PROTOCOL

TITLE:	**EVALUATION OF A SCREEN AND TREAT PROTOCL FOR INFLUENZA IN SOCIALLY VULNERABLE COMMUNITIES**
STUDY NUMBER:	ML44485
VERSION NUMBER:	2.2
TEST PRODUCTS:	XOFLUZA® (baloxavir marboxil) (RO7191686)
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SUPPORT PROVIDED BY:	Genentech, Inc.
PROTOCOL DATE:	09 Oct 2023

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AERO	adverse event reporting online
AESI	adverse event of special interest
AUC	area under the curve
CIOMS	Council for International Organizations of Medical Sciences
ClinRO	clinician-reported outcome
C_{max}	maximum concentration observed
CTCAE	Common Terminology Criteria for Adverse Events
DSUR	Development Safety Update Report
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
HA	hemagglutinin complex
HAHA	human anti-human antibody
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
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
IRC	Independent Review Committee
IRF	Independent Review Facility
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit
M2	matrix-2
mITTI	modified intent-to-treat (influenza) infected (population)
MN	mobile nursing
NA	neuraminidase

Abbreviation	Definition
NAI	neuraminidase inhibitor
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
ObsRO	observer-reported outcome
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
RIDT	Rapid Influenza Diagnostic Test
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
$TCID_{50}$	50% tissue culture infectious dose
t_{max}	time to maximum concentration
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
USPI	U.S. Package Insert
Vc/F	apparent volume of distribution for the central compartment
WES	whole exome sequencing
WGS	whole genome sequencing

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

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

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

1.2 BACKGROUND ON 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 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. Xofluza is now indicated for treatment of acute uncomplicated influenza in patients who have been symptomatic for no more than 48 hours and who are otherwise healthy adults and pediatric patients 5 years of age and older. Also, Xofluza has been approved for post-exposure prophylaxis of influenza in patients 5 years of age and older following contact with an individual who has influenza.

Xofluza is approved for use in Japan (since February 2018) for the treatment of influenza A or B virus infection in all age groups (≥10 kg) and in the United States (since October 2018), Hong Kong (since February 2019), and Thailand (since

March 2019). In the US 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 as well as pediatric patients 5 years of age and older. In addition, Xofluza is approved in Thailand 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 as well as post-exposure prophylaxis. Regulatory filings in other global regions are either completed, ongoing, or planned to gain market authorization for the use of Xofluza for the treatment of influenza.

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.

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. The difference in the median time was −26.5 hours between the Xofluza group and the placebo group. The Xofluza group showed a significantly greater reduction in the time to alleviation of symptoms compared with the placebo 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).

The safety and effectiveness of Xofluza in otherwise healthy pediatric subjects 5 to less than 12 years of age is supported by one randomized, double-blind, controlled trial, Trial CP40563 with a primary endpoint of safety. In this trial, 118 otherwise healthy pediatric subjects were randomized and treated in a 2:1 ratio and received either Xofluza (N=79) or oseltamivir (N=39). Efficacy was extrapolated from adults and adolescents based on comparable pharmacokinetic (PK) exposures in adults, adolescents and pediatric subjects 5 to less than 12 years of age. The median time to alleviation of signs and symptoms in influenza-infected subjects was comparable in the Xofluza and oseltamivir arms. Adverse events (AEs) reported with Xofluza in pediatric subjects were similar to those observed in adults and adolescents except for vomiting and diarrhea, which were both more commonly reported in pediatric subjects.

The safety and effectiveness of Xofluza for post-exposure prophylaxis in pediatric and adolescent subjects 5 to less than 18 years of age is supported by one randomized, double-blind, controlled trial conducted in Japan Trial T0834. Subjects in this trial were randomized in a 1:1 ratio to receive Xofluza or placebo. A total of 69 subjects from 5 to < 18 years of age in Trial T0834 received Xofluza. The incidence of reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed symptomatic influenza in pediatric subjects 5 to < 18 years of age was similar to that observed in adult subjects. Efficacy was extrapolated from adults based on comparable PK exposures in adults, adolescents and pediatric subjects 5 to < 18 years of age. Adverse events reported in pediatric and adolescent subjects were similar to those reported in adults in the same trial.

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 serious adverse events (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.

In a placebo-controlled clinical trial (post-exposure prophylaxis of influenza), Trial T0834, conducted in adults, and pediatric subjects ≥ 5 years of age, a total of 360 subjects received Xofluza, of which 291 (81%) were adults ≥ 18 years; 12 (3%) subjects were adolescents ≥ 12 to 17 years and 57 (16%) were pediatric subjects 5 to < 12 years of age. The safety profile was similar in pediatric patients ages 5 to < 12 years old as that reported in adults and adolescents 12 years of age and older.

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

Influenza A and B viruses are highly contagious (Vanderlinden and Naesens 2014). Most individuals with influenza infection are advised to stay at home until they have been afebrile for at least 24 hours, which puts other household members at risk of infection (CDC 2018a). Once one household member is infected with influenza, the risk of transmission to a household contact can be up to 38%, with a delay between onset in the index patient and infection of the household contact of around 3 days (Tsang et al. 2016).

Successful methods to mitigate the spread of respiratory viruses, including COVID-19 and influenza, through testing include identifying and deploying testing capacity to communities where viral transmission is highest and communities where insufficient testing is being conducted. We have developed a data-analytics driven algorithm based on laboratory data and the social vulnerability index (SVI) that identifies testing deserts and hot spots to identify vulnerable communities with active spread of respiratory infection (hot spots) and locations without enough testing penetration to effectively determine viral activity (testing deserts).

It has been well described that socially vulnerable communities lack access to testing because testing locations may not be able to be reached by public transportation, long wait times because of centralized testing locations and lack of testing hours outside of the traditional work-day (5-10). Mobilization of a

COVID-19 and influenza testing unit to communities where individuals already gather for other social events provides increased access to testing addresses many of these challenges that are experienced in underserved and socially vulnerable communities. However, identification and testing of individuals who may reside in hot spots for respiratory viruses is not sufficient to completely mitigate the spread of disease or reduce the effects of infection. Rapid access to effective therapeutics within the narrow antiviral therapeutic window (48 hours from symptom onset) is necessary to reduce the spread of infection and reduce disease severity.

In this study will use our Respiratory Infection Hot Spot Algorithm that identifies and supports deployment of mobile testing units to community centers, parks and senior centers in socially and economically disadvantaged communities to deploy a mobile test-to-treat model for Influenza A&B, along with testing for SARS-COV-2 in socially vulnerable communities. Use of a point care test (POCT) for Influenza A&B and SARS-CoV-2 and a mobile pharmacist model enables the test-to-treat model that will target vulnerable communities that may lack access to testing and/or providers for treatment for influenza.

Xofluza is a first-in-class influenza antiviral that blocks RNA replication by inhibiting cap-dependent endonuclease activity (Omoto et al. 2018). Xofluza is administered by a convenient and unique one-dose, one-time regimen. In the Phase III CAPSTONE-1 double-blind randomized study in otherwise healthy patients (Hayden et al. 2018), a single treatment of Xofluza (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 reduce 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

Study ML44485 was therefore designed to use our Respiratory Infection Hot Spot Algorithm that identifies and supports deployment of mobile testing units to community centers, parks and senior centers in socially and economically disadvantaged communities to deploy a mobile test-to-treat model for Influenza A&B, along with testing for SARS-COV-2 in socially vulnerable communities. This study will target communities with high rates of respiratory infection or insufficient testing for a screen and treat program for influenza. Matched communities based on the census track-based SVI will be compared to assess impact of the screen and treat program on influenza rates at a population level.

This study seeks to demonstrate that the laboratory can mitigate respiratory virus transmission in underserved populations through (1) use of analytics to identify

communities that are at risk for uncontrolled viral spread and (2) patient perception of a mobile screen and treat model for influenza.

In summary, there is a strong rationale and a positive benefit risk assessment for studying Xofluza in a screen and treat model for socially vulnerable communities and results from the Hayden et al study suggests that Xofluza has an acceptable clinical safety profile and could benefit patients who test positive for influenza. The benefit-risk ratio for Xofluza is expected to be acceptable in this setting.

2. OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE(S)

This study seeks to demonstrate that the laboratory can mitigate respiratory virus transmission in underserved populations by using laboratory data to identify communities at risk for increase vial activity (hot spots) and intervening with a test-to-treat model provides increased access to influenza diagnostics and treatment in vulnerable and underserved communities.

1. The hot-spot frequency and hot spot score trend will be measured for each census tract to determine if the screen and treat intervention has an impact on reducing hot spot identification or hot spot score.

    a. Following each mobile intervention, we will evaluate the hot spot score for the census tracts receiving a mobile screen and treat intervention and SVI-matched census tract not receiving an intervention for 14-days following the screen and treat intervention.

    b. Patients will receive a follow-up phone call 14-days following their initial screening visit to assess patient and household symptoms and the socioeconomic impact of their test result and treatment access.

2.2 SECONDARY OBJECTIVE(S)

1. Secondarily, this study seeks to understand patient perception of a mobile screen and treat model for influenza, and patients will be provided a survey to better understand their experiences in access to testing for COVID and influenza and access to therapeutics for influenza at a mobile screen and treat unit.
2. All patients will be provided a survey to better understand their experiences in access to testing and therapeutics for COVID and influenza at a mobile screen and treat unit.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

We have developed an analytic algorithm that uses measures from the CDC COVID-19 Hot Spot Criteria and Brown University School of Public Health to determine COVID-19 and Influenza Hot Spots and Testing Deserts, respectively.

The Hot Spot designation was based on the CDC county-specific Hot Spot criteria that has been used to deploy resources for interventions (i.e., laboratory testing, community mitigation, health communications and health care) specific needs for the communities of interest. The CDC hot spot criteria is based on COVID-19 rates at the county level. We have adapted these criteria in several ways: (1) we have narrowed the scope of the population of interest to the census tract (2) we have included influenza transmission data (3) we have based our calculations on the proportion of the respiratory virus testing performed by TriCore Laboratories relative to the total testing in the State of New Mexico (approximately 40%) and (4) we have incorporated social determinants of health data to aid in identifying the most vulnerable community. The adaptations to the criteria allows interventions to focus on a concentrated community and deliver the interventions in places that the community is already engaging, such as community centers, senior centers and parks. The identification of communities with insufficient testing to assess the respiratory virus transmission rate, or testing deserts, in our algorithm is based on the Brown University School of Public Health testing targets which has identified a goal of 532/100,000 or 1582/100,0000 COVID-19 or influenza tests for as the minimum target or suppression target, respectively. The algorithm also incorporates the social vulnerability index in the testing desert tool.

Using a longitudinal patient database with an active system to prospectively geocode addresses entered into our system, we are able to determine, at the census tract level, neighborhoods that are at high risk for viral transmission because they are a hot spot or testing desert. We are then able to incorporate the social vulnerability index as an additional weighted measure to the hot spot or desert score in order to calculate an identified hot spot or desert risk for a census tract. Through collaboration with local community centers, we are able to deploy a mobile testing unit to a community center, park or senior center that is in close proximity to the identified neighborhood for rapid onsite testing for Influenza A&B and SARS-CoV2 using the cobas Liat system.

New Mexico has adopted “New Mexico Board of Pharmacy Protocol for Pharmacists Prescribing of Dangerous Drugs in Conjunction with Point of Care Testing” (NMBOP POCT Protocol, Appendix 5) that allows pharmacists the prescriptive authority to prescribe Influenza antiviral therapy in conjunction with a positive point of care test (POCT). TriCore employs two (2) on-site clinical pharmacists who will follow all of the pharmacist mandates included in the regulation to prescribe and distribute Xofluza according to the approved protocol in the test-to-treat model presented in this study. The NMBOP PCOT Protocol documents the eligibility and requirements of the certified prescribing pharmacists (pharmacist) following this protocol.

The pharmacist will perform a screening physical assessment, health assessment and medical history for the patient. If the subject meets the inclusion criteria, they will have a point of care test performed. If the subject meets the exclusion criteria, they will be excluded from the study. Testing will be performed using the cobas® SARS-CoV-2 & Influenza A/B assay on the cobas® Liat® system from a self-collected nasal swab. Subjects who test positive for influenza A or B will be prescribed Xofluza with no additional refills. The pharmacist will follow-up with the patient 24-48 hours following administration for evaluation of

signs/symptoms and will refer the patient to their primary care provider, provider, or clinic for recommended laboratory testing and follow-up if appropriate.
All subjects eligible for Xofluza will receive patient education and counseling on drug information, adherence, side effects, and other patient educational materials, as appropriate. All subjects eligible for influenza antiviral therapy, but having contraindications to the therapy, or do not wish to use the therapy will be referred to their primary care provider, provider, or clinic for further evaluation.

Subjects testing positive for SARS-CoV-2 will be preferred by the pharmacist to the subjects' primary care provider, provider, or clinic for further medical assessment and follow-up, if appropriate. Subjects testing negative for all targets (SARS-CoV-2 and Influenza A&B) with a high index of suspicion for influenza, will be referred by the pharmacist to the subjects' primary care provider, provider, or clinic for further medical assessment and follow-up, if appropriate. All subjects will receive a follow-up call 14-days following the study visit to assess their symptom resolution and the impact of their illness on their well-being (Appendix 1).

The mobile testing unit will be deployed a minimum of 2 times per week following the determination of the influenza season by the New Mexico Department of Health. We expect to screen 50-100 patients per week for the duration of the influenza season (approximately 12 weeks) for a total of 600-1,2000 patients. With an anticipated 10% positivity rate for influenza, we expect at least 5-10 patients per week to be eligible for treatment for a total of 60-120 subjects eligible over the course of the study. All subjects will be provided a survey to evaluated their ability to access respiratory virus testing and their acceptance of and trust in using a mobile unit for access to treatment and therapeutics. Patients positive for SARS-CoV-2 will be counseled on options for treatment and follow up for COVID-19 infection. All subjects enrolled in the study will receive a follow-up phone call 14-days following the initial screening visit.

Description of Xofluza treatment schedule:
Xofluza will be administered as a single oral dose as soon as possible and within 48-hours of influenza symptom onset. Dosing will be delivered based on the package insert.:

Patient Body Weight (kg)	**Recommended Single Oral Dose in Patients 5 years of Age and Older (Tablets)**
20 kg to less than 80 kg	One 40 mg tablet (blister card contains one 40 mg tablet)
At least 80 kg	One 80 mg tablet (blister card contains one 80 mg tablet)

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when 12 weeks of mobile testing and treating deployment has concluded or the end of “influenza season” as defined by the New Mexico Department of Health, whichever is last. As this is a single dose observational study, there are no follow-up visits scheduled as part of the study. All subjects receiving the therapeutic will receive a follow-up phone call 24-48 hours following administration of Xofluza. All enrolled subjects will receive a follow-up phone call 14-days following the initial screening visit to assess symptom resolution and socioeconomic impact of their test result. The end of the study is expected to occur 12 months after the last patient is enrolled to allow for complete data analysis and evaluation. 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 15 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 Xofluza package insert.

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 see if a test and treat model would have significant impact on community transmission in socially vulnerable communities.

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

The study eligibility criteria allow for the inclusion of index patients who are minors. This is also consistent with the labels approved to date for baloxavir marboxil, which is approved for use in individuals aged ≥5 years of age.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 600-1,200 patients will be enrolled in the study to be screened for influenza A&B and SARS-CoV2. We expect approximately 10% positivity rate for 60-120 patients to be eligible for treatment.

There are approximately 140 census tracts in the Albuquerque Metropolitan Area that will be tracked during this study.

Zip Code	Race/Ethnicity (% population)							
	Hispanic	Non-Hispanic/White	Black	Native Indian	Asian	Hawaiian	Other	2 or More
87108	51.5	33.7	3.7	4.7	1.4	0.0	0.2	2.6
87123	44.3	40.7	3.5	3.5	4.6	0	0.1	3.7
87121	82.5	9.7	2.3	3.8	0.4	0.2	0.1	1
87102	61.4	26.6	3.1	5.6	10.7	0	0.31	1.5
87105	79.6	14.1	0.6	4.4	0.3	0.1	0.1	0.6
87106	38.1	48.2	3.3	3.1	3.9	0	0.5	2.9

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Adult patients: Signed informed consent by any patient capable of giving consent, or, where the patient is not capable of giving consent, by his or her legal/authorized representative.
- Adolescent patients not able to legally consent: written informed consent for study participation is obtained from patient's parents or legal guardian, with assent as appropriate by the patient, depending on the patient's level of understanding and capability to provide assent
- Age ≥ 5 years at the time of signing the Informed Consent Form/Assent Form
- Ability to comply with the study protocol, in the investigator's judgment.
- Presence of (a) fever (≥38.0 °C per tympanic or rectal thermometer; ≥37.5 °C per axillary, oral or forehead/temporal thermometer) or (b) any influenza symptoms (cough, sore throat, nasal congestion, headache, feverishness or chills, muscle or joint pain, fatigue).
- The time interval between the onset of fever or influenza symptoms 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 (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

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

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

4.1.2 Exclusion Criteria

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

- Patients who have received more than 48 hours of antiviral treatment for the current influenza infection prior to screening
- Patients who have received Xofluza for the current influenza infection
- Known contraindication to neuraminidase inhibitors
- Patients weighing < 20 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 drug within 5 half-lives or 30 days (whichever is longer) of randomization
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Known hypersensitivity to Xofluza (baloxavir marboxil) or the drug product excipients

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an observational study; all patients will be assigned to the treatment group.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is Xofluza.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Xofluza

Xofluza will be supplied by the Sponsor as tablets.

For information on the formulation and handling of Xofluza, see the Xofluza Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

The study treatment will be administered by a certified prescribing provider at mobile testing sites.

Any overdose or incorrect administration of Xofluza 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 Xofluza

The treatment regimens are summarized in Section 3.1.

Xofluza will be administered orally according to body weight (40 mg for patients weighing 20 to $<$ 80 kg; 80 mg for patients weighing $\geq$ 80 kg) either in tablet form (20 mg or 40 mg tablets).

4.4 CONCOMITANT THERAPY

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

4.4.1 Permitted Therapy

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

4.4.2 Cautionary Therapy

Polyvalent cation–containing products may decrease plasma concentrations of 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. Live attenuated influenza vaccines may be affected by antivirals.

4.4.3 Prohibited Therapy

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

- Investigational therapy (other than the protocol-mandated study treatment) is prohibited within 5 half-lives or 30 days (whichever is longer) prior to initiation of study treatment and during the study
- Influenza antiviral drugs (peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir or amantadine)
- Immunosuppressants (including biologics)
- Investigational therapy (other than protocol-mandated study treatment)
- 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.

At applicable sites, certain study assessments may be performed by certified prescribing pharmacist (CPP) professional at the mobile testing location. The Investigator will ensure that all CPPs are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed.

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. 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 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 Examinations

A limited, symptom-directed physical examinations will be performed to assess symptoms of influenza-like-illness (cough, sore throat, nasal congestion, headache, feverishness or chills, muscle or joint pain, fatigue).

4.5.4 Vital Signs

Vital signs will include measurements of weight, respiratory rate, pulse rate, and systolic and diastolic blood pressure, oxygen saturation rate and temperature.

Vital signs should be measured within 60 minutes prior to each Xofluza treatment.

4.5.5 Rapid Influenza Diagnostic Test

For patients to be eligible for this study, RT-PCR is required to be performed to inform a diagnosis of influenza.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exception:

- Self-collected nasal swab samples collected for influenza testing may be required to be accessible to the New Mexico Department of Health (NMDOH) for serotyping or other analysis performed for routine influenza

surveillance. If not required for the NMDOH will be destroyed no later than 1 year after the closure of the study or earlier depending on local regulations.

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

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

4.6 TREATMENT, PATIENT, AND STUDY DISCONTINUATION

Patients must permanently discontinue study treatment (Xofluza) 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 not 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 will 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 are not limited to, the following:

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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

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

5.1.1 Potential Risks Associated with Xofluza

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

5.1.1.1 Hypersensitivity

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

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

5.1.1.2 Increased Incidence of Treatment-Emergent Resistance in Patients Less Than 5 Years of Age

Xofluza is not indicated in patients less than 5 years of age due to increased incidence of treatment-emergent resistance in this age group. In clinical trials, the incidence of virus with treatment-emergent substitutions associated with reduced susceptibility to baloxavir (resistance) was higher in pediatric subjects younger than 5 years of age (43%, 36/83) **than in pediatric subjects ≥5 years** to < 12 years of age (16%,19/117) **or subjects ≥12 years of age (7%, 60/842)**. The potential for transmission of resistant strains in the community has not been determined.

Refer to the current USPI for XOFLUZA (baloxavir marboxil) for details.

5.1.1.3 Risk of Bacterial Infections

There is no evidence of efficacy of Xofluza in any illness caused by pathogens other than influenza viruses. Serious bacterial infections may begin with influenza-like symptoms or may coexist with, or occur as, a complication of influenza. Xofluza has not been shown to prevent such complications. Prescribers should be alert to potential secondary bacterial infections and treat them as appropriate.

Refer to the current USPI for XOFLUZA (baloxavir marboxil) for details.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications

No dose modification will be permitted during the study.

5.1.2.2 Treatment Interruption

Treatment interruption is not allowed in this study. Study treatment should be discontinued in patients who meet the criteria listed in Section 4.1.2

5.2 SAFETY REPORTING OF ADVERSE EVENTS

5.2.1 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.

5.2.2 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 influenza that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- 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.

5.2.3 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 results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- 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 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).

5.3.1 Adverse Event Reporting Period

The study period during which AEs and SAEs as described in Section 5.4.2.10 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 14 days following the last 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 (Modify statement depending up on AESI Section 5.4.2.7.

5.3.2 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 Xofluza (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 Xofluza, 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 Xofluza or with similar treatments; and/or the AE abates or resolves upon discontinuation of Xofluza or dose reduction and, if applicable, reappears upon re-challenge.

No

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

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

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

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 clinic 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 **Error! Reference source not found.**), 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 for diagnostic or elective surgical procedures for preexisting conditions
- 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 AE severity grading scale for the NCI CTCAE (v5.0) will be used for assessing AE severity. Table below should be used for assessing severity for AES that are not specifically listed in the NCI CTCAE.

Table 1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE Grade Severity

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

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

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

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

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

c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event

d. Grade 4 and 5 events must be reported as serious adverse events

5.4.2.6 Pregnancy

If a female subject becomes pregnant while receiving Xofluza or within 14 days after the last dose of Xofluza, or if the female partner of a male study subject becomes pregnant while the study subject is receiving Xofluza or within 14 days, a report should be completed and expeditiously submitted to Genentech, Inc. Pregnancies will be followed-up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information. 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 Xofluza should be reported as an SAE.

5.4.2.7 Adverse Events of Special Interest

Adverse events of special interest (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.

AESIs 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.

There are no products specific AESIs for Xofluza.

5.4.2.8 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

5.4.2.9 Product Complaints

A product complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

5.4.2.10 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 Xofluza 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 Patient Safety during the follow-up period.

5.4.2.11 Exchange of Single Case Reports with Genentech

TriCore Laboratories 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. The Roche reporting Tool (AE reporting online "AERO") should be sent to the Genentech contact specified below. 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

Batch ID/lot ID for biologics associated with AE/SSR/PC/AESI must be included when submitting the case reports to Genentech.

All Product Complaints *without* an AE should call via:

PC Hotline Number: (800) 334-0290 (M-F: 5 a.m. to 5 p.m. 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	

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

5.4.2.12 Case Transmission Verification of Single Case Reports

If Single Case Reports are exchanged via AERO, use the following:

- Roche shall extract and review the AERO report listing on a quarterly basis. If any Single Case Report(s) is not correctly transmitted, Roche will request TriCore to immediately re-send the missing Single Case Report(s) and follow-up until resolution.

Monthly or quarterly line listings, Non-serious line listings, and cumulative/final CTV should be sent to: ctvistsa@gene.com

5.5 REPORTING REQUIREMENTS FOR ADVERSE EVENTS ORIGINATING FROM PATIENT-REPORTED OUTCOMES

Although sites are not expected to review the PRO data, if physician/study personnel become aware of a potential adverse event during site review of the PRO questionnaire data, he/she will determine whether the criteria for an adverse event have been met and, if so, these must be reported using the Adverse Event and Special Situation Reporting Form or MedWatch form.

5.6 MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographics (Section A) and suspect medication information (Sections 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

5.6.1 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., initials, 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

5.7 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.

TriCore as the Sponsor of the study will be responsible for the expedited reporting of safety reports originating from the study to the European Medicine Agency (EMA) through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

TriCore will be responsible for the expedited reporting of safety reports originating from the study to the Independent Ethics Committees/Institutional Review Boards (IEC/IRB) of the Concerned Member States, where applicable.

TriCore 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.

TriCore will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

And TriCore will be responsible for the distribution of safety information to site IRB:

WCG IRB

For questions related to safety reporting, please contact Genentech Patient Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

5.8 AGGREGATE REPORTS

Development Safety Update Report

The Parties agree that aggregate reporting obligations for the study (including Development Safety Update Report [DSURs] and/or Investigational New Drug [IND]) Annual Reports) in accordance with the applicable laws and regulations in the concerned countries will reside with TriCore, as the Sponsor of the study.

Upon request, TriCore, agrees to share a copy of their own DSUR with Genentech as soon as reasonably possible after completion.

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

Other Reports

TriCore will forward a copy of the final study report to Genentech upon completion of the study.

Note: Investigators should also report events to their IRB as required.

5.9 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:

xofluza-gsur-d@gene.com

And to Genentech Patient Safety CTV oversight mailbox at: ctvistsa@gene.com

5.10 QUERIES

Queries related to the study will be answered by TriCore. However, responses to all safety queries from Regulatory Authorities, Ethics Committees, and Institutional Review Board, 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. TriCore 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 from Regulatory Authorities and/or IRB/IEC 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.

5.11 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 TriCore, as Sponsor of the study, will be primarily responsible for assessment of the benefit-risk balance of the study.

If TriCore 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 Genentech within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist TriCore with signal and risk management activities related to the Product within the study.

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

5.12 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 an 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.

6. STATISTICAL CONSIDERATIONS

6.1 DETERMINATION OF SAMPLE SIZE

The algorithms that we use to determine the community of interest is based on meeting the hot-spot or testing desert criteria and a weighted value of the social vulnerability index (SVI) which defined from 0-1.0 and is determined at the census tract level. This includes factors such as socioeconomic status, household composition, race/ethnicity, housing and transportation access. Each census tract is composed of 2500-4000 individuals and we anticipate enrolling 200-250 patients at each deployment resulting in approximately 5-10% of the census tract tested at each deployment. The 20 community centers that we will partner with have an average SVI pf 0.85 (0.55-1.0). There are

approximately 140 census tracts in the Albuquerque Metropolitan Area that will be tracked during this study. These high vulnerability locations are aggregated in six zip codes with the following demographic composition of race and ethnicity.

While test positivity rate will change based on the current epidemiology, we expect 10-20% positivity for Influenza during the treatment study period as we anticipate beginning the study period during respiratory virus season with increased viral positivity. Based on this, we expect 20-50 patients will be eligible for influenza treatment at each deployment with an additional 20-50 patients positive for COVID-19 who will receive referrals for COVID-19 treatment at other treatment locations. We expect that we will be able to provide treatment to approximately 430 individuals based on the assumption that 90% will be in the treatment window and 80% will test positive.

The mobile testing unit will be deployed a minimum of 2 times per week following the determination of the influenza season by the New Mexico Department of Health. We expect to screen 50-100 patients per week for the duration of the influenza season (approximately 12 weeks) for a total of 600-1,2000 patients. With an anticipated 20-10% positivity rate for influenza, we expect at least 5-10 patients per week to be eligible for treatment for a total of 60-120 patients eligible over the course of the study. All subjects will be provided a survey to evaluated their ability to access respiratory virus testing and their acceptance of and trust in using a mobile unit for access to treatment and therapeutics. As per the New Mexico Test to Treat protocol, all patients will receive a follow-up phone call 24-48 hours following treatment. Additionally, all patients enrolled in the study will receive a follow-up phone call 14-days following the initial screening visit.

	Enrollment per deployment	Number of Deployments	Total Enrolled	Positivity Rate (Influenza)	Within Treatment Window	Expected Treated (total study)
Influenza Test to Treat	50-100	12	600-1200	10-20% (60-240)	90%	54-180

6.2 PLANNED EFFICACY EVALUATIONS

This is an observational study of the population. Individual patient efficacy will not be assessed.

6.3 SECONDARY EFFICACY VARIABLES

Census tracts and hot spot/testing desert scores are the efficacy variables.

6.4 SAFETY ANALYSES

The safety analysis population will consist of all patients who received at least one dose of study drug.

6.5 METHOD OF ANALYSIS

The analysis population for the efficacy analyses will consist of measuring the hot spot score in SVI-paired census tracts not receiving intervention during the study.

7. INVESTIGATOR REQUIREMENTS

7.1 RETENTION OF RECORDS

FDA regulations (21 CFR §312.62[c]) and the International Council for Harmonisation (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.

7.2 STUDY MEDICAL MONITORING REQUIREMENTS

This clinical research study will be monitored both internally by the PI and externally by the WCG IRB. In terms of internal review, the PI will continuously monitor and tabulate AEs. Appropriate reporting to the WCG 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.

7.3 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 WCG IRB.

8. 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 Xofluza 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.

8.2 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.

8.3 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.).

8.4 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.

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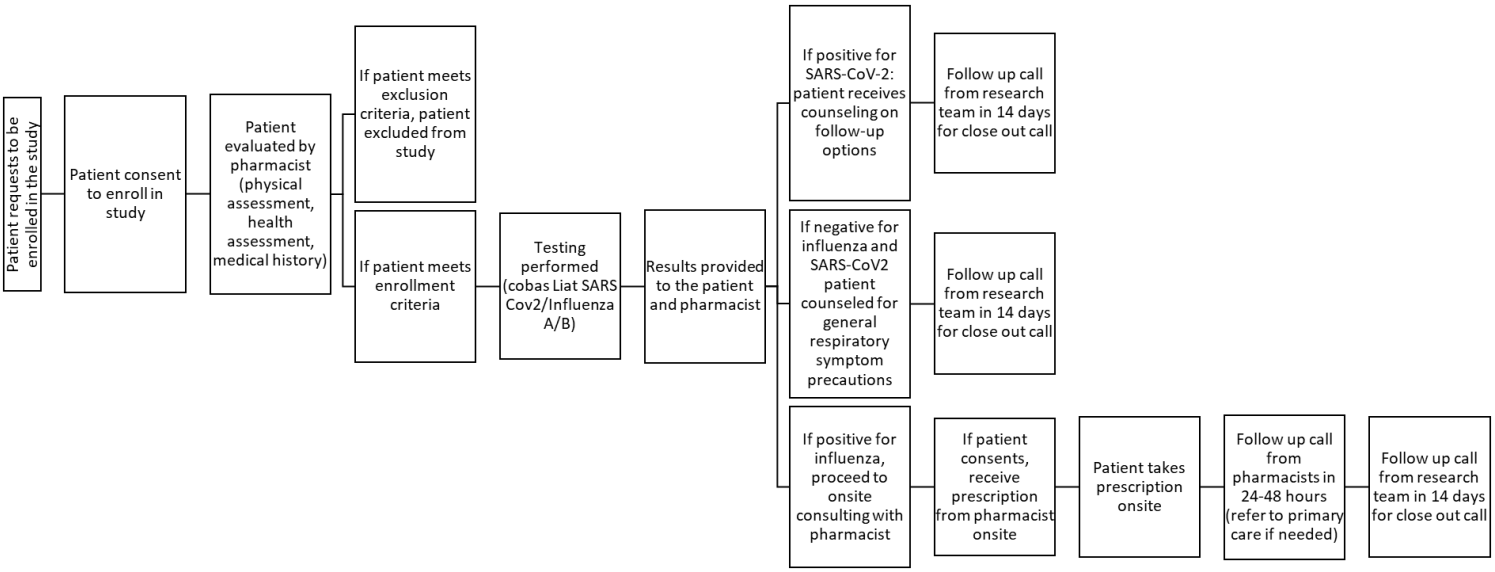
Appendix 1
Study Flowchart



Appendix 1: Study Flowchart

Patient Case Report Form

Study Number: _____ Patient DOB: _____

ENROLLMENT INFORMATION:

Informed Consent and assent form completed: ___ YES ____ No

Conforms with Inclusion and Exclusion Criteria: ___ YES ____ No

MUST HAVE CONSENT AND PATIENT MUST MEET CRITERIA TO CONTINUE

Physical assessment and medical history documented
___ YES ____ No

TESTING:
Cobas Liat SARS-CoV2 and Influenza A&B Test Result:

	Result	Action Taken
SARS CoV 2		□ Patient counseling □ Provider referral
Influenza A		□ Prescription provided □ Patient counseling □ Provider referral
Influenza B		

VISIT COMPLETION

Survey returned: ___ YES ____ No

14- Day Follow-Up Survey

Subject Number: _____

Did anyone else in your household test positive at the testing event:
Influenza: ___ YES ____ No COVID: ___ YES ____ No

Did anyone else in your household test positive for influenza or COVID following the testing event:
Influenza: ___ YES ____ No COVID: ___ YES ____ No

Did anyone else in your household have any of the symptoms above following the testing event? ___ YES ____ No

Symptom assessment

	***Present at First** Visit*	**Date Resolved**
Fever or chills		
Cough		
Sore throat	___ YES ____ No	
Runny or stuffy nose		
Muscle or body aches		
Headaches		
Fatigue (tiredness)		

Did your illness cause you (or household members) to miss

	Self	Household Member	Days Missed	Was there any additional requirement to allow return to activity? (I.e., required days at home or negative test)
Work				
School				
Grocery	___ ***YES***	____ ***No***		
Shopping	___ ***YES***	____ ***No***		
Faith-based activity	___ ***YES***	____ ***No***		
Fitness	___ ***YES***	____ ***No***		
Other: Name	___ ***YES***	____ ***No***		

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

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Appendix 3
FDA MedWatch 3500 Form

This form is included in the study start-up zip file to be sent to sites via email.

Appendix 4
Management Criteria for Abnormal Liver Function Tests

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

Abnormal Liver Chemistry Criteria

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

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

Action to be Taken by Investigator

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

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