed in household contacts aged ≥ 12 years of age	
Qualifying respiratory symptoms	• Cough • Sore throat • Nasal congestion
Qualifying general systemic symptoms	• Headache • Feverishness or chills • Muscle or joint pain • Fatigue
Symptoms assessed in household contacts aged ≥ 2 to < 12 years of age	
Qualifying upper respiratory tract infection symptoms	• Cough • Nasal congestion or rhinorrhea

Assessment of influenza symptoms for full study HHC ≥ 12 years old

DAY 0 prior to enrollment

HCP asks HHC ► about symptom (x) ▼	Have you had (x) in the last 7 days?	Is your (x) mild or is it *worse* than mild?	What is causing your (x)? (record the cause or write "not known")	Action
Cough	Y or N	Mild or Worse	Cause:	Do **NOT** enroll if any symptom is (1) **worse than mild** or (2) cause is **not known** or likely **infection**.
Sore throat	Y or N	Mild or Worse	Cause:	
Nasal congestion	Y or N	Mild or Worse	Cause:	
Headache	Y or N	Mild or Worse	Cause:	
Feverishness or chills	Y or N	Mild or Worse	Cause:	
Muscle or joint pain	Y or N	Mild or Worse	Cause:	
Fatigue	Y or N	Mild or Worse	Cause:	

Record Day 0 temperature.	__ __ · __ °C Site:	Do **NOT** enroll if **≥38.0 °C**
HCP obtains swab	Is local influenza A/B, or local SARS-CoV-2 positive? Y or N	Do **NOT** enroll if **Y**

Appendix 2: Symptoms Assessed in the Full Study Household Contacts (cont.)

DAYS 5, 9, AND UNSCHEDULED for full study HHC ≥12 years old

	HCP asks HHC ► about symptom (x) ▼	For symptoms present at baseline: is your (x) worse since you enrolled?	For symptoms not present at baseline: do you have (x)?
Respiratory	Cough	Y or N	Y or N
	Sore throat	Y or N	Y or N
	Nasal congestion	Y or N	Y or N
General Systemic	Headache	Y or N	Y or N
	Feverishness or chills	Y or N	Y or N
	Muscle or joint pain	Y or N	Y or N
	Fatigue	Y or N	Y or N

Review HHC temperature log. HHC to obtain temperature if not yet done.* Record highest temperature here ►	__ __ . __ °C	Date:
	Site:	Time:

HCP obtains swab	Is local influenza A/B positive? Y or N **	If **Y**, refer HHC to investigator for standard of care (including anti-viral medicine). No more samples for this HHC needed. Continue to monitor for symptoms at subsequent visit if symptoms endpoint not *yet* met.
		If **N**, continue sampling at next visit. However, investigator may initiate standard of care if suspicion for influenza is high due to symptoms.

* Temperature obtained from tympanic thermometers provided to households (or exceptionally from other thermometers/locations in case of tympanic thermometer failure for any reason).

** Test SARS-CoV-2 via local test if HHC develops symptoms or fever versus baseline. If positive, withdraw all study subjects in household from the study.

Assessment of influenza symptoms for full study HHC ages ≥2 to <12 years old

DAY 0 prior to enrollment

HCP asks adult ► about symptom (x) ▼	Has your child had (x) in the last 7 days?	Is (x) mild or is it *worse* than mild?	What is causing (x)? (record the cause or write "not known")	Decision
Cough	Y or N	Mild or Worse	Cause:	Do **NOT** enroll if any symptom is (1) **worse than mild** or (2) cause is **not known** or likely **infection**.
Nasal congestion or rhinorrhea (stuffy or runny nose)	Y or N	Mild or Worse	Cause:	

Record Day 0 temperature.	__ __ . __ °C	Do **NOT** enroll if **≥38.0 °C**
	Site:	

HCP obtains swab	Is local influenza A/B, or local SARS-CoV-2 positive? Y or N	Do **NOT** enroll if **Y**

Appendix 2: Symptoms Assessed in the Full Study Household Contacts (cont.)

DAYS 5, 9, AND UNSCHEDULED for full study HHC ages ≥ 2 to < 12 years old

HCP asks adult ► about symptom (x) ▼	For symptoms present at baseline: is your child's (x) worse since your child enrolled?	For symptoms not present at baseline: does your child have (x)?
Cough	Y or N	Y or N
Nasal congestion or rhinorrhea (stuffy or runny nose)	Y or N	Y or N

Review HHC temperature log. Obtain child's temperature if not yet done.* Record highest temperature here ►	__ __ . __°C	Date:
	Site:	Time:

HCP obtains swab	Is local influenza A/B positive? Y or N **	If **Y**, refer HHC to investigator for standard of care (including anti-viral medicine). No more samples for this HHC needed. Continue to monitor for symptoms at subsequent visit if symptoms endpoint not *yet* met.
		If **N**, continue sampling at next visit. However, investigator may initiate standard of care if suspicion for influenza is high due to symptoms.

* Temperature obtained from tympanic thermometers provided to households (or exceptionally from other thermometers/locations in case of tympanic thermometer failure for any reason).

** Test SARS-CoV-2 via local test if HHC develops symptoms or fever versus baseline. If positive, withdraw all study subjects in household from the study.

Appendix 3
EQ-5D-5L to Measure Quality of Life

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

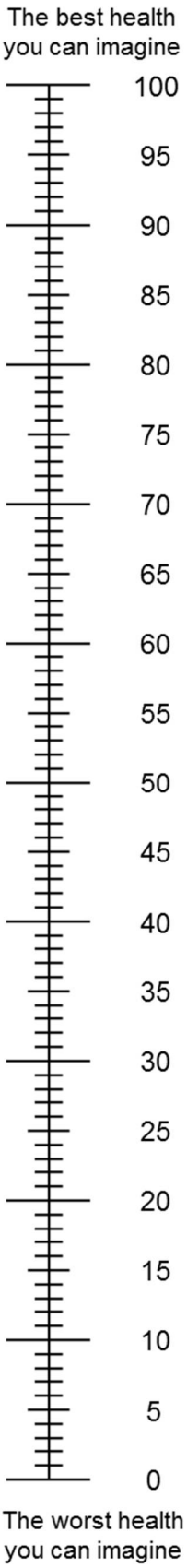
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 4
Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: SHP, Version 2 (WPAI+CIQ:SHP, V2)

The following questions ask about the effect of your **influenza/flu** on your ability to work, attend classes, and perform regular daily activities. *Please fill in the blanks or circle a number, as indicated.*

1) Are you currently employed (working for pay)? ____NO ___YES

If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2) During the past seven days, how many hours did you miss from work because of problems associated with your **influenza/flu**? *Include hours you missed on sick days, times you went in late, left early, etc., because of **influenza/flu**. Do not include time you missed to participate in this study.*

_____HOURS

3) During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

_____HOURS

4) During the past seven days, how many hours did you actually work?

_____HOURS *(If "0", skip to question 6)*

Appendix 4: Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: SHP, Version 2 (WPAI+CIQ:SHP, V2) (cont.)

5) During the past seven days, how much did **influenza/flu** affect your productivity while you were working?

*Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If **influenza/flu** affected your work only a little, choose a low number. Choose a high number if **influenza/flu** affected your work a great deal.*

Consider only how much **influenza/flu** affected productivity while you were working.

Influenza/flu had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	**Influenza/flu** completely prevented me from working

Circle a number

6) Do you currently attend classes in an academic setting (middle school, high school, college, graduate school, additional course work, etc.)?
___NO ___YES

If NO, check "NO" and skip to question 10.

7) During the past seven days, how many hours did you miss from class or school because of problems associated with your **influenza/flu**? *Do not include time you missed to participate in this study.*

_____ HOURS

8) During the past seven days, how many hours did you actually attend class or school?

_____ HOURS *(If "0", skip to question 10.)*

Appendix 4: Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: SHP, Version 2 (WPAI+CIQ:SHP, V2) (cont.)

9) During the past seven days, how much did your **influenza/flu** affect your productivity while in school or attending classes in an academic setting?

*Think about days your attention span was limited, you had trouble with comprehension or days in which you could not take tests as effectively as usual. If **influenza/flu** affected your productivity at school or in class only a little, choose a low number. Choose a high number if **influenza/flu** affected your productivity at school or in class a great deal.*

Consider only how much **influenza/flu** affected productivity while in school or attending classes.

Influenza/flu had no effect on my class work	0	1	2	3	4	5	6	7	8	9	10	**Influenza/flu** completely prevented me from doing my class work

Circle a number

10) During the past seven days, how much did **influenza/flu** affect your ability to do your regular daily activities, other than work at a job or attending classes?

*By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If **influenza/flu** affected your activities only a little, choose a low number. Choose a high number if **influenza/flu** affected your activities a great deal.*

Consider only how much **influenza/flu** affected your ability to do your regular daily activities, other than work at a job or attending classes.

Influenza/flu had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	**Influenza/flu** completely prevented me from doing my daily activities

Circle a number

Adapted from: Reilly MC, Tanner A, Meltzer EO: Work, classroom and activity impairment instruments: validation studies in allergic rhinitis. Clin Drug Invest 1996;11:278-88.

Appendix 5
Palatability and Acceptability Questionnaire of Study Drug (Index Patients Aged 5 Years Old to <12 Years Old)

Instructions: *Please answer the following questions to help us understand your experience with the study medicine. For the question with a face, indicate which of the faces best matches how you felt about the medicine.*

For children who cannot read yet*, parents or caregiver, please help us understand your child's experience with the study medicine. Invite your child to look at the cartoon, ask him or her the questions, and record his or her answer.*

If your child cannot answer the question, please skip the question.

The questions below are to be answered as soon as possible after swallowing the medicine.

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

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

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

☐ *Yes*

☐ *No*

☐ *Not sure/no answer*