Protocol Cover Sheet

Protocol Title:	Randomized double-blind, placebo-controlled pilot study of the efficacy and safety of baloxavir in combination with standard of care in stem cell transplant patients hospitalized for influenza
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PROTOCOL TITLE:	**Randomized double-blind, placebo-controlled single center pilot study to evaluate the efficacy and safety of baloxavir in combination with oseltamivir in adult allogeneic bone marrow transplant recipients with influenza**
STUDY NUMBER:	20-12023076
VERSION NUMBER:	3.0
TEST PRODUCTS:	Xofluza (baloxavir marboxil) (RO7191686)
INDICATION:	
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LIST OF ABBREVIATIONS AND DEFITIONS OF TERMS

Abbreviation	Definition
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation	Definition
cfDNA	Cell-Free DNA
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
HA	hemagglutinin complex
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
ICU	intensive care unit
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
LPLV	last patient, last visit
mITTI	modified intent-to-treat (influenza) infected (population)
NA	neuraminidase
NAI	neuraminidase inhibitor
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PK	pharmacokinetic
PRO	patient-reported outcome
SCT	Stem cell transplant
SOC	standard of care
$TCID_{50}$	50% tissue culture infectious dose
TQT	Thorough QT
TTAS	time to alleviation of symptoms
TTCI	time to clinical improvement
TTIIS	time to improvement of influenza symptoms
ULN	upper limit of normal
Vc/F	apparent volume of distribution for the central compartment

1. BACKGROUND

1.1 BACKGROUND ON INFLUENZA

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

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

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

In addition to Xofluza (baloxavir), the following anti-influenza virus drugs are currently available for treatment of acute, uncomplicated influenza in different countries: the M2 ion channel inhibitors amantadine and rimantadine, the RNA polymerase inhibitor favipiravir (not approved in the US), and the NA inhibitors (i.e., oseltamivir, zanamivir, and peramivir). Many viral isolates causing seasonal influenza infection are resistant to amantadine and rimantadine, hence the use of these drugs in clinical practice is limited. NA inhibitor (NAI) oral formulations need to be administered for 5 days, potentially resulting in poor patient compliance and convenience, while inhalation formulations can only be used in patients who are able to inhale the drug. These factors contribute to an unmet medical need for new antiviral influenza drugs that can be easily and less frequently administered, particularly in patients who are severely ill.

In February 2019, intravenous zanamivir (Dectova®) received a positive opinion for use under exceptional circumstances from the European Medicines Agency for the treatment of complicated and potentially life-threatening influenza A or B virus infections in adult and pediatric patients (aged $\geq$ 6 months). Zanamivir is only indicated when the influenza virus is resistant to other antiviral drugs, or when other antiviral drugs are not suitable, and, therefore, have limited scope in treating influenza in hospitalized patients. Currently, there are no other licensed drugs specifically approved for the treatment of influenza in hospitalized patients. Despite this, NAIs are widely used as the mainstay of treatment for hospitalized patients, and evidence shows a potential reduction in mortality in hospitalized patients treated with NAIs, especially if initiated as early as possible (Muthuri et al. 2014).

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

1.2 BACKGROUND ON XOFLUZA

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

Xofluza has a novel mechanism of action. In fact it acts on cap-dependent endonuclease, an enzyme specific to influenza viruses, and inhibits viral cap-snatching, thereby suppressing the replication of influenza viruses.
To date, one Phase II study in otherwise healthy adults and two Phase III studies in adults and adolescents (i.e., one in otherwise healthy patients and one in patients with high risk of influenza-related complications) have been completed and are summarized below. Currently, the drug is also approved for post-exposure prophylaxis, the reduction of influenza transmission, and otherwise healthy pediatrics ($<$ 12 years of age).

Xofluza is approved for use in Japan (since February 2018) for the treatment of influenza A or B virus infection in all age groups ($\geq$10 kg) and in the United States (since October 2018). It is approved for the treatment of influenza in otherwise healthy patients aged 12 years and above who have been symptomatic for no more than 48 hours. In addition, Xofluza is approved in Thailand and Japan for the treatment of influenza in patients aged 12 years and above who have been symptomatic for no more than 48 hours and are at high risk of developing influenza-related complications. Currently baloxavir is approved for influenza treatment in more than 60 countries).
Detailed profiles of Xofluza are provided in the Xofluza Investigator's Brochure.

1.2.1 OVERVIEW OF XOFLUZA CLINICAL DEVELOPMENT

The efficacy and safety of Xofluza have been established in randomized placebo-controlled Phase 2 and 3 studies. In clinical studies in adult and adolescent patients who were otherwise healthy (Phase 3 study T0831 and Phase 2 study T0821) or at high risk of developing influenza complications (Phase 3 study T0832), Xofluza was shown to be efficacious and well tolerated. Clinical efficacy was demonstrated against both influenza A virus subtypes (A/H1N1 and A/H3N2) and against type B virus. The potent antiviral effect of Xofluza was also seen in terms of the median time to cessation of viral shedding by virus titer, with at least a 2-day reduction over placebo and, in the Phase 3 studies in which oseltamivir was included as an active control group (T0832 and T0831), a 2-day reduction over oseltamivir. Xofluza is unique in achieving this degree of anti-viral effect with a single oral dose administration. Multiple administrations of Xofluza (at day 1, 4 and 7) have been used in the Flagstone study for the treatment of hospitalized patients with influenza to maintain sustained efficacious plasma concentrations.

1.2.1.1 EFFICACY

In the Phase 3 double-blind randomized study in otherwise healthy patients (Study 1601T0831/CAPSTONE-1; Hayden et al 2018), efficacy and safety of a single dose of Xofluza in adult and adolescent patients with influenza were investigated. Doses studied were 40 mg for patients who weigh <80 kg and 80 mg for patients who weigh ≥80 kg. The median time to alleviation of symptoms was 53.7 hours in the Xofluza group compared with 80.2 hours in the placebo group with a difference of −26.5 hours for Xofluza group (two-sided P value <0.0001). In the adult stratum of patients, the median time to alleviation of symptoms was 53.5 hours in the Xofluza group compared with 53.8 hours in the oseltamivir group, and no significant difference was found.

A phase 3 open-label study in otherwise healthy pediatric patients (Study 1618T0822) investigated the efficacy of a single dose of Xofluza in patients aged 6 months to 11 years. Dosages studied were 5, 10, 20 and 40 mg for patients weighing 5 to <10 kg, 10 to <20 kg, 20 to <40 kg and ≥40 kg, respectively. The median time to alleviation of influenza illness, i.e., alleviation of cough, nasal discharge/nasal congestion and fever, (primary endpoint) was 44.6 hours. The median time to resolution of fever (a secondary endpoint) was 21.4 hours.

A phase 3 double-blind randomized study in people aged 12 years or older who were at a high risk of complications from the flu (N=2184; Study 1601T0832/CAPSTONE-2) compared the efficacy of a single oral dose of Xofluza (40 mg or 80 mg according to body weight) with placebo or 75 mg of oseltamivir twice a day for 5 days. The time to improvement of influenza symptoms (TTIIS) was significantly shorter with Xofluza 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 was shorter with Xofluza than with placebo (median: 75.4 vs 100.4 hours; p=0.0141). TTIIS in patients with influenza B was also significantly shorter with Xofluza (74.6 hours) than either placebo (100.6 hours; p=0.0138) or oseltamivir (101.6 hours; p=0.0251).

1.2.1.2 SAFETY

In the phase 3 double-blind randomized study in otherwise healthy patients (Study 1601T0831/CAPSTONE-1), patients in the 20 to 64 years of age stratum received a single dose of 40 or 80 mg (depending on the patient's weight) of Xofluza, repeated dose of 75 mg oseltamivir twice daily for 5 days, or placebo, and patients in the 12 to 19 years of age stratum received a single dose of 40 or 80 mg (depending on the patient's weight) of Xofluza or placebo. A total of 1,432 patients received the study drug: 610 in the Xofluza group, 309 in the placebo group, and 513 in the oseltamivir group. No deaths were reported in all the 3 groups. Two SAEs (1 event each of meningitis viral and incarcerated inguinal hernia) were reported in 2 of 610 patients (0.3%) in the Xofluza group. The events resolved and were considered not related to the study drug. A total of 9 AEs leading to withdrawal of study drug were reported: 3 events in 2 of 610 patients (0.3%) in the Xofluza group, 4 events in 1 of 309 patients (0.3%) in the placebo group, and 2 events in 2 of 513 patients (0.4%) in the oseltamivir group.

All of the AEs leading to withdrawal of study drug in the Xofluza group were considered not related to the study drug.

In the phase 3 double-blind randomized study in people 12 years or older who were at a high risk of complications from the flu (N=2184; Study 1602T0832/CAPSTONE-2), the incidence of any adverse event (25.1–29.7%) or any serious adverse events (0.7–1.2%) did not differ significantly between the groups treated with a single oral dose of Xofluza (40 mg or 80 mg according to body weight), placebo, or 75 mg of oseltamivir twice a day for 5 days.

In the phase 3 open-label study in otherwise healthy pediatric patients (Study 1618T0822), 2, 31, 66, and 8 patients (a total of 107) received a single 5, 10, 20, and 40 mg dose of Xofluza, respectively. No deaths, serious AEs or discontinuations due to AEs were reported in the study.

In the phase 3 open-label study in otherwise healthy pediatric patients (weighing ≤20 kg and aged ≤12 years) with influenza (Study 1705T0833), a total of 33 patients received a single dose of Xofluza. The dosage was 10 mg of Xofluza in patients weighing ≥10 kg and 1 mg/kg of Xofluza in patients weighing <10 kg. No deaths, serious AEs or discontinuations due to AEs were reported in the study. Most common AEs reported were vomiting, diarrhea and pharyngitis. Treatment-related AEs (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 resolved or were resolving.

Refer to the Xofluza Investigator's Brochure for details on nonclinical and clinical studies.

1.2.2 POST-MARKETING SAFETY DATA

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

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

1.3 STUDY RATIONAL AND BENEFIT-RISK ASSESSMENT

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 (WHO 2017a, WHO 2018, Baxter 2016). Influenza also places significant demands on healthcare services each season, and impacts society through lost workforce productivity (WHO 2018). Influenza virus infection can be especially severe in stem cell transplant (SCT) recipients. In these patients the clinical course is often prolonged with a higher frequency of progression of the disease to the lower respiratory tract, protracted viral shedding and increased death[1,2]. Neuraminidase inhibitors (NAI), including oseltamivir, are the mainstay of influenza therapy. However, because the paucity of initial symptoms and the frequent absence of fever[3,4] the diagnosis of influenza is often delayed in this population, and treatment with NAI is often started later than 48-hours after the onset of influenza, that is the period during which NAI

treatment is most effective. Moreover, while low rates of NAI resistance are reported in the general population, high viral replication associated with prolonged therapeutic courses favor the rapid emergence and transmission of NAI-resistant influenza in SCT recipients[5].

Baloxavir (Xofluza™) is a first-in-class influenza antiviral that blocks influenza virus RNA replication by inhibiting cap-dependent endonuclease activity (Omoto *et al* 2018). Baloxavir has a prolonged half-life allowing the administration in single dosing and it was recently approved for use in the US for the treatment of uncomplicated influenza. In the Phase III CAPSTONE-1 double-blind randomized study in otherwise healthy patients (Hayden et al 2018), a single treatment of baloxavir (40 mg for patients <80 kg and 80 mg for patients ≥80 kg) significantly reduced the time to alleviation of symptoms 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 time to cessation of viral shedding

Although it was shown that baloxavir is effective against oseltamivir--resistant influenza strains in vitro (Taniguchi *et al* 2019), and it was effective in treating influenza in the immunocompromised mouse model (Fukao *et al* 2019), no randomized--controlled trials are available on the use of baloxavir in SCT recipients or in other immunocompromised patients. In a pilot study, we administered baloxavir to 5 SCT recipients who were still symptomatic and shedding influenza after treatment with oseltamivir. Two of these patients had the codon variant H275Y, that is known to confer resistance to oseltamivir. We found that after one or two administrations of baloxavir, the patients could clear the virus and improve the influenza symptoms. One of the patients developed the I38T variant in the PA subunit of the IAV polymerase. High rates of the I38X PA variant have emerged during baloxavir treatment in clinical trials, and it has been associated with resistance to the drug (Hayden *et al* 2018). Despite the limitations of a small number of patients and lack of control group, our preliminary data (Salvatore *et al* 2020) suggest that baloxavir may be a useful treatment option for infections with influenza SCT patients, although the low barrier to resistance and the potential for transmissibility of baloxavir-resistant influenza virus raises concern.

Combination treatment with baloxavir and oseltamivir in vitro and in mice produced synergistic responses against influenza virus infections. In this model, a suboptimal dose of baloxavir marboxil (0.5 mg/kg twice daily) in combination with oseltamivir phosphate provided additional efficacy compared with monotherapy in terms of virus-induced mortality, elevation of cytokine/chemokine levels and pathological changes in the lung suggesting that treating humans with the combination may be beneficial (Fukao *et al* 2019 b). Despite this treatment option may be more effective in clearing influenza virus infection and decrease the rate of emergence of resistant influenza in immunocompromised hosts no data about combination therapy in human are currently available. This study was therefore designed with the primary objective to compare the efficacy of the combination therapy of baloxavir with oseltamivir with oseltamivir plus placebo.

In the Flagstone study, the incidence of adverse events was comparable between the two treatment arms regardless of the number of Xofluza or placebo doses that were received. One serious adverse event (orthostatic hypotension) in the placebo arm was considered treatment related.

Table 4: FLAGSTONE – Incidence of Adverse Events*			
	Baloxavir + SoC NAI (n=239)	Placebo + SoC NAI (n=124)	All Patients (n=363)
Patients with ≥1 AE	108 (45.2%)	62 (50.0%)	170 (46.8%)
Total number of AEs	279	180	459
Deaths	4 (1.7%)	7 (5.6%)	11 (3.0%)
Patients withdrawn from treatment due to AE	3 (1.3%)	4 (3.2%)	7 (1.9%)
Serious AEs, patients (%)	29 (12.1%)	19 (15.3%)	48 (13.2%)
Treatment-related serious AEs, patients (%)	0	1 (0.8%)	1 (0.3%)
Treatment-related AEs, patients (%)	8 (3.3%)	8 (6.5%)	16 (4.4%)
Notes: *Safety population. Investigator text for AEs encoded using the MedDRA version 23.0. Related AEs are related to study drugonly. Abbreviations: AE(s)=adverse event(s); MedDRA=Medical Dictionary for Regulatory Activities; NAI=neuraminidase inhibitor; SoC=standard of care			

Our study will randomize SCT recipients with influenza to receive baloxavir + oseltamivir (SOC) or oseltamivir + baloxavir matching placebo and assess if the combination of baloxavir with oseltamivir will translate in a more rapid decrease of viral load and faster symptoms resolutions when compared to oseltamivir alone. It will also test if combination therapy may lower the incidence of drug-resistant influenza variants.

In summary, there is a strong rationale and a positive benefit-risk assessment for studying Xofluza combination therapy in SCT recipients. Safety and efficacy results suggest that Xofluza has an acceptable clinical safety profile and could benefit in immunocompromised patients. Given the poor treatment responses to single therapy in SCT, this population is considered appropriate for trials of combination therapy. The benefit-risk ratio for Xofluza in combination with oseltamivir is expected to be acceptable in this setting.

2. OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

The primary objective is to evaluate the efficacy of both the combination therapy of baloxavir with oseltamivir and that of oseltamivir plus placebo in SCT patients with influenza as measured by changes in influenza viral RNA loads at day 10 from baseline (day 1) and compare between arm differences in decline of viral load

The co-primary efficacy endpoints are:

- Change of influenza viral RNA loads from baseline (day 1) at the end of treatment (day 10) as measured by quantitative real time polymerase chain reaction (qRT-PCR, nucleic acid).

- Between-treatment-arm difference in the change of influenza viral RNA loads from baseline (day 1) at the end of treatment (day 10) as assessed by quantitative real time polymerase chain reaction as measured by (qRT-PCR, nucleic acid) and by Influenza plaque assay (replicating virus).

The secondary efficacy endpoints are:

1. **Change of influenza viral RNA load from baseline (day 1) at day 4 and day 7 and 10** as measured by quantitative real time polymerase chain reaction (qRT-PCR, nucleic acid) in each treatment arm.
2. **Difference in change of influenza viral loads from baseline (day 1) at day 4, 7 and 10 between the two treatment arms** as measured by quantitative real time polymerase chain reaction (qRT-PCR, nucleic acid)
3. **Change of influenza viral loads from baseline (day 1) at day 4, 7 and 10** as measured by Influenza plaque assay (replicating virus) in each treatment arm.
4. **Difference in change of influenza viral loads from baseline (day 1) at day 4, 7 and 10 between the two treatment arms** as measured by Influenza plaque assay (replicating virus).
5. **Time to Improvement of Individual Influenza Symptoms** [Time Frame: From Day 1 pre-treatment up to Day 30] defined as the time from the initiation of the study treatment to the improvement of influenza symptoms as assessed by patient-reported outcome measures on a single scale as specified in section 4.5.7 . Time to improvement of symptoms is defined as the time from the start of treatment to the time when each of the influenza symptoms will be alleviated, maintained, or improved, for a duration of at least 24 hours.
   Participants will assess the severity of 7 influenza-associated symptoms (cough, sore throat, headache, nasal congestion, feverishness/chills, muscle/joint pain, and fatigue) on a 4-point scale (0 = no symptoms, 1= mild, 2 = moderate, and 3 = severe) as specified in section 4.5.7. Improvement is defined as: improvement pre-existing symptoms (i.e cough, fatigue, or muscle/join pain that existed prior to influenza) that were worse at baseline and improve at least 1 point from baseline; pre-existing symptoms not worse at baseline that maintain baseline severity; and new symptoms that are alleviated, defined as a symptom score of non (0) or mild (1).

   Once all patient's influenza symptoms are alleviated, maintained, or improved (hereafter all will be called 'improvement') as defined above, the endpoint will be reached.
6. **Percentage of patients who experience each influenza-related complication** (hospitalization, death, sinusitis, otitis media, bronchitis, and radiologically-confirmed pneumonia) as an adverse event after the initiation of study treatment symptoms [symptoms [Time Frame: From Day 1 pre-treatment up to Day 30].
7. **Time to Return to Preinfluenza Health Status** [Time Frame: From Day 1 pre-treatment up to Day 30]. Participants will be asked to record their preinfluenza health status on a scale from 0 (worst possible health) to 10 (normal health [for someone same age and condition]), and their health status at baseline and every day after initiation of study treatment on the same scale as specified in section 4.5.7. Return to preinfluenza health status is defined as time from the initiation of the study treatment to the first time when the health status score was equal to or higher than the preinfluenza health status score.
8. **Time to viral clearance,** as assessed by difference in Percentage of Participants Positive by Influenza plaque assay and qPCR at each time-point (in each treatment group) The definition of the time to sustained cessation of infectious virus detection is the time

between the start of treatment and when virus titer remained below the detection limit on all subsequent sampling time points.

9. Measure treatment-emergent variants of neuraminidase and polymerase known to confer antiviral resistance to oseltamivir in each arm by direct next-generation sequencing symptoms [Time Frame: From Day 1 pre-treatment up to Day 30]
10. Safety and tolerability of Baloxavir in Combination with SOC treatment as assessed by Percentage of Participants with Adverse Events (AEs) [Time Frame: From first dose of study drug to Day 15]

1.2.1 EXPLORATORY EFFICACY OBJECTIVES

1. To evaluate the use of cell-free DNA as surrogate for organ damage and treatment response

The exploratory efficacy endpoint is:

1. Measure change in organ damage and response to treatment by using cell-free DNA as surrogate.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a randomized double-blind placebo-controlled pilot study of the efficacy and safety of baloxavir in combination with oseltamivir (SOC) for the treatment of influenza in allogeneic stem cell transplant patients.

30 SCT recipients with influenza will take part in the study. Participants with be randomly assigned (1:1) to either baloxavir + oseltamivir or baloxavir-matched placebo +oseltamivir. Randomization will be performed by research pharmacy using an interactive web randomizer. Before randomization, patients will be stratified by hospitalization status (yes or no), influenza type A (yes or no).

Patients in the baloxavir combination arm will receive weight-adjusted baloxavir (40 mg for patients weighing <80 kg and 80 mg for those weighing ≥80 kg) at baseline and at day 4 and day 7. They will also receive oseltamivir 75 mg twice daily for 10 days.

Patients in the baloxavir-matched placebo + oseltamivir arm will receive baloxavir-matched placebo at baseline and at day 4 and day 7 and oseltamivir 75 mg twice daily for 10 days.

Nasopharyngeal swabs will be collected on days 1 (at diagnosis, pre-meds), 2, (optional visit), 4, 7 and 10 for viral quantitation and viral sequencing. Influenza virus polymerase and neuraminidase sequencing will be also performed in all patients. Patients will have follow-up visits day 15 (+/- 2 days) and day 30 (+/- 2 days, EOT). Patients who will not clear the virus by day 10 will perform additional NP swabs at these visits.

Paracetamol (acetaminophen; maximum 3000 mg per day) or NSAIDS can be given for severe discomfort or fever. No other antiviral drugs for the treatment of influenza, will be permitted, except antibiotics for the treatment of suspected bacterial infections.

For the first 10 days, patients will receive a daily call from one member of the study team to review symptoms and severity scale.
To assess the **time to improvement of individual influenza symptoms** (with modification for preexisting symptoms), participants will be given a diary to self-assess the severity of seven influenza-associated symptoms on a four-point scale. To evaluate patient-reported **time to return to pre-illness health status**, patients will also rate **daily the interference of influenza symptoms in daily activities** on a 5-point severity scale.

Oral temperature will be measured by the patient (in the outpatient setting) or by the staff for inpatients in the am and pm daily until day 10.

To evaluate **incidence of complications associated with influenza** after the start of study treatment, at each study visit investigators will assess whether each of the complications (sinusitis, otitis, bronchitis, pneumonia) is present or not. If present, the report form shown in section will be completed. For pneumonia, a radiological confirmation will be required.

On days 1, 7 and 15 safety laboratory tests (CBC, blood chemistry with LFTs) will be done.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) has occurred, patient has become lost to follow up, patient has withdrawn consent, or patient has completed at least 1 months of follow-up after randomization. The end of the clinical part of the study is expected to occur two months after the last patient is enrolled. After that the study will be open for analysis only. In addition, the Investigator may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 24 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 RATIONALE FOR XOFLUZA DOSE

The dose of Xofluza for this study was selected based on the results of Study 1601T0831 (CAPSTONE-1). This study compared the effects of a single dose of Xofluza (40 mg for patients <80 kg and 80 mg for patients ≥80 kg administered as 20 mg tablets) with placebo or oseltamivir in otherwise healthy patients with influenza aged ≥12 to ≤64 years of age. Study 1601T0831 demonstrated that a single 40 mg/80 mg dose on Day 1 was well tolerated and significantly reduced the time to alleviation of symptoms. This dose and regimen were also effective at reducing viral load. In the Flagstone study, baloxavir dosing at day 0, 4 and optional day 7 was used for treatment of influenza on hospitalized patients. Since SCT recipients are immunocompromised and have severe and prolonged disease we will use the same dose of baloxavir that is used for hospitalized patients in SCT with influenza treated both as outpatients or inpatients.

3.3.2 RATIONALE FOR PATIENT POPULATION

As described above, treatment with Xofluza has been shown to reduce viral load and symptoms in patients with influenza A or B. Therefore, this study was designed to determine if adding baloxavir to oseltamivir will translate into a reduction in viral titer and symptoms.

3.3.3 RATIONALE FOR THE CONTROL GROUP

This is a placebo+oseltamivir -controlled study because oseltamivir is standard of care treatment for influenza in SCT. Since SCT patients usually are unable to clear infection after 5 day-course of oseltamivir, we will use a 10-day course that is the standard of care (SOC) in the Weill Cornell Medicine BMT clinic. Comparison with placebo + oseltamivir will enable the analysis of the effect of combination therapy with baloxavir on influenza viral titers and clearance.

3.3.4 RATIONALE FOR BIOMARKER ASSESSMENTS

Short fragments of cell-free DNA (cfDNA) circulate in blood. These molecules are the circulating debris of the genomes of dead cells, and their importance in diagnostic medicine has been widely established. The value of cfDNA as a quantitative marker of tissue and organ injury was first recognized in solid-organ transplantation, where the level of transplant donor derived cfDNA in the blood is now widely used as a marker of transplant rejection. More recently, several approaches have been developed to quantify the cell-, tissue-, and organ-of-origin of cfDNA and to thereby monitor injury to any cell, tissue or organ types. This is achieved by profiling of cell-, tissue-, or organ-specific epigenetic marks within cfDNA by quantitative molecular measurement technologies such as DNA sequencing. Here, we will test the hypothesis that profiling the cfDNA tissues-of-origin would enable identifying specific tissue cell types that are directly or indirectly targeted and injured by influenza infection, and follow their recovery under therapy.

3.3.5 RATIONALE FOR PATIENT-REPORTED OUTCOME ASSESSMENTS

PROs provide an understanding of the impact a treatment has on a patient. As for previous Baloxavir studies we will use patient-reported outcome measurements.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 30 patients with allogeneic bone marrow transplant will be enrolled in this study.

4.1.1 INCLUSION CRITERIA

Patient must meet the following criteria for study entry:

- Adult patients: Signed informed consent by any patient capable of giving consent, or, where the patient is not capable of giving consent, by his or her legal/authorized representative
- Age $\geq$ 18 years at the time of signing the Informed Consent Form/Assent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Be defined as immunocompromised*, as defined by:
    1. Have received allogeneic bone marrow transplant, or
    2. Is currently receiving treatment with chemotherapy and/or CAR-T cell therapy for hematologic malignancies (e.g., leukemia, myeloma, lymphoma), or

3. Received treatment with chemotherapy and/or CAR-T cell therapy for hematologic malignancies (e.g., leukemia, myeloma, lymphoma) within the past 1 year.

- Tested positive for influenza infection after the onset of symptoms using a polymerase chain reaction (PCR)-based diagnostic assay.
- Presence of (a) fever ($\geqslant$38.0 °C per tympanic or rectal thermometer; $\geqslant$ 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).
- The time interval between the diagnosis of influenza and the pre-dose examinations is 48 hours or less.
- For women of childbearing potential: Agreement to remain abstinent (refrain from heterosexual intercourse):

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

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

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

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

*This study will enroll a minimum of 10 patients who have received allogeneic bone marrow transplant.

4.1.2 EXCLUSION CRITERIA

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

- Patients who have received more than 48 hours of antiviral treatment for the current influenza infection prior to screening
- Patients who have received Baloxavir for the current influenza infection
- Known contraindication to neuraminidase inhibitors
- Patients weighing $<$ 40 kg

- Patients unable to swallow tablets
- Patients with known severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m^2) or receiving continuous renal replacement therapy, hemodialysis, peritoneal dialysis
- Patients with any of the following laboratory abnormalities detected within 24 hours prior to or during screening (according to local laboratory reference ranges:
    - ALT or AST level >5 times the upper limit of normal (ULN) OR
    - ALT or AST >3 times the ULN and total bilirubin level > 2 times the ULN
- Pregnant or breastfeeding, or positive pregnancy test in a predose examination, or intending to become pregnant during the study or within 28 days after the last dose of study treatment
- Exposure to an investigational antimicrobial within 5 half-lives or 30 days (whichever is longer) of randomization
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Known hypersensitivity to baloxavir marboxil or the drug product excipients
- Known COVID-19 coinfection
- Unwilling to undergo nasopharyngeal (NP) swabs as per study schedule

4.2 SAMPLE COLLECTION AND PROCESSING

4.2.1 NASOPHARYNGEAL SAMPLING AND VIROLOGICAL ASSAYS

Two nasopharyngeal swabs will be collected at each visit and put immediately into viral transport medium and frozen. Pharyngeal swabs will be collected when if it is not possible to collect nasopharyngeal swabs. At the end of the clinical study period, samples will be used for viral sequencing and virological assessment.

Viral RNA in pre- and last post-treatment swab samples will be extracted using conventional RNA extraction kit without virus amplification and used for viral RNA quantification by q-PCR and for viral sequencing. Swabs will also be used to calculate viral titers by plaque assays on MDCK cells.

4.2.2 BLOOD SAMPLE FOR BIOMARKER ASSESSMENT

This will be collected at each visit, plasma will be separated by PBMC PI laboratory and samples will be kept frozen at -80C until use.

4.3 METHOD OF TREATMENT ASSIGNMENT

Participants will be and randomly assigned (1:1) to either the baloxavir + oseltamivir group, or the placebo + oseltamivir group. Before randomization, patients will be stratified by hospitalization (yes or no), influenza type A (yes or no). To maintain blinding, patients in the oseltamivir group will receive baloxavir-matched placebo.

The design randomization schema will be developed and managed by the Weill Cornell investigational pharmacy. Unblinding will be done when last patient completed the study follow up period.

Study Treatment: The investigational medicinal product (IMP) for this study is baloxavir in combination with oseltamivir.

4.3.1 STUDY TREATMENT FORMULATION, PACKAGING, AND HANDLING

4.3.1.1 Xofluza

Xofluza will be supplied by the Genentech, Inc. as tablets.
For information on the formulation and handling of Xofluza, see the Xofluza Investigator's Brochure.

4.3.1.2 Placebo

Baloxavir-matched placebo will be supplied by Genentech, Inc. as tablets.

4.3.1.3 Oseltamivir

Oseltamivir will be supplied by Genentech, Inc. as 75 mg tablets for oral administration. For information on the formulation, packaging, and handling of Oseltamivir see the local prescribing information for Oseltamivir.

4.3.2 STUDY TREATMENT DOSAGE, ADMINISTRATION, AND COMPLIANCE

The treatment regimens are summarized in Section 3.1.

Treatment will be self-administered in case of outpatient, the first dose will be taken during the clinic visit.

For hospitalized patients, treatment will be administered by a trained nursing professional.

Any overdose or incorrect administration of baloxavir or oseltamivir should be noted in the patient's medical records and reported according to Section 5.5 (Special Situations Reports). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded in the patient's medical records.

4.3.2.1 Baloxavir and Oseltamivir

The treatment regimens are summarized in Section 3.1.

Patients in the baloxavir combination group will receive an oral dose of baloxavir at baseline (40 mg for patients weighing <80 kg and 80 mg for those weighing ≥80 kg) and at day 4 and 7. They will also receive oseltamivir 75 mg twice daily for 10 days.

4.3.2.2 Placebo and Oseltamivir

Patients in the standard-of-care group will receive oseltamivir 75 mg twice daily for 10 days and an oral dose of baloxavir-matched placebo at baseline and at day 4 and 7.

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

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

4.4.1 PERMITTED THRAPY

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

4.4.2 CAUTIONARY THERAPY

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

4.4.3 PROHIBITED THERAPY

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

- Investigational antimicrobial therapy (other than the protocol-mandated study treatment) is prohibited within 5 half-lives or 30 days (whichever is longer) prior to initiation of study treatment and during the study
- Concomitant use of herbal therapies is prohibited as their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

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.

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

4.5.2 MEDICAL HISTORY, CONCOMITANT MEDICATION, AND DEMOGRAPHIC DATA

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies, current cancer stage, and procedures), menstrual

history, fertility history, and puberty history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient in addition to protocol-mandated treatment within 7 days prior to initiation of study treatment until 30 days after the final dose of study drug will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

4.5.3 PHYSICAL EXAMINATION

A complete physical examination, will be performed at screening and other specified visits. Any abnormality identified at baseline will be recorded in the patient's medical records.

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

4.5.4 VITAL SIGNS

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, and temperature and will be performed at specified timepoints as outlined in the schedule of activities (see Appendix 1). They may be performed by a MN professional.

4.5.5 INFLUENZA DIAGNOSTIC TEST

For patients to be eligible for this study, a RT-PCR is required to be performed to inform a diagnosis of influenza. If a site has performed a RT-PCR test within the 24 hours prior to screening, the local RIDT or RT-PCR result can be used. Screening test for COVID-19 will also be performed before enrollment.

4.5.6 PHYSICIAN ASSESSMENTS

1. **Time to improvement of respiratory status.** This is defined as decreased or no need for oxygen supplementation to maintain optimal O2 saturation (>94%)
2. **Measurement of the incidence of influenza complications**
   We will record the incidence of following influenza complications associated with influenza after the start of study treatment: 1. Sinusitis; 2. Otitis Media; 3. Bronchitis; 4. Radiologically Confirmed Pneumonia, and 5. Hospitalization. At each study visit investigators will ask whether Sinusitis, Otitis Media, Bronchitis, Radiologically Confirmed Pneumonia and Hospitalization is present or not. If any of these is present, a specific report form shown below will be completed.

Form: Sinusitis

Did these symptoms start after the influenza treatment was given on Day 1?	Yes ☐ No ☐
Does the patient have a purulent nasal discharge?	Yes ☐ No ☐
Does the patient have facial pain, pressure sensation, or sensation of fullness?	Yes ☐ No ☐
Does the patient have nasal obstruction, congestion or stuffiness?	Yes ☐ No ☐
Have antibiotics been given to treat the sinusitis?	Yes ☐ No ☐

Form: Otitis Media

Did these symptoms start after the influenza treatment was given on Day 1?	Yes ☐ No ☐
Does the patient have pain or fullness in one or more ears?	Yes ☐ No ☐
Does the patient have tympanic membrane bulging or fullness on otoscopy?	Yes ☐ No ☐
Have antibiotics been given to treat the otitis media?	Yes ☐ No ☐

Form: Bronchitis

Did these symptoms start after the influenza treatment was given on Day 1?	Yes ☐ No ☐
Does the subject have a productive cough that has got worse after Day 1?	Yes ☐ No ☐
Has pneumonia been excluded?	Yes ☐ No ☐
Have antibiotics been given to treat the bronchitis?	Yes ☐ No ☐

Form: Pneumonia

Did these symptoms start after the influenza treatment was given on Day 1?	Yes ☐ No ☐
Does the patient have worsening cough since starting study treatment?	Yes ☐ No ☐
Does a Chest X Ray confirm pneumonia i.e. consolidation?	Yes ☐ No ☐
Have antibiotics been given to treat the pneumonia?	Yes ☐ No ☐

3. **<u>Hospital Recovery Scale</u>**

   We will use the hospital recovery scale to assess participant's clinical status from day 1 to day 30. The hospital recovery scale provides 6 mutually exclusive conditions ordered from best to worst, and the score reflects the subject's worst situation on the day of assessment:

   1. Not hospitalized
   2. Non-ICU hospitalization, not requiring supplemental oxygen
   3. Non-ICU hospitalization, requiring supplemental oxygen
   4. Admitted to the ICU, not requiring invasive mechanical ventilation
   5. Requiring invasive mechanical ventilation
   6. Death

4.5.7 SELF ASSESSED MEASUREMENTS

1. TIME TO SYMPTOMS IMPROVEMENT

This is defined as time from the start of treatment to patient reported improvement in all seven influenza-associated symptoms for a duration of at least 24 hours. Symptoms that were present before the development of influenza symptoms will have to improve by at least one level. If patient was not experiencing any symptom, all symptoms will have to be rated as mild or absent. Patients will be given a diary to self-assess daily the severity of the following influenza-associated symptoms on a 4 points scale, at baseline and then for the first 15 days of the study.

	Date			
	No symptoms Score 0	Mild symptoms Score 1	Moderate symptoms Score 2	Severe symptoms Score 3
cough				
sore throat				
headache				
nasal congestion				
feverishness				
chills				
muscle or joint pain				

At baseline (i.e., the predose examinations), patients will be asked if preexisting symptoms existed (within the last 30 days) and if they were worsened by influenza. Patients will be asked to rate the severity at baseline
that needs to improve. The modification for preexisting symptoms will be done as follows (ISON et al 2020, DOI:https://doi.org/10.1016/S1473-3099(20)30004-9)

A. Symptoms that **existed prior to developing influenza** that are judged by the patient to be **worse at baseline** (before therapy) must improve from baseline severity

o Improvement in baseline severity is defined as follows:
Severe to moderate, mild, or absent
Moderate to mild or absent
Mild to mild or absent
Absent to mild or absent

B. Symptoms that existed prior to developing influenza that were judged by the patient to **NOT be worse at baseline** (before therapy) must have their baseline severity maintained

o Maintenance of baseline severity is as follows:
Severe is defined as severe or less than severe
Moderate is defined as moderate or less than moderate
Mild is defined as mild or absent
Absent is defined as mild or absent

• For **new symptoms at baseline** (before therapy), alleviation of symptoms assessment must be achieved

o Alleviation of symptoms is defined as follows:
Severe is mild or absent
Moderate is mild or absent
Mild is mild or absent
Absent is mild or absent

Time to improvement of influenza symptoms is defined as the time from the initiation of the study treatment to the improvement of influenza symptoms for a duration of at least 24 hours. Once the patient's influenza symptoms will be alleviated, maintained, or improved (hereafter all will be called 'improvement') as defined above, the endpoint for that patient will be reached.
Patients who did not experience improvement of symptoms will be censored at the last observation time point.

2. TIME TO RETURN TO PRE-INFLUENZA HEALTH AND ACTIVITIES

Participants will be asked to record their preinfluenza health status on a scale from 0 (worst possible health) to 10 (normal health [for someone your age and condition]), and their health status at baseline and every day after initiation of study treatment on the same scale. Return to preinfluenza health status is defined as time from the initiation of the study treatment to the first time when the health status score was equal to or higher than the preinfluenza health status score.

3. PATIENT GLOBAL ASSESSMENT OF INTERFERENCE OF FLU IN DAILY ACTIVITIES

This scale will be used by the patient for self-assessment of the interference in daily activities due to influenza symptoms during that day. Return to daily activities will be assessed once daily by means of the subject's response to the question 'Over the past 24 hours, how much has influenza (flu) interfered with your ability to carry out your daily activities?'
Answer will be recorded using the following scale:

1. Not at all
2. A little bit
3. Somewhat
4. Quite a bit
5. Very much

4.5.8 LABORATORY, BIOMARKER, AND OTHER BIOLOGICAL SAMPLES

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis as routinely done for standard of care:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST
- Pregnancy test
    - All women of childbearing potential will have a serum pregnancy test at screening
    - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other

than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

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

- NP swabs
- Blood samples for exploratory research on biomarkers
    - Exploratory biomarkers will include analysis of cfDNA, analysis of genes or gene signatures associated with influenza severity or recovery from influenza. This research will involve extraction of DNA, and genomic profiling through use of next-generation sequencing of a comprehensive panel of genes. NGS methods will not include whole genome sequencing (WGS).
    - Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research, biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exception:
        - Blood samples collected for biomarker research will be destroyed no later than 10 years after the final Clinical Study Report has been completed.

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

Data arising from sample analysis, will be subject to the confidentiality standards described in Section 8.4. Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Investigator policy on study data publication.

4.6 TREATMENT, PATIENT, AND STUDY DISCONTINUATION

Patients must permanently discontinue study treatment (Xolfuza and oseltamivir) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator determines it is in the best interest of the patient
- Pregnancy
- Anaphylaxis or other severe hypersensitivity reaction
- Loss of clinical benefit as determined by the investigator after an integrated assessment of clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details)

The primary reason for study treatment discontinuation should be documented in the patient's medical records. Patients who discontinue study treatment prematurely will be replaced.

4.6.1 PATIENT DISCONTINUATION FROM STUDY

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

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

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented in the patient's medical records. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study may be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.2 STUDY DISCONTINUATION

The investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but 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

5. ASSESSMENT OF SAFETY

5.1 SPECIFICATION OF SAFETY VARIABLES

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

5.2 ADVERSE EVENTS

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with SCT patients with influenza that were not present prior to the AE reporting period.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

5.3 SERIOUS ADVERSE EVENTS

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

5.3.1 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports)

5.3.2 ADVERSE EVENT REPORTING PERIOD

The study period during which AEs and SAEs as described in ***section J*** where the patient has been exposed to Genentech product must be reported. Reporting period begins after informed consent is obtained and initiation of study treatment and ends 30 days following the first administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

5.3.3 ASSESSMENT OF ADVERSE EVENTS

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the baloxavir combination therapy (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

YES

There is a plausible temporal relationship between the onset of the AE and administration of the baloxavir combination therapy and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the baloxavir combination therapy or with similar treatments; and/or the AE abates or resolves upon discontinuation of the baloxavir combination therapy or dose reduction and, if applicable, reappears upon re- challenge.

NO
Evidence exists that the AE has an etiology other than the baloxavir combination therapy (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to baloxavir combination therapy administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I)
or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

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

5.3.4 Management Criteria for Abnormal Liver Function Tests and Data and Safety Monitoring Plan (DSMP)

Management Criteria for Abnormal Liver Function tests have been designed to ensure patient safety and evaluate liver event etiology (see Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, FDA: 2009; available from: https://www.fda.gov/downloads/Guidances/UCM174090.pdf).
The Weill Cornell Medicine DSMB will be used for this investigator-initiated study. The following information will be submitted to the WCM DSMB:

Laboratory results

- Blood hematology and chemistry
- Blood liver chemistry

Adverse Events and Stopping Rules

The following adverse events will be submitted to the WCM DSMB and may cause the subject to terminate protocol treatment, **at the discretion of the PI**:

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

Action to be Taken by Investigator

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

- consider discontinuation only if transaminase elevation is not otherwise explained
- Following the initial observed elevation, every effort should be made to have the patient return to the clinic within 72 hours (if already discharged from hospital) to repeat liver function chemistries and for further hepatic evaluation.
- Every effort should be made to have the patients monitored 2 to 3 times per week until liver function chemistries (i.e., ALT, AST, ALP, TBL) resolve, stabilize per investigator judgement, or return to within the normal range or to baseline levels.
- Consultation with a specialist, such as a hepatologist, and liver imaging (i.e., ultrasound, magnetic resonance imaging [MRI], computerized tomography) should be considered for worsening laboratory values or symptoms.

WCM IRB policies will be followed for this study, including the Immediate Report Policy. Any SAEs will be reported to the IRB following these policies, and will also be reported to the funding source (Genentech Inc.) within 30 days of the study team learning of the SAE. The WCM DSMB comments/review will be submitted to the IRB at the time of continuing review and submitted to the funding source (Genentech, Inc.) at the time of each WCM DSMB completion.

5.4 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

5.4.1 ELICITING ADVERSE EVENTS

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

5.4.2 SPECIFIC INSTRUCTIONS FOR RECORDING ADVERSE EVENTS

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

5.4.2.1 Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported 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, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

5.4.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section I), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

5.4.2.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.4.2.4 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

5.4.2.5 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v 5.0 Update current versions) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE v 5,0 which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

5.4.3 PREGNANCY

If a female subject becomes pregnant while receiving the study drug or within *90 days* after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within *90 days* after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

5.4.4 AEs OF SECIAL INTERESTS (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

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

5.4.5 OTHER SPECIAL SITUATIONS REPORTS

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population.

5.4.7 POST-STUDY ADVERSE EVENTS

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior baloxavir exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [add if applicable-including pregnancy occurring in the partner of a male study subject] who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up period.

5.4.8 EXCHANGE OF SINGLE CASE REPORTS

Weill Cornell Medical College will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product. Weill Cornell Medical College will submit SAEs, AESIs, Special Situations, and any pregnancy to Genentech using the MedWatch Form. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should call via:
PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Type of Report	Timelines
Serious Adverse Events (related and not related to the Product)	30 calendar days from awareness date
Special Situation Reports (With or without AE and pregnancy)	
Product Complaints (With or without AE)	
AESI	

5.4.9 CASE TRANSMISSION VERIFICATION OF SINGLE CASE REPORTS

- The parties will verify that all single case reports have been adequately received by Genentech by emailing Genentech a Quarterly line-listing documenting single case reports sent to Genentech in the preceding time period.
- The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.
- If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.
- Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech: ctvis_drugsafety@gene.com

MEDWATCH 3500a REPORTING GUIDELINES

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

- Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at:
https://www.fda.gov/media/69876/download

5.4.10 REPORTING TO REGULATORY AUTHORITIES, ETHICS COMMITTEES AND INVESTIGATORS

Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations. *WCMC*, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

WCMC will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

WCMC as the Sponsor of the Study, will be responsible for the preparation of six-monthly Suspected Unexpected Serious Adverse Reaction (SUSAR) reports and their submission to Investigators, Regulatory Authorities and the Institutional Review Board/Independent Ethics Committee (IRB/IEC), where applicable
WCMC will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

5.4.11 AGGREGATED REPORTS

Development Safety Update Reports
WCMC as the Sponsor of the Study, will be responsible for the preparation of their own Development Safety Update Report (DSUR) for the Study and for the submission of the report to the regulatory authorities and Ethics Committees of the concerned Member States, where applicable. WCMC agrees to share a copy of their own DSUR with Genentech as soon as reasonably possible after completion.

Genentech agrees to forward to WCMC an executive summary of the Genentech DSUR upon request. Furthermore, Genentech agrees that WCMC may cross-reference the executive summary of the Genentech DSUR, as applicable.

Other Reports

WCMC will forward a copy of the Publication to Genentech upon completion of the Study.

5.4.12 STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned

Clinical Operations contact for the study:

Ron Obmaces
obmaces.ronald@gene.com

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

Queries
Queries related to the Study will be answered by WCMC. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. WCMC agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

Signal Management and Risk Management
Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that **WCMC,** as Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.

If **WCMC** issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the Study and / or triggers any changes to the Study) this will be sent to Roche within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist **WCMC** with signal and risk management activities related to the Product within the Study.

Genentech will also provide **WCMC** with any new relevant information that may modify or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

Compliance with Pharmacovigilance Agreement / Audit
The Parties shall follow their own procedures for adherence to AE reporting timelines.

Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

STATISTICAL CONSIDERATIONS

The study plans to enroll a total of 30 allogeneic bone marrow transplant patients who will be randomized at 1:1 to the two study arms. The primary endpoint data will be analyzed on the basis of a modified intention-to-treat (ITT) principle for patients with viral loads measurements at both the baseline and day 10.

For the first co-primary objective, the effects of the study drugs will be evaluated separately for each study arm by estimating the change in viral RNA loads from baseline (day1) at the end of treatment (day10) as measured by qRT-PCR. Summary statistics including mean, standard deviation, median and range of the primary endpoints will be calculated for each arm. Difference in log transformed viral RNA loads measuremed at the end of treatment and at baseline will be evaluated using paired t-test or the Wilcoxon signed rank test for each arm separately. For the second co-primary endpoint, efficacy of the baloxavir + oseltamivir will be assessed through estimating the differences in the magnitude of change in viral RNA loads from baseline at the end of treatment between the two treatment arms along with the 95% confidence intervals. Given the pilot nature of the study, the sample size is primarily based on feasibility and logistic considerations. However, based on prior studies [ref: Infect Dis Ther (2019) 8:613–626], the expected baseline viral RNA loads for the immunocompromised patients would be around 6.5 log10 vp/mL with standard deviation around 3 log10 vp/mL. With 15 patients in a study arm, we would have 80% power to detect a difference of 2.33 log10 vp/mL in viral RNA loads at the end of treatment vs. at the baseline assuming similar level of standard deviation at the end of treatment with a two-sided 0.05 significance level using a paired t-test. We expect to have adequate power to detect this level of change for both the study arms since prior study has observed a decrease of at least 3 log10 vp/mL with Oseltamivir alone in immune compromised patients [ref: Infect Dis Ther (2019) 8:613–626]. For the second co-primary endpoint, i.e., the between arm differences in change in viral loads, 15 patients per arm will allow 80% power to detect effects size as small as 1.1 standard deviation at a two-sided 0.05 significance level. It is likely the study is under-powered but is expected to generate meaningful preliminary efficacy data [Machin, D, Campbell, M.J., Tan, S.B, Tan, S.H. 2018. 'Sample Sizes for Clinical, Laboratory and Epidemiology Studies, Fourth Edition', Chapter 16. John Wiley and Sons. Hoboken, New Jersey.].

For secondary viral loads related endpoints, summary statistics in terms of mean, standard deviation, median and range will be calculated for each arm at each time points among patients with relevant measurements. Longitudinal analyses using mixed effects repeated measures will be used to model the mean viral loads overall time. Contrasts of interest including between arm differences will be explored using simultaneous tests of general linear hypotheses. If normality is a concern, log-transformed and standardized viral load data will be used. Longitudinal analysis will be carried out among patients with at least one relevant viral load measurement. Kaplan-Meier estimates will be generated for time to events endpoints such as time to Improvement of Individual Influenza Symptoms, the time to viral clearance and time to return to preinfluenza health status for each study arm. Between study arm difference in these endpoints will be explored using the generalized Wilcoxon test.

Categorical data such as the occurrence of treatment-emergent variants of neuraminidase and polymerase by direct next-generation sequencing and AE’s will be summarized in terms of counts and proportions separately for each arm.

Between arm difference in the categorical variable will be explored using Fisher's exact test. The study is likely will not have adequate power to detect between arm differences and all the between arms comparisons are considered exploratory. Summary statistics generated for study endpoints for each arm will provide useful information for planning future studies.

The power calculations were performed using PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass. All comparisons will be two-tailed, with a significance level at 0.05 and 95% confidence intervals will also be reported. All analyses will be performed in SAS Version 9.4 (2019), SAS Institute, Inc., Cary, NC; and R Version 4.0.4 (2021).

Note: The statistical considerations section was written by Kaylee Ho, MS, and revised by Xi Kathy Zhou, PhD, in the Division of Biostatistics, Department of Population Health Sciences, Weill Cornell Medicine.

Influenza sequence analysis will be performed by Elodie Ghedin, Director of
Systems Genomics Section at the Laboratory of Parasitic Diseases of NIAID/NIH and expert in Influenza evolution.
No interim analysis is planned for this study

6.1 EXPLORATORY ENDPOINTS

Non-invasive methods for monitoring health-related biomarkers in liquids such as plasma ("liquid biopsy") have already been successfully introduced in a wide range of contexts. cfDNA is extremely dynamic and responsive, providing strong indicators of immune response or infection, also revealing the cells of origin undergoing apoptosis or necrosis. We will profile cfDNA isolated from plasma samples before, during, and after influenza therapy to evaluate the utility of cfDNA as a means to monitor damage caused by viral infection as response to therapy. cfDNA analysis will be performed by our collaborator Iwijn De Vladmick

5.2 METHOD OF ANALYSIS

Plasma from patients of each arm was centrifuged at 16,000 g for 10 minutes. cfDNA extraction will be performed according to manufacturer recommendations (QIAGEN MinElute Circulating Nucleic Acid Kit, reference #55204 or QIAGEN EZ1 Virus Mini Kit v2.0 955134) at 0.4-1 mL plasma input. DNA sequencing of bisulfite-treated cfDNA will be used to reveal methylation patterns with single nucleotide resolution. Because these patterns are cell, tissue, and organ types specific, they can inform the origins of cfDNA. Levels of cdDNA and tissue of origins will be compared for patients in each arm begore during and after therapy as described(Bezdan, Grigorev et al. 2020)

6. INVESTIGATOR REQUIREMENTS

7.1 RETENTION OF RECORDS

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the U.S. under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

6.2 STUDY MEDICAL MONITORING REQUIREMENTS

This clinical research study will be monitored both internally by the PI and externally by the Weill Cornell Medicine IRB. In terms of internal review, the PI will continuously monitor and tabulate AEs. Appropriate reporting to the Weill Cornell Medicine IRB will be made. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled,
- Stopping rules for toxicity and/or response are met,
- Risk/benefit ratio is not altered to the detriment of the subjects,
- Appropriate internal monitoring of AEs and outcomes is done,
- Over-accrual does not occur,
- Under-accrual is addressed with appropriate amendments or actions, and
- Data are being appropriately collected in a reasonably timely manner.

Routine monitoring will be carried out via a periodic team conference among investigators during which toxicity data, including all SAEs, will be reviewed and other issues relevant to the study such as interim assessment of accrual, outcome, and compliance with study guidelines, will be discussed. Monitoring will be carried out on an ongoing basis. The severity, relatedness, and whether or not the event is expected will be reviewed.

6.3 STUDY MEDICATION ACCOUNTABILITY

The Sponsor Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62 and Genentech requirements.

All unused remaining product at the end of the study should be disposed of at the study site according to institutional standard operating procedure. If there is no SOP at the site for drug destruction, return study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

6.4 DATA COLLECTION

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA and the Weill Cornell Medicine IRB.

7. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

Patients who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond Cycle 1 at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to receive MPDL3280A treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in Section 4.6.

7.2 INFORMED CONSENT

The informed consent document must be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

7.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA, applicable national and local health authorities, and IRB requirements. The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator's Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech (e.g., IND safety report, Investigator's Brochure, safety amendments and updates, etc.).

7.4 CONFIDENTIALITY

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

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

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Genentech representatives and collaborators, and the IRB/Ethics Committee (EC) for each study site, if appropriate.

8. REFERENCES

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Appendix 1 - Study Flowchart

Day(s)	*D1*	*D2[a]*	*D3*	*D4*	*D5*	*D6*	*D7*	*D8*	*D9*	*D10*	*D11 – D14*	*D15[b]*	*EOS D30[b,c]*	*Unsched Visit*
On-site study visit	*x*	*(x)*		*x*			*x*			*x*		*x*	*x*	
Phone Visit		*x*	*x*		*x*	*x*		*x*	*x*					
Screening	*x*													
Informed consent and assent	*x*													
Inclusion/Exclusion criteria	*x*													
Randomization[d]	*x*													
Demographics	*x*													
Medical history	*x*													
Concomitant medication monitoring	*x*			*x*			*x*			*x*		*x*	*x*	*x*
Physical examination[e]	*x[e]*	*x*		*x*			*x*			*x*		*x[f]*	*x[f]*	*x[g]*
Body weight	*x*											*x[f]*		
Vital sign measurements[h]	*x*	*Daily through Day 10*										*x[f]*	*x[f]*	*x[g]*
Presence or absence of respiratory support[i]	*x*	*x*		*x*			*x*			*x*		*x[f]*	*x[f]*	*x[g]*
Blood hematology and chemistry[j,]	*x*			*x[f]*			*x*			*x*		*x[f]*	*x[f]*	*x[g]*
Blood liver chemistry[k]	*x*			*x*			*x*			*x*		*x[f]*	*x[f]*	
Blood for exploratory biomarkers	*x*	*x*		*x*			*x*			*x*		*x*	*x*	
NP swab[l]	*x*	*x*		*x*			*x*			*x*		*x*	*x*	*x[a]*
Chest X-ray/CT Scan[m]	*x*													

Day(s)	*D1*	*D2[a]*	*D3*	*D4*	*D5*	*D6*	*D7*	*D8*	*D9*	*D10*	*D11 – D14*	*D15[b]*	*EOS D30[b,c]*	*Unsched Visit*
On-site study visit	*x*	*(x)*		*x*			*x*			*x*		*x*	*x*	
Phone Visit		*x*	*x*		*x*	*x*		*x*	*x*					
Pregnancy test[n]	*x*													
Adverse events		*x*		*x*			*x*			*x*		*x*	*x*	*x*
Patient self assessment[o]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Xofluza/Placebo[p]	*x*			*x*			*x*							
NAI SOC (Oseltamivir)[q]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*				

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

a. *Optional visit*
b. *A visit window of ± 2 days applicable.*
c. *The EOS visit should occur approximately 20 days after the last dose of study drug.*
d. *Randomization should occur as soon as possible, after screening and informed consent.*
e. *A complete physical examination should be conducted at screening. At post baseline visits and as clinically indicated, limited, symptom directed physical examinations should be performed.*
f. *Clinical procedures may be undertaken at investigator's discretion if symptoms and signs persist beyond the treatment period or if viral shedding is detected beyond Day 10.*
g. *Perform assessments at any unscheduled visits based upon clinician's discretion.*
h. *During the study treatment period (Day 1/Visit 1 to Day 10), all vital sign measurements (i.e., respiratory rate, pulse rate, peripheral oxygen saturation, systolic and diastolic blood pressures, and body temperature) should be recorded when on-site. For all other visits, the only vital signs measurement taken will be temperature. After day 10 vital sign measurements and specific assessments are to be recorded at the investigators' discretion (e.g., if symptoms and signs persist during follow-up).*
i. *Presence or absence and type of respiratory support; oxygen saturation.*
j. *See Section X for tests included in laboratory panels.*

k. *Liver function test results to be reviewed by the investigator before Xofluza, or its matching placebo, is administered. On Day 1, prior blood results if tests conducted within 24 hours prior to screening. On Day 4 and day 7, blood liver chemistry panel should be reviewed before the patient will receive Xofluza or matching placebo on this study day.*

l. *Nasopharyngeal swabs for RT-PCR: RT-PCR for influenza and covid-19 should be performed at screening.*

m. *If a chest X-ray has not been taken within the 24 hours prior to screening, it will be performed per clinical provider decision. If the SOC is a chest CT scan, this can be used as alternative to the chest X-ray per clinical provider decision.*

n. *All women of childbearing potential will have a pregnancy test at screening (urine or serum).*

o. *Self-assessment of seven influenza-associated symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) on a four-point scale (with 0 indicating no symptoms, 1 mild symptoms, 2 moderate symptoms, and 3 severe symptoms) twice daily from enrolment (day 1) until day 9 and once daily on days 10–15, and record their results in the patient diary.*

p. *Baloxavir treatment or Baloxavir-matched placebo dosing will occur on Day 1 and Day 4, with a further dose at Day 7*

q. *The SOC NAI (Oseltamivir) will be administered from Day 1 through Day 10.*

Appendix 2 - Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET
Genentech Supported Research
AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

Reset Form

U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH

FORM FDA 3500A (2/19)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page 1 of 2

Form Approved: OMB No. 0910-0291, Expires: 11/30/2021
See PRA statement on reverse.

Mfr Report #

UF/Importer Report #

FDA Use Only

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jul-2018.

A. PATIENT INFORMATION

1. **Patient Identifier**
In Confidence

2. **Age**
☐ Year(s) ☐ Month(s) ☐ Week(s) ☐ Day(s)
or Date of Birth *(e.g., 08 Feb 1925)*

3. **Gender** *(check one)*
☐ Female ☐ Male ☐ Intersex ☐ Transgender ☐ Prefer not to disclose

4. **Weight**
☐ lb ☐ kg

5. **Ethnicity** *(check one)*
☐ Hispanic/Latino ☐ Not Hispanic/Latino

6. **Race** *(check all that apply)*
☐ Asian ☐ American Indian or Alaskan Native ☐ Black or African American ☐ White ☐ Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. **Type of Report** *(check all that apply)*
☐ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*

2. **Outcome Attributed to Adverse Event** *(check all that apply)*
☐ Death *Date of death (dd-mmm-yyyy):*
☐ Life-threatening ☐ Disability or Permanent Damage
☐ Hospitalization (initial or prolonged) ☐ Congenital Anomaly/Birth Defects
☐ Other Serious or Important Medical Events
☐ Required Intervention to Prevent Permanent Impairment/Damage

3. **Date of Event** *(dd-mmm-yyyy)*

4. **Date of this Report** *(dd-mmm-yyyy)*

5. **Describe Event or Problem**

(Continue on page 3)

6. **Relevant Tests/Laboratory Data** **Date** *(dd-mmm-yyyy)*

(Continue on page 3)

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

(Continue on page 3)

C. SUSPECT PRODUCTS

1. **Name, Strength, Manufacturer/Compounder**

#1 – Name and Strength	#1 – NDC # or Unique ID
#1 – Manufacturer/Compounder	#1 – Lot #
#2 – Name and Strength	#2 – NDC # or Unique ID
#2 – Manufacturer/Compounder	#2 – Lot #

2. **List Medical Product and Treatment Given at the Same Time Of the Event and Date** *(Do not include treatment for initial event)*

(Continue on page 3)

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

3. Dose	Frequency	Route Used
#1		
#2		

4. **Treatment Dates/Therapy Dates** *(give length of treatment (start/stop) or your best estimate.)*
#1 Start
#1 Stop
#2 Start
#2 Stop

5. **Diagnosis for Use** *(Indication)*
#1
#2

6. **Product Type** *(Check all that apply)*
#1 ☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar
#2 ☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar

7. **Expiration Date** *(dd-mmm-yyyy)*
#1
#2

8. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☐ No ☐ Doesn't apply
#2 ☐ Yes ☐ No ☐ Doesn't apply

9. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☐ Doesn't apply
#2 ☐ Yes ☐ No ☐ Doesn't apply

D. SUSPECT MEDICAL DEVICE

1. **Brand Name**

2a. **Common Device Name** 2b. **Procode**

3. **Manufacturer Name, City and State**

4. **Model #** **Lot #**
Catalog # **Expiration Date** *(dd-mmm-yyyy)*
Serial # **Unique Identifier** *(UDI) #*

5. **Operator of Device**
☐ Health Professional ☐ Patient/Consumer ☐ Other

6a. **If Implanted, Give Date** *(dd-mmm-yyyy)* 6b. **If Explanted, Give Date** *(dd-mmm-yyyy)*

7a. **Is this a single-use device that was reprocessed and reused on a patient?** ☐ Yes ☐ No

7b. **If yes, Enter Name and Address of Reprocessor**

8. **Was this device serviced by a third party?** ☐ Yes ☐ No ☐ Unknown

9. **Device Available for Evaluation?** *(Do not send to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on:

10. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event)*

(Continue on page 3)

E. INITIAL REPORTER

1. **Name and Address**

Last Name:	First Name:
Address:	
City:	State/Province/Region:
ZIP/Postal Code:	Country:
Phone #:	Email:

2. **Health Professional?** ☐ Yes ☐ No

3. **Occupation** *(Select from list)*

4. **Initial Reporter Also Sent Report to FDA** ☐ Yes ☐ No ☐ Unk

Reset Form

MEDWATCH

FORM FDA 3500A (2/19) *(continued)*

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

FDA USE ONLY

F. FOR USE BY USER FACILITY/IMPORTER *(Devices Only)*

1. **Check One** ☐ User Facility ☐ Importer
2. **User Facility/Importer Report Number**
3. **User Facility or Importer Name/Address**
4. **Contact Person**
5. **Phone Number**
6. **Date User Facility or Importer Became Aware of Event** *(dd-mmm-yyyy)*
7. **Type of Report** ☐ Initial ☐ Follow-up #_____
8. **Date of This Report** *(dd-mmm-yyyy)*
9. **Approximate Age of Device**
10. **Adverse Event Problem** *(Refer to coding manual)*
   Health Effect - Clinical Code | Health Effect - Impact Code | Medical Device Problem Code | Component Code
11. **Report Sent to FDA?** *(If Yes, enter date (dd-mmm-yyyy))* ☐ Yes ☐ No
12. **Location Where Event Occurred** ☐ Ambulatory Surgical Facility ☐ Home ☐ Hospital ☐ Nursing Home ☐ Outpatient Diagnostic Facility ☐ Outpatient Treatment Facility ☐ Other: _____ *(Specify)*
13. **Report Sent to Manufacturer?** *(If Yes, enter date (dd-mmm-yyyy))* ☐ Yes ☐ No
14. **Manufacturer Name/Address**

G. ALL MANUFACTURERS

1. **Contact Office (and Manufacturing Site for Devices) or Compounding Outsourcing Facility**
   Name
   Email Address
   Address
   Phone Number
   Compounding Outsourcing Facility 503B? ☐ Check box if applicable
   Outsourcing Facility _____
2. **Report Source** *(check all that apply)* ☐ Foreign ☐ Study ☐ Literature ☐ Consumer ☐ Health Professional ☐ User Facility ☐ Company Representative ☐ Distributor/Importer ☐ Other *(Please list)*:
3. **Date Received by Manufacturer** *(dd-mmm-yyyy)*
4. NDA #_____ ANDA #_____ IND #_____ BLA #_____ PMA/510(k) #_____
5. **If IND/PreANDA, Give Protocol #**
6. **Type of Report** *(check all that apply)* ☐ 5-day ☐ 7-day ☐ 15-day ☐ 30-day ☐ Periodic ☐ Initial ☐ Follow-up #____
   Check all that apply: Combination Product ☐ PreANDA ☐ Pre-1938 ☐ OTC ☐ Compounded Product ☐
7. **Adverse Event Term(s)**
8. **Manufacturer Report Number**

H. DEVICE MANUFACTURERS ONLY

1. **Type of Reportable Event** *(check all that apply.)* ☐ Death ☐ Serious Injury ☐ Malfunction ☐ Summary Report No. of events summarized
2. **If Follow-up, What Type?** ☐ Correction ☐ Additional Information ☐ Response to FDA Request ☐ Device Evaluation
3. **Device Evaluated by Manufacturer?** ☐ Yes ☐ No *(Attach page to explain why not)* or provide code: ☐ Not Returned to Manufacturer ☐ Evaluation Summary Attached
4. **Device Manufacture Date** *(dd-mmm-yyyy)*
5. **Labeled for Single Use?** ☐ Yes ☐ No
6. **Adverse Event Problem** *(Refer to coding manual)*
   Health Effect - Clinical Code | Health Effect - Impact Code | Medical Device Problem Code | Component Code | Type of Investigation | Investigation Findings | Investigation Conclusions
7. **If Remedial Action Initiated, Check Type** ☐ Recall ☐ Repair ☐ Replace ☐ Relabeling ☐ Other: ☐ Notification ☐ Inspection ☐ Patient Monitoring ☐ Modification/Adjustment
8. **Usage of Device** ☐ Initial Use of Device ☐ Reuse ☐ Unknown
9. **If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:**
10. **Additional Manufacturer Narrative**
11. **Corrected Data**

This section applies only to requirements of the Paperwork Reduction Act of 1995.
This section applies only to requirements of the Paperwork Reduction Act of 1995. The public reporting burden for this collection of information has been estimated to average 73 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to:

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Food and Drug Administration
Office of Chief Information Officer
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PRAStaff@fda.hhs.gov

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