Official Title: **A Phase 2 Randomized, Double-Blind Placebo-Controlled Trial of MHAA4549A, a Monoclonal Antibody, in Combination with Oseltamivir Versus Oseltamivir for Treatment of Severe Influenza Infection**

NCT Number: **NCT02293863**

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Protocol Version 5: 20-Mar-2015

Protocol Version 7: 16-May-2016

PROTOCOL

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY, IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION**
PROTOCOL NUMBER:	GV29216
VERSION NUMBER:	1
EUDRACT NUMBER:	2014-000461-43
IND NUMBER:	117,318
TEST PRODUCT:	MHAA4549A
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	Genentech, Inc./Roche Registration Ltd.
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	30-May-2014 23:24:25

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PROTOCOL ACCEPTANCE FORM

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION**
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INDICATION:	INFLUENZA A
SPONSOR:	Genentech, Inc./Roche Registration Ltd.

Objectives

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety of MHAA4549A in combination with oseltamivir compared with placebo and oseltamivir in patients with severe influenza A, focusing on the nature, frequency, and severity of serious and non-serious adverse events, as well as effects on laboratory values, vital signs, electrocardiogram (ECG) parameters, anti-therapeutic antibodies (ATA), or other safety biomarkers

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To determine the time to normalization of respiratory function of patients dosed with MHAA4549A in combination with oseltamivir compared to patients dosed with placebo and oseltamivir

The secondary efficacy objectives for this study are as follows:

- To measure clinical failure after 24 hours post-infusion of study drug
- To determine the time to clinical resolution of vital signs
- To measure mortality in patients
- To determine changes in the extent and duration of viral shedding in upper respiratory samples
- To measure the duration of hospital and/or intensive care unit (ICU) stay
- To measure antibiotic usage for respiratory indications
- To measure the frequency and severity of the following secondary complications of influenza:
  - Pneumonia (hospital acquired pneumonia [HAP]/ ventilator acquired pneumonia [VAP])
  - Exacerbations of chronic lung disease
  - Myocarditis
  - Acute respiratory distress syndrome (ARDS)

  - Otitis media
  - Other related complications
  - Readmission rates at 30 days after study treatment
- To measure duration of positive pressure ventilation (PPV)
- To measure readmission rates

Pharmacokinetic Objectives

The major pharmacokinetic (PK) objective for this study is as follows:

- To characterize the PK profile of MHAA4549A in serum

The exploratory PK objectives for this study are as follows:

[redacted]

Objectives

[redacted]

Study Design

Description of Study

This is a Phase 2b randomized, double-blind, placebo-controlled study designed to assess the safety and clinical activity of a single IV dose of MHAA4549A in hospitalized patients with severe influenza A in combination with oseltamivir versus a comparator arm of oseltamivir with placebo.

Patients will be randomized 1:1 into two treatment groups: a single intravenous (IV) dose of 3600 mg of MHAA4549A with oseltamivir or a single IV dose of placebo with oseltamivir. All patients will receive oseltamivir, a NAI, as standard therapy for a minimum of 5 days, starting after study drug administration. Oseltamivir at doses of 75 mg twice daily (BID) or 150 mg BID is permitted in order to be consistent with local standard of care (SOC) practice. Treatment for longer than 5 days is permitted based on local investigator discretion. The patients must start Sponsor-supplied oseltamivir within 8 hours of study drug administration.

Patients hospitalized with an oxygen (O_2) or PPV requirement will be evaluated for influenza A infection. Enrollment in this study requires ongoing treatment within 24 hours of hospital admission with one of the following: any PPV or any supplemental O_2 to maintain oxygen saturation (SpO_2) $>$ 92%.

A Sponsor-supplied rapid influenza test and/or a local polymerase chain reaction (PCR) test must be used as an aid in the diagnosis of influenza A infection.

At the time of randomization, patients who are eligible for enrollment will be randomized to receive either a single IV infusion of MHAA4549A or a single IV infusion of placebo that will be administered on Day 1. All patients must have the study drug infused within 48 hours of hospital admission or sooner if possible; therefore, screening must be completed within this

window. All patients will receive oseltamivir for a minimum of 5 days (10 doses), starting on Day 1 beginning no later than 8 hours after study drug administration. All patients will be followed for 30 days from the time of study drug administration.

Number of Patients

The study has a planned enrollment of approximately 334 patients (adult men and women) globally. Patients will receive MHAA4549A or placebo in 1:1 ratio. The number of patients on PPV should not exceed 45% of the total enrolled patients.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Men or women $\geq$18 years of age on day of signing informed consent or obtaining surrogate consent from an authorized representative
- Diagnosis of influenza A as determined by the Sponsor-supplied rapid influenza test
  - If negative rapid influenza A test, a positive local molecular test (PCR) is required
- One of the following markers of severity within 24 hours of hospital admission:
  - Requirement for PPV, OR
  - Requirement for O_2 supplementation to maintain $SpO_2 > 92\%$
- A negative urine or serum pregnancy test for women of childbearing potential
- Patients of reproductive potential must agree to use reliable means of contraception as described below as a minimum (adherence to more stringent local requirements may be required):
  - For female patients: Use of two acceptable methods of contraception throughout the trial, including the active treatment phase AND for 24 weeks after the last dose of MHAA4549A. Acceptable methods of contraception include: intrauterine device, systemic hormonal contraception (oral or depot), vaginal ring, tubal ligation of the female partner, vasectomy of the male partner, use of latex condoms plus spermicide by the male partner, or cervical cap plus spermicide (where the spermicide could be foam, vaginal suppository, gel, cream, etc.).
  - For male patients: Use of condoms for 30 days after dosing when circulating drug levels remain high.
  - Non-reproductive potential is defined below (but could be superseded by local definitions, if they are more stringent):

    Women who are postmenopausal (i.e., spontaneous amenorrhea for the past year confirmed by an follicle stimulating hormone [FSH] level greater than 40 mIU/mL unless the patient is receiving a hormonal therapy for their menopause)

    Women who are surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)

    Men who are surgically sterile (castration)

Exclusion Criteria

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

- Pregnant or lactating, or intending to become pregnant during the study
  - Women who are not postmenopausal ($\geq$12 months of non-therapy-induced amenorrhea) or who are not surgically sterile must have a negative urine or serum pregnancy test result within 2 days prior to study treatment
- Hypersensitivity to monoclonal antibodies or any constituents of study drug
- Investigational therapy within the 30 days prior to study treatment
- Received prior therapy with any anti-influenza monoclonal antibody therapy including MHAA4549A 8 months prior to study treatment

- Current treatment (within 7 days of dosing) with amantadine or rimantidine
- Patients who have taken more than a total of 3 days (6 doses) of approved anti-influenza therapy (i.e., oral oseltamivir, inhaled zanamivir, or oral ribavirin) in the period from onset of symptoms and prior to enrollment
- Admission $>$ 48 hours prior to study treatment
- Onset of influenza symptoms $>$ 5 days prior to study treatment
- Positive influenza B or influenza A + B infection within 2 weeks prior to study treatment
- High probability of mortality in the next 48 hours as determined by the investigator
- Patient requiring home or baseline oxygenation therapy
- Patient with history of chronic lung disease resulting in baseline $SpO_2 < 95\%$
- Patient on chronic dose of corticosteroids exceeding 10 mg/day of prednisone or equivalent steroid dose for a duration of greater than 14 days within 30 days of entry into study
- Patients with the following significant immune suppression:
  - Bone marrow or solid organ transplant in the previous 12 months
  - Cancer chemotherapy in the previous 12 month
  - HIV infection with most recent CD4 $<$ 200 cells/mL
  - Other significant immune suppression as determined by the investigator in discussion with the Sponsor Medical Monitor or representative
- Patient on extracorporeal membrane oxygenation (ECMO) at time of randomization
- Any disease or condition that would, in the opinion of the site investigator or Sponsor, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol

Length of Study

This study will consist of the following study periods:

- A screening period of 48 hours, beginning at time of hospital submission
- A treatment period of 1 day, during which patients will receive a single dose of MHAA4549A or placebo and up to 10 days of oseltamivir.
- A follow-up period beginning at hospital discharge through 30 days post study drug (MHAA4594A/placebo) administration

End of Study

The end of the study is defined as the first day when all patients have had a study completion visit or early termination visit or have otherwise been discontinued from the study.

Outcome Measures

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Adverse events and clinical laboratory abnormalities
- Vital signs, physical findings, ATAs, and clinical laboratory results during and following administration of MHAA4549A

Efficacy Outcome Measures

The primary outcome measure for this study is as follows:

- Time to normalization of respiratory function defined as:
  - The time to cessation of O_2 support resulting in a stable $SpO_2 > 95\%$ for at least 24 hours

The secondary efficacy outcome measures for this study are as follows:

- Clinical failure 24 hours post-infusion of study drug defined as:
  - Progression to increased O_2 requirement defined by an increase in oxygen supplementation from low flow oxygen (2 – 6 L/min) to high flow oxygen ($>$ 6 L/min) or from oxygen supplementation alone to any PPV

  - Progression to ICU
  - Prolonged ventilation or O_2 support defined by > 2 weeks, or
  - Death
- Time to clinical normalization of vital signs (3/5 criteria must be met):
  - SpO_2 > 95% without supplemental O_2 for at least 24 hours
  - Respiratory rate < 24 without supplemental O_2 for at least 24 hours
  - Core temperature < 37.2°C immediately prior to receipt of any antipyretic drug, and at least 6-8 hours from the last dose of antipyretic or core temperature > 36°C in patients who are initially hypothermic
  - Heart rate (HR) < 100/minute
  - Systolic blood pressure (SBP) > 90 mmHg
- All-cause mortality at Day 14 and Day 30
- Influenza A viral load in nasopharyngeal samples
  - Area under viral load–time curve (AUEC)
  - Peak viral load
  - Time to resolution of infection
- Duration of hospitalization
- Duration of ICU stay
- Antibiotic usage for respiratory infections
- Complications of influenza:
  - Pneumonia (HAP/VAP)
  - Exacerbations of chronic lung disease
  - Myocarditis
  - Acute respiratory distress syndrome (ARDS)
  - Otitis media
  - Other related complications
- All-cause readmission at Day 30
- Duration of ventilation

Pharmacokinetic Outcome Measures

The primary PK outcome measures for this study are as follows:

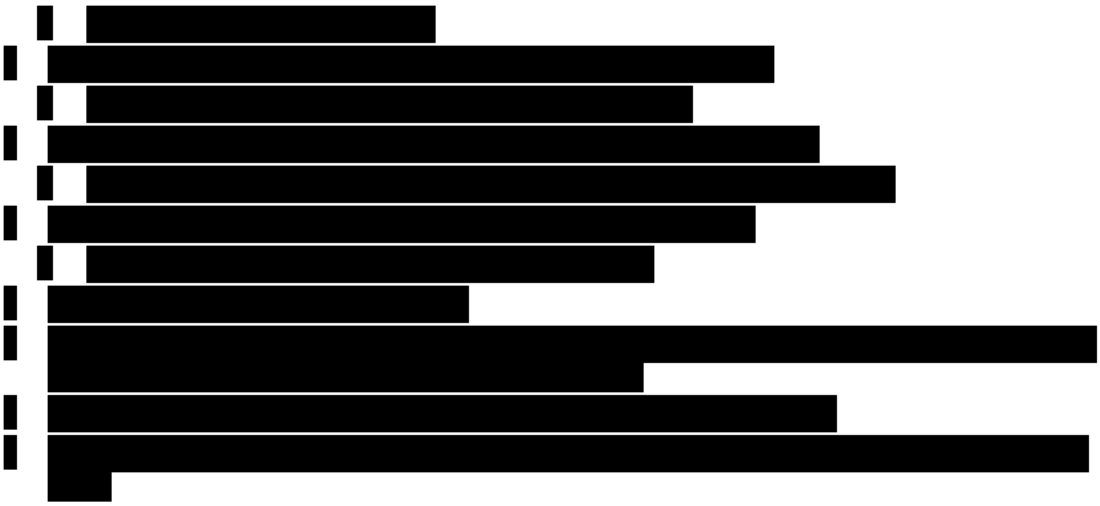
- PK parameters for MHAA4549A in serum including total exposure (i.e., AUC), maximum observed concentration (C_{max}), clearance, half-life, and volume of distribution, when appropriate, as data allow

The exploratory PK outcome measures for this study are as follows:

[redacted]

Exploratory Outcome Measures

[redacted]



Investigational Medicinal Products

An investigational medicinal product (IMP) is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, excluding marketed products unless the product is 1) used or assembled (formulated or packaged) differently than the authorized form, 2) used for an unauthorized indication, or 3) used to gain further information about the authorized form (Directive 2001/20/EC Article 2[d]). A non-investigational medicinal product (NIMP) is a medicinal product that is intended for use in a clinical trial per the protocol but does not fall under the definition of IMP. Further details can be found in the following EU guidance: Guidance on Investigational Medicinal Products and Non-Investigational Medicinal Products (effective March 2011).

MHAA4549A and Placebo

A single 3600-mg dose of MHAA4549A or dose of placebo will be delivered by IV infusion following dilution in 0.9% normal saline over approximately 60 minutes. Study drug should be delivered using a 0.22 μm in-line filter. Placebo will be identical to active MHAA4549A in formulation and appearance, but will not contain active drug substance.

Oseltamivir (Tamiflu®)

Sponsor-supplied oseltamivir (Tamiflu) 75 mg or 150 mg will be administered BID for up to a 10-day course. Dosage and administration should follow local prescribing information for oseltamivir. Capsules can be opened and the granules administered via nasogastric tube, if required.

Statistical Methods

Primary Analysis

All efficacy analyses will be conducted according to the intent-to-treat principle and will include all patients who meet the following condition with patients allocated to the treatment arm to which they were randomized: randomized patients who have confirmed influenza A infection as confirmed by a central PCR test from Day 1 samples.

The primary and secondary efficacy analyses will include all randomized patients who are confirmed to be influenza A infected, with patients grouped according to the treatment assigned at randomization.

Time to event data will be computed using Kaplan-Meier methodology and stratified Cox proportional hazards models and will be summarized using n, median when estimable, hazard ratios, and 95% confidence intervals. Patients who are lost to follow-up (while event free) will be censored at the time that they are last known to be event free.

Estimation of the treatment difference of proportions and its 95% confidence interval will be calculated using stratum-adjusted Mantel-Haenszel methodology. For continuous endpoints, Analysis of Covariance methods (after appropriate transformation of data) will be used to estimate treatment differences at 95% confidence intervals.

Interim Analyses

In order to adapt to information that may emerge during the course of this study (e.g., additional results of competitor studies) the Sponsor may choose to conduct one interim efficacy analysis. Section 6.7 contains the specifications in place to ensure the study continues to meet the highest standards of integrity when such an optional IA is executed.

If conducted, an interim analysis would be for administrative purposes only (i.e., internal planning or decision making) and would not impact the conduct of the current study in any way. A nominal type I error penalty of 0.0001 will be taken.

Determination of Sample Size

A total of 334 patients will be enrolled in this study in order to obtain approximately 300 evaluable patients (an estimated dropout rate of 10%). It is assumed that the median time to normalization of respiratory function in the control arm is 5 days

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
[redacted]	[redacted]
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
ATA	Anti-therapeutic antibody
AUC	Area under serum concentration–time curve
AUEC	Area under viral load–time curve
BID	Twice a day
°C	Celsius
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CPK	Creatine phosphokinase
CRO	Contract (or Clinical) Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECMO	Extracorporeal membrane oxygenation
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HA	Hemagglutinin
HAI	Hemagglutinin inhibition
HAP	Hospital Acquired Pneumonia
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart rate
[redacted]	[redacted]
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IDCC	Independent Data Coordinating Center
iDMC	Independent Data Monitoring Committee

Abbreviation	Definition
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRR	Infusion-related reactions
IV	Intravenous
LFTs	Liver function tests
mAB	Monoclonal antibody
NAI	Neuraminidase inhibitor
NP	Nasopharyngeal
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
PPV	Positive pressure ventilation
qPCR	Quantitative Polymerase Chain Reaction
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SOC	Standard of care
SpO2	Oxygen saturation
SUSAR	Suspected unexpected serious adverse reactions
TCID50	50% tissue culture infection dose
ULN	Upper limit of normal
VAP	Ventilation Acquired Pneumonia
WBC	White blood cell
w/v	Weight/volume

1. BACKGROUND

1.1 BACKGROUND ON INFLUENZA

Influenza A is a membrane-enveloped RNA virus that causes significant morbidity and mortality. Currently, there is a great need in hospitalized influenza patients for a parenteral therapeutic option that is well tolerated, can rapidly resolve influenza-related signs and symptoms, decrease mortality, reduce hospital and intensive care unit (ICU) stays, as well as have a prolonged window for initiation of treatment beyond the current standard of care (SOC) (i.e., within 48 hours of the onset of flu symptoms).

Approximately 200,000 to 278,000 patients are hospitalized with severe influenza infections annually in the United States (U.S.) (Thompson et al. 2004; Zhou et al. 2012), and assuming the same rate reported in the U.S., an estimated 319,000 to 445,000 patients are hospitalized in the European Union (E.U.). Hospitalization due to severe influenza is associated with high mortality (4%–8%), ICU admission (5%–17%; Lee and Ison 2012), mechanical ventilation support in an ICU setting (7%–11%; Doshi et al. 2011), and prolonged hospital stays (5−9 days; Lee and Ison 2012). 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).

Influenza infection is an upper and lower respiratory disease with a broad spectrum of presentations that can result in fever, shortness-of-breath, pneumonia, respiratory failure, secondary respiratory infections, and even death. The SOC therapy for patients hospitalized with influenza consists of supportive measures and administration of available antiviral agents, primarily neuraminidase inhibitors (NAI) that include but are not limited to oseltamivir, zanamivir, and peramivir. However, a significant unmet medical need still exists in the severely ill patient population, as evidenced by the considerable degree of morbidity and mortality in this setting. To address this need, Genentech Inc. /F.Hoffmann-La Roche Ltd. (Genentech) is developing a highly-specific, anti-influenza A (MHAA4549A) antibody therapy for treatment of hospitalized patients with severe influenza.

1.2 BACKGROUND ON MHAA4549A

MHAA4549A is a human monoclonal IgG1 antibody (mAb) that binds to the influenza A virus and is cloned from a single-human plasmablast cell isolated from an influenza vaccinated donor (Nakamura et al. 2013). This antibody binds to a highly conserved epitope on the influenza A hemagglutinin stalk region, which allows broad neutralization of the influenza A virus by blocking the hemagglutinin-mediated, membrane-fusion event in the late endosome.

In vitro, MHAA4549A is capable of neutralizing all current clinically relevant influenza A strains. In vivo, efficacy of MHAA4549A has been demonstrated in mouse models of influenza A infection, both as a single agent and in combination with oseltamivir. MHAA4549A specifically targets an epitope on the human influenza A hemagglutinin

glycoprotein, which does not appear to be endogenously expressed on human or rat tissues and, therefore, is unlikely to be present in the absence of viral infection. Weekly administration of MHAA4549A (total of 5 doses) in Sprague-Dawley rats was well tolerated up to the maximum feasible dose of 150 mg/kg. The results of the ex vivo tissue cross-reactivity study indicates no specific binding of MHAA4549A to any of the human or rat tissues examined.

Clinical experience with MHAA4549A has consisted of two studies in 122 healthy volunteers, and has been shown to be safe and well tolerated to date. The first study was a Phase 1 study (GV28916) in 21 healthy volunteers where single doses of 1.5 mg/kg, 5 mg/kg, 15 mg/kg, and 45 mg/kg were tested with an extended follow-up period of 120 days. MHAA4549A was safe and well tolerated with no serious adverse events (SAEs). All adverse events (AEs) were mild or mild-to-moderate and resolved fully. In addition, the observed pharmacokinetics were generally dose proportional, appeared to have a pharmacokinetic (PK) profile consistent with that of a IgG1 human antibody that lack known endogenous host targets, and no anti-therapeutic antibodies (ATAs) were detected with available samples.

The second study was a Phase 2a (GV28985) challenge study in 101 healthy volunteers infected with a H3N2 strain of influenza virus. Fixed dosing was selected for this study and is further described in Section 1.3.2.3. Three doses were tested: 400 mg, 1200 mg, and 3600 mg. All subjects have completed dosing, and interim PK and efficacy data are available for the 1200-mg and 3600-mg dose groups. During the Phase 2a (GV28985) study, the related AEs that were observed included elevated liver function tests (LFTs) and amylase levels. No dose relationship was observed for LFTs (i.e., placebo 30.8%, 1200 mg 40%, 3600 mg 35%), and no SAEs were observed that were related to MHAA4549A. Based on this data, MHAA4549A is considered generally safe and well tolerated to date at all doses tested including the 3600 mg dose. Analysis of efficacy from the 3600-mg dose level demonstrated a statistically significant decrease in viral shedding from upper respiratory tract as measured by area under the curve (97% reduction by quantitative polymerase chain reaction [qPCR]) and peak viral load (77% reduction by qPCR) as outlined in Table 1. In this study, oseltamivir was started on Day 7 for a 5-day course, and there were no observed AEs or imbalances in safety events that were considered attributable to interactions between oseltamivir and MHAA4549A. The PK profile of MHAA4549A and oseltamivir are being analyzed in GV28985 to exclude potential drug-drug interactions and will be available before the start of this study. Testing for ATAs in the Phase 2a has not been concluded.

Table 1 Interim Efficacy Results from Phase 2a Challenge Study (GV28985)

Endpoint	Placebo	MHAA4549A 1200 mg % reduction (p-value)[a]	MHAA4549A 3600 mg % reduction (p-value)[a]
Median qPCR Viral AUEC (log_{10} vc/mL x hour)	458.1	444.4 3.0% (0.9174)	11.3 97.5% (0.0092)
Median qPCR Peak Viral Load (log_{10} vc/mL)	6.38	6.36 0.3% (1.0000)	1.45 77.3% (0.0054)
Median Total Clinical Symptom AUEC	207.7	192.1 7.5% (0.8846)	37.7 81.8% (0.2922)

AUEC = area under viral load–time curve; qPCR = quantitative polymerase chain reaction.

[a] Comparison of 3600 mg to placebo using nonparametric Wilcoxon rank-sum test. All p-values are unadjusted for multiple testing.

See the MHAA4549A Investigator's Brochure for additional details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

The Phase 1 and Phase 2a studies have demonstrated that MHAA4549A is safe and well tolerated to date in healthy volunteers including those who were inoculated with influenza A virus. Preliminary data from the Phase 2a study also provides evidence that the 3600 mg dose of MHAA4549A is effective in reducing viral titers in healthy volunteers inoculated with influenza A virus. These findings, when combined with previous nonclinical studies showing MHAA4549A to have in vitro and in vivo efficacy, a well-tolerated safety profile, and anti-viral activity, support further clinical development of MHAA4549A.

In this Phase 2b study (GV29216), MHAA4549A is being evaluated in combination with the current SOC (oseltamivir), to decrease the severity and duration of viral infection with influenza A virus with the ultimate goal of reducing the clinical symptoms of infection as compared to oseltamivir with placebo. There are three primary goals for this Phase 2b study:

- Demonstrate the safety and efficacy of MHAA4549A in combination with oseltamivir in hospitalized influenza A patients
- [redacted]

- Demonstrate and evaluate the optimal endpoints for study in hospitalized patients with influenza A, given the lack of precedence for approval in patients hospitalized with influenza infection, an area of high unmet medical need

This Phase 2b study has been designed to estimate the improvement in outcome of a combination therapy of MHAA4549A 3600 mg with oseltamivir versus placebo with oseltamivir. All patients will be on oseltamivir which is part of the recommended SOC. In addition, and as discussed above, MHAA4549A is a human monoclonal antibody that has, to date, shown an acceptable safety profile, a PK profile consistent with that of a IgG1 human antibody that lacks known endogenous host targets, and a demonstrated antiviral activity at the planned dose level of 3600 mg.

1.3.2 Benefit-Risk Assessment

1.3.2.1 Treatment in Combination with Oseltamivir

All patients in the study will receive the current SOC treatment of oseltamivir either with or without MHAA4549A. Therefore, all patients at minimum will be treated with SOC for influenza. Given that MHAA4549A is an antibody, the potential for interaction with oseltamivir is very low. In the ongoing Phase 2a challenge study (GV28985), several study subjects received MHAA4549A followed by oseltamivir with no AEs attributable to the combination therapy noted to date. In addition, the PK profile of oseltamivir in concomitantly treated subjects will be assessed.

1.3.2.2 Drug Mechanism and Preclinical Studies

The available pre-clinical data suggest that there is low risk for drug target-related safety events in healthy humans since MHAA4549A specifically targets an epitope on a viral protein (i.e., the human influenza A virus hemagglutinin glycoprotein), which is not endogenously expressed in human tissues. Furthermore, there were no adverse MHAA4549A-related findings demonstrated in nonclinical studies at doses up to 150 mg/kg administered weekly for 5 weeks and no evidence of target present in host tissues.

1.3.2.3 Rationale for Selection of Phase 2b Study Population

The target patient population of hospitalized patients with severe influenza A requiring oxygen (O_2) or positive pressure ventilation (PPV) is considered an appropriate population to test MHAA4549A for the following reasons:

- Nonclinical safety data does not show any expected or unexpected toxicity.
- Clinical safety data for MHAA4549A demonstrates a well-tolerated safety profile. There were mild, related AEs observed in the Phase 1 study (GV28916) and MHAA4549A was well tolerated. No ATAs were detected. Safety data from the ongoing Phase 2a challenge study (GV28985) was observed to have mild and moderate transient elevations in alanine transaminase (ALT), aspartate transaminase (AST), and amylase that may be related to either MHAA4549A or to influenza infection. There was no dose-dependent relationship of LFT elevations with MHAA4549A and the overall event rate was in line with that of previous

challenge studies (27/100 [27%] in the study vs. approximately 26%) (Polakos 2006). No SAEs that were related to study drug were observed. Testing for ATAs in Study GV28985 has not yet been concluded.

- The Phase 2a challenge study (GV28985) interim efficacy data demonstrated a significant decrease in viral shedding in the upper respiratory tract at the 3600 mg dose. There was a 97.5% ($p = 0.0092$) decrease in the area under viral load–time curve (AUEC) and a 77% ($p = 0.0054$) decrease in peak viral load by qPCR measurement in comparison to the placebo group, thus confirming proof of antiviral activity at the 3600 mg dose level.

1.3.2.4 Patient Monitoring and Supervision

MHAA4549A will be administered to enrolled patients in a hospital environment under close medical supervision by physician investigators. Medical staff will be available for prompt evaluation and treatment of any adverse events. Emergency resuscitation equipment and emergency facilities will be readily available. Patients will undergo screening assessments to confirm eligibility, will be closely monitored during the administration of MHAA4549A, and will be resident for at least 24 hours following the administration of MHAA4549A. Furthermore, safety laboratory tests relating to the blood chemistries, including liver function tests, will be conducted.

An independent Data Monitoring Committee (iDMC) will evaluate the safety of MHAA4549A at a timepoint to be specified in the iDMC charter.

The 120-day follow-up period in the Phase 1 and 2a studies allowed for monitoring of subjects for approximately 5 half-lives of the study drug. No ATAs were detected in the Phase 1 study, and the ATA testing for the Phase 2a study is ongoing. The Phase 2b study will also include an appropriate safety follow-up period of up to 30 days and an unlimited collection of all SAEs believed related to MHAA4549A.

Based on the above data and design of this study, the Sponsor concludes that the benefit–risk profile of MHAA4549A in the population with severe influenza is favorable.

2. OBJECTIVES

2.1 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety of MHAA4549A in combination with oseltamivir compared with placebo and oseltamivir in patients with severe influenza A, focusing on the nature, frequency, and severity of serious and non-serious adverse events as well as effects on laboratory values, vital signs, electrocardiogram (ECG) parameters, ATAs, or other safety biomarkers

2.2 PRIMARY EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To determine the time to normalization of respiratory function of patients dosed with MHAA4549A in combination with oseltamivir compared to patients dosed with placebo and oseltamivir.

2.3 SECONDARY EFFICACY OBJECTIVES

The secondary efficacy objectives for this study are as follows:

- To measure clinical failure, as defined in Section 3.3.3, after 24 hours post-infusion of study drug
- To determine the time to clinical resolution of vital signs
- To measure mortality in patients
- To determine changes in the extent and duration of viral shedding in upper respiratory samples
- To measure the duration of hospital and/or ICU stay
- To measure antibiotic usage for respiratory indications
- To measure the frequency and severity of the following secondary complications of influenza:
    - Pneumonia (hospital acquired pneumonia [HAP]/ ventilator acquired pneumonia [VAP])
    - Exacerbations of chronic lung disease
    - Myocarditis
    - Acute respiratory distress syndrome (ARDS)
    - Otitis media
    - Other related complications
    - Readmission rates at 30 days after study treatment
- To measure duration of PPV
- To measure readmission rates

2.4 PHARMACOKINETIC OBJECTIVES

The major PK objective for this study is as follows:

- To characterize the PK profile of MHAA4549A in serum

The exploratory PK objectives for this study are as follows:

- [redacted]
- [redacted]

2.5 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are as follows:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase 2b, randomized, double-blind, placebo-controlled study designed to assess the safety and clinical activity of a single intravenous (IV) dose of MHAA4549A in hospitalized patients with severe influenza A in combination with oseltamivir versus a comparator arm of placebo with oseltamivir. This study is planned to take place in approximately 170 study centers globally.

Patients will be randomized 1:1 into two treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir or a single IV dose of placebo with oseltamivir. All patients will receive oseltamivir, a NAI, as standard therapy for a minimum of 5 days after study drug administration. Oseltamivir at doses of 75 BID or 150 mg BID is permitted in order to be consistent with local SOC practice. Treatment for longer than 5 days is permitted based on local investigator discretion. The patient must start Sponsor-supplied oseltamivir within 8 hours of study drug administration. The study has a planned enrollment of approximately 334 patients globally.

Hospitalized patients with an O_2 or PPV requirement will be evaluated for influenza A infection. Enrollment in this study requires ongoing treatment within 24 hours of hospital admission with one of the following:

- any PPV or
- any supplemental O_2 to maintain oxygen saturation (SpO_2) >92% (see Section 3.3.2)

Patients on PPV should not exceed 45% of the total patients enrolled.

A Sponsor-supplied rapid influenza test and/or a local polymerase chain reaction (PCR) test must be used as an aid in the diagnosis of influenza A infection.

[redacted]

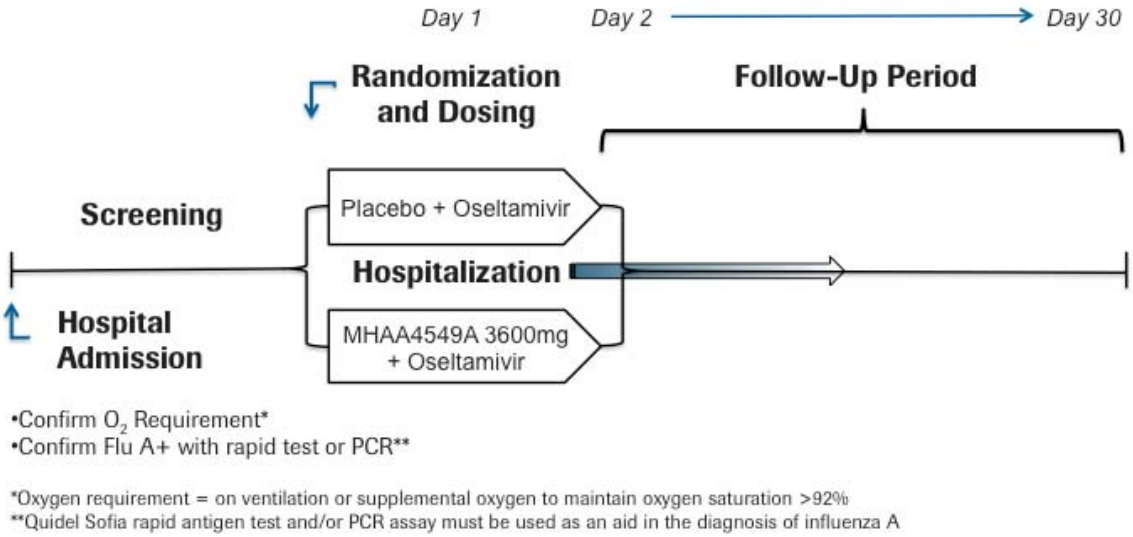
At the time of randomization, patients who are eligible for enrollment as described above, will be randomized to receive MHAA4549A at a dose of 3600 mg or placebo. Patients will be stratified by country, PPV versus supplemental O_2 on the day of admission, and suspected or confirmed bacterial pneumonia versus no bacterial pneumonia based on the status on the day of admission.

Eligible patients who are enrolled into the study will receive either a single IV infusion of MHAA4549A or a single IV infusion of placebo on Day 1. All patients must have the study drug infused within 48 hours of hospital admission or sooner if possible. All patients will receive oseltamivir for a minimum of 5 days (10 doses), starting on Day 1, beginning no later than 8 hours after study drug administration.

All patients will be followed and evaluated at minimum on a daily basis for the duration of their hospital stay consistent with the planned schedule of assessments. Any suspicion of bacterial superinfection should be thoroughly evaluated including microbiological confirmation, if possible. A follow-up study visit should occur on Day 14 ± 1 (if discharged before Day 14) and Day 30 ± 4 days, if discharged before Day 30.

A schedule of assessments is provided in Appendix 1a and Appendix 1b. A diagram of the study design is presented in Figure 1.

Figure 1 Phase 2b Study Design (GV29216)



3.1.2 Independent Data Monitoring Committee

An iDMC, which consists of two independent physicians and one independent biostatistician, will review safety data of the trial to ensure the safety of the patients enrolled. This should allow early detection of any potential safety concern and, thus, ensure the best possible protection of patients' safety. In addition, it includes a non-voting biostatistician from an independent data coordinating center (IDCC) who prepares the safety reports, including information on patient accrual and SAEs from the study. The iDMC reviews the safety reports, addresses any safety concerns, and informs the Sponsor whether or not to continue the study.

A detailed description of the procedures, data flow, and meeting schedule of the iDMC will be provided in a separate iDMC charter.

3.1.3 End of Study

The end of study is defined as the first day when all patients have had a study completion visit or early termination visit or have otherwise been discontinued from the study.

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Study Design

Hospitalized influenza A infection represents a high unmet need, which, when left untreated, may progress to a more serious disease that may result in significant morbidity and mortality in otherwise healthy adults as well as in vulnerable populations.

This study is designed to estimate the improvement in outcome of a combination regimen of MHAA4549A with oseltamivir compared to a SOC arm of placebo with

oseltamivir. The study population will include hospitalized patients with influenza A requiring O_2 support and/or PPV support within 24 hours of hospital admission.

Study GV29216 will be a Phase 2b study involving approximately 334 patients. The sample size was determined based on an expected clinically meaningful difference of 1 – 2 days improvement in time to normalization of respiratory function between the control and treatment arms, assuming a 5-day median time to the time to normalization of respiratory function in the SOC arm (Blackwood 2011; PREMIER® database).

This design ensures that all patients in the trial will receive the current NAI treatment, oseltamivir, as SOC at a minimum, and will evaluate the clinical benefit of combining MHAA4549A with this SOC regimen. Therefore, this study aims to identify a regimen that could deliver maximum benefit in this high unmet need disease, while still treating all enrolled patients with the currently accepted SOC.

3.2.2 Rationale for Patient Population and Primary Endpoint

Severe influenza, for the purpose of this study, is defined as requiring one of the following treatments: PPV or any supplemental O_2 to maintain an $SpO_2 > 92\%$. PPV is defined as any mechanical positive pressure device to maintain oxygenation; this can include mask ventilation and intubation. A Sponsor-supplied rapid influenza test and/or a local PCR must be used as an aid in the diagnosis of influenza A infection.

This patient population was chosen based on the rationale that respiratory failure is a hallmark of influenza and a major driver of morbidity and mortality, as well as hospitalization. The recovery from ventilator support has been shown to be directly proportional to time spent in the ICU (Blackwood 2011; PREMIER® database). Based upon an analysis of morbidity and mortality, the patient population that requires supplemental O_2 or ventilation on their first day of admission was determined to have a high unmet medical need as they have an estimated mortality of 9%–32%, and 27% require admission to the ICU, according to analysis of a database of over 70,000 hospitalized patients in the US from 2005–2012 (PREMIER® database).

Support for use of the respiratory endpoint in this population comes from recently published data demonstrating that a composite endpoint that captured respiratory rate, fever, heart rate, and blood pressure resolution was primarily driven by the respiratory component of the endpoint (Marty et al. 2014).

3.2.3 Rationale for Control Group and Treatment Window

In this study, the SOC regimen for the control or comparator group is oseltamivir, an NAI. In the treatment groups, MHAA4549A will be dosed in addition to an oseltamivir SOC regimen. The oseltamivir dose will be consistent with the local investigator practice at each site where the study will be conducted. Either 75 mg or 150 mg orally BID oseltamivir for a minimum of 5 days is permitted following treatment with MHAA4549A. Treatment for longer than 5 days is permitted based on local investigator discretion. The

oseltamivir dosing regimen, including the renal dosing adjustment, is listed in Table 2. This control treatment was based on consideration of safety, ethics, and efficacy for treatment of severe influenza and is consistent with guidelines for antiviral treatment of hospitalized patients with influenza (Harper et al. 2009, Fiore 2011).

Table 2 Oseltamivir Dosing Regimen

Neuraminidase Inhibitor	Dosing Regimen	Duration of Therapy
Oseltamivir	75 mg or 150 mg orally BID [a] 75 mg oral once daily for adult patients with creatinine clearance (CrCL) between 10 and 30 mL/min [b]	5 days [c]

[a] 75 mg or 150 mg dose at the discretion of the investigator, and dose must be documented. Capsules can be opened and the granules administered via nasogastric tube, if required.

[b] No recommended dosing regimens are available for patients with end-stage renal disease undergoing routine hemodialysis or continuous peritoneal dialysis treatment.

[c] Longer treatment times are at the discretion of the investigator.

From a safety standpoint there are no expected drug interactions between MHAA4549A, a monoclonal antibody, and any NAI, which are small molecule drugs that bind to a different viral protein than MHAA4549A. In the Phase 2a challenge study, all subjects that were dosed with MHAA4549A also received a 5-day course of oseltamivir starting on Day 7. There were no safety effects attributable to the combination when the drugs were present concurrently. The pharmacokinetics of oseltamivir and its potential interaction with MHAA4549A are being assessed from this Phase 2a.

For this Phase 2b study, a combination of MHAA4549A and oseltamivir was determined to be the most clinically feasible treatment regimen, both from an ethical as well as a practical perspective. The treatment of all patients with oseltamivir ensures that all patients will receive SOC given the high morbidity and mortality of hospitalized patients with influenza A along with guidelines from Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) stating NAIs are the SOC for hospitalized patients with influenza A (Harper et al. 2009 and CDC Website). Further, pre-clinical efficacy data from a study using MHAA4549A and oseltamivir in combination, showed a potential synergistic effect of both compounds which may be due to the different and potentially complementary mechanisms of action, i.e. targeting viral hemagglutinin and neuramindase.

Dosing of MHAA4549A is confined to a treatment window designed for best expected treatment success and to ensure that any observed effects can be attributed to the study drug with high confidence. MHAA4549A shall only be dosed within 5 days of symptom onset, within 3 days of initial treatment with a NAI, and no later than 48 hours after admission to the hospital. This proposed window is supported by data demonstrating

that hospitalized influenza patients benefit from NAI treatment even at 5 days from symptom onset (Louie et al. 2012).

3.2.4 Rationale for MHAA4549A Dosage

A single IV dose of 3600 mg of MHAA4549A was selected to assess the efficacy of MHAA4549A and to provide data for further clinical development. The selection of dose in this study for severely ill patients was based on the observed human pharmacokinetics in Phase 1 and the relationship between the pharmacokinetics, pharmacodynamics, and efficacy observed in a Phase 2a human challenge model of influenza. The dose is adequately supported by safety data from the completed Phase 1 study and ongoing Phase 2a study in healthy volunteers, which has completed dosing. MHAA4549A was shown to be safe and well-tolerated at all dose levels (ranging from 1.5 mg/kg to 45 mg/kg for Phase 1 and 400-3600 mg for Phase 2a) through a follow-up period of 120 days post-dose in the Phase 1 study. The dose level used in this study was determined following an interim analysis of the 1200-mg and 3600-mg doses in the Phase 2a study, GV28985, which demonstrated the following:

- The 3600-mg dose demonstrated a significant decrease in viral shedding in upper respiratory samples. Based on current interim analysis data, there was a 97.5% ($p = 0.0092$) decrease in AUEC and a 77.3% decrease in peak viral load by qPCR measurement compared to the placebo group.
- The 1200-mg dose level was not efficacious.
- There are no safety concerns at the 3600-mg dose level to date.
- Hospitalized patients generally have a longer duration of viral shedding and significantly more viral burden in the lower lung compartments; therefore, high concentrations of mAb are likely needed to achieve sufficient occupancy of the virus binding sites in the upper and lower respiratory compartments. Furthermore, higher concentrations of mAb are necessary to mitigate the risk of resistance for MHAA4549A and neuramindase inhibitors such as oseltamivir.

The Phase 1 study was conducted using body-weight based dosing followed by a fixed dosing strategy that was used in the Phase 2 study. Thus, the fixed dosing regimen that was used in the Phase 2a study will be used for this study, given the practical advantages and positive safety profile of MHAA4549A to date. Further, fixed dosing is generally recommended with monoclonal antibodies, due to their minimal PK variability (Bai et al. 2012). The PK variability introduced by different dosing regimens (i.e., body-weight based dosing versus fixed dosing) is moderate relative to the variability generally observed in pharmacodynamics, efficacy, and safety and would not be expected to be clinically meaningful.

3.2.5 Rationale for Biomarker Assessments

[redacted]

[redacted]

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Adverse events and clinical laboratory abnormalities
- Vital signs, physical findings, ATAs, and clinical laboratory results during and following administration of MHAA4549A

3.3.2 Primary Efficacy Outcome Measure

The primary outcome measure for this study is as follows:

- Time to normalization of respiratory function defined as:
  - The time to cessation of O_2 support resulting in a stable $SpO_2 > 95\%$ for at least 24 hours (see Appendix 2 for details)

3.3.3 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- Clinical failure 24 hours post-infusion of study drug; defined as:
  - Progression to increased O_2 requirement defined by an increase in oxygen supplementation from low flow oxygen ($2-6$ L/min) to high flow oxygen (>6 L/min) or from oxygen supplementation alone to any PPV
  - Progression to ICU
  - Prolonged ventilation or O_2 support defined by >2 weeks, or
  - Death
- Time to clinical normalization of vital signs (3/5 criteria must be met):
  - $SpO_2 > 95\%$ without supplemental O_2 for at least 24 hours
  - Respiratory rate < 24 without supplemental O_2 for at least 24 hours
  - Core temperature < 37.2°C immediately prior to receipt of any antipyretic drug, and at least 6-8 hours from the last dose of antipyretic or core temperature >36°C in patients who are initially hypothermic
  - Heart rate (HR) <100/minute
  - Systolic blood pressure (SBP) >90 mmHg

- All-cause mortality at Day 14 and Day 30
- Influenza A viral load in nasopharyngeal samples
  - AUEC
  - Peak viral load
  - Time to resolution of infection
- Duration of hospitalization
- Duration of ICU stay
- Antibiotic usage for respiratory infections
- Complications of influenza:
  - Pneumonia (HAP/VAP)
  - Exacerbations of chronic lung disease
  - Myocarditis
  - ARDS
  - Otitis media
  - Other related complications
- All-cause readmission at Day 30
- Duration of ventilation

3.3.4 Pharmacokinetic Outcome Measures

The primary PK outcome measures for this study are as follows:

- PK parameters for MHAA4549A in serum including total exposure (i.e., AUC), maximum observed concentration (C_{max}), clearance, half-life, and volume of distribution, when appropriate, as data allow

The exploratory PK outcome measures for this study are as follows:

[redacted]

3.3.5 Exploratory Outcome Measures

[redacted]

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

This study aims to enroll approximately 334 men and women and is designed to assess the safety and clinical activity of a single IV administration of MHAA4549A in adult patients hospitalized with severe influenza A.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Hospitalized men or women ≥ 18 years of age on the day of signing the informed consent or obtaining surrogate consent from an authorized representative
- Diagnosis of influenza A as determined by the Sponsored-supplied rapid influenza test
  - If negative rapid influenza A test, a positive local molecular test (PCR) is required
- One of the following markers of severity within 24 hours of hospital admission:
  - Requirement for PPV – or –
  - Requirement for O_2 supplementation to maintain $SpO_2 > 92\%$
- A negative urine or serum pregnancy test for women of child-bearing potential
- Patients of reproductive potential must agree to use reliable means of contraception as described below as a minimum (adherence to more stringent local requirements may be required):
  - For female patients: Use of two acceptable methods of contraception throughout the trial, including the active treatment phase AND for 24 weeks after

the last dose of MHAA4549A. Acceptable methods of contraception include: intrauterine device, systemic hormonal contraception (oral or depot), vaginal ring, tubal ligation of the female partner, vasectomy of the male partner, use of latex condoms plus spermicide by the male partner, or cervical cap plus spermicide (where the spermicide could be foam, vaginal suppository, gel, cream, etc.).

- For male patients: Use of condoms for 30 days after dosing when circulating drug levels remain high.
- Non-reproductive potential is defined below (but could be superseded by local definitions, if they are more stringent):

  Women who are postmenopausal (i.e., spontaneous amenorrhea for the past year confirmed by an FSH level greater than 40 mIU/mL unless the patient is receiving a hormonal therapy for their menopause)

  Women who are surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)

  Men who are surgically sterile (castration)

4.1.2 Exclusion Criteria

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

- Pregnant or lactating or intending to become pregnant during the study
  - Women who are not postmenopausal ($\geq$12 months of non-therapy-induced amenorrhea) or who are not surgically sterile must have a negative urine or serum pregnancy test result within 2 days prior to study treatment.
- Hypersensitivity to mABs or any constituents of study drug
- Investigational therapy within the 30 days prior to study treatment
- Received prior therapy with any anti-influenza monoclonal antibody therapy including MHAA4549A 8 months prior to study treatment
- Current treatment (within 7 days of dosing) with amantadine or rimantidine
- Patients who have taken more than a total of 3 days (6 doses) of approved anti-influenza therapy (e.g., oral oseltamivir, inhaled zanamivir, or oral ribavirin) in the period from onset of symptoms and prior to enrollment
- Admission $>$48 hours prior to study treatment
- Onset of influenza symptoms $>$5 days prior to study treatment
- Positive influenza B or influenza A$+$B infection within 2 weeks prior to study treatment
- High probability of mortality in the next 48 hours as determined by the investigator
- Patient requiring home or baseline oxygenation therapy
- Patient with history of chronic lung disease resulting in baseline $SpO_2 < 95\%$

- Patient on a chronic dose of corticosteroids exceeding 10 mg/day of prednisone or equivalent steroid dose for a duration of greater than 14 days within 30 days of entry into study
- Patients with the following significant immune suppression:
  - Bone marrow or solid organ transplant in the previous 12 months
  - Cancer chemotherapy in the previous 12 month
  - HIV infection with most recent CD4 $<$ 200 cells/mL
  - Other significant immune suppression as determined by the investigator in discussion with the Sponsor Medical Monitor or representative
- Patient on extracorporeal membrane oxygenation (ECMO) at time of randomization
- Any disease or condition that would, in the opinion of the site investigator or Sponsor, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The randomization of patients will be managed by a central Interactive Voice and Web Response System (IxRS). All patients will be randomly assigned to receive either MHAA4549A 3600 mg or placebo at a 1:1 ratio stratified by country, whether patient is on PPV vs supplemental O_2 on the day of admission, and whether the patient has suspected or confirmed bacterial pneumonia vs no bacterial pneumonia on the day of admission. All patients will receive oseltamivir (75 mg or 150 mg BID) for a minimum of 5 days. Treatment for longer than 5 days is permitted based on local investigator discretion.

The treatment assignments will be unblinded to an external IDCC to facilitate the iDMC assessment of safety.

Blinded personnel at each study site will make appropriate preparations and perform the IV infusions of study drug, as described in Section 4.3.3. The other parties who are involved in the conduct of the study (i.e., patients and blinded site personnel) will remain blinded to patient-specific treatment assignments until the final database lock after the completion of the study.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this trial. Bioanalytical laboratory personnel responsible for performing PK assays will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed. Samples from patients assigned to the comparator arm will not be analyzed except by request (e.g., to evaluate a possible error in study drug administration).

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code in IxRS. Treatment codes should not be broken except in emergency situations. *If the investigator wishes to know the identity of the study drug for any other reason, they should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event)*.

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all suspected unexpected serious adverse reactions (SUSAR)(see Section 5.6) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 MHAA4549A and Placebo

MHAA4549A, matching placebo, and up to 10-day supply of oseltamivir (Tamiflu®) will be supplied by the Sponsor. For information on the formulation, packaging, and handling of MHAA4549A and placebo; see the Pharmacy Manual and the MHAA4549A Investigator's Brochure.

The MHAA4549A vial delivers 10 mL (500 mg) of drug product solution, but may contain more (approximately 10.3 mL) than the stated volume to enable delivery of the entire 10 mL volume. MHAA4549A is formulated as 50 mg/mL in 10 mM sodium succinate, 240 mM sucrose, and 0.02% (w/v) polysorbate 20 at pH 5.5 and is contained in a 15 mL forma vitrum (USP/PH. Eur. Type 1) glass vial. The drug product is suitable for single use only and contains no preservatives.

Placebo for MHAA4549A has the same composition as the drug product (without MHAA4549A) and is supplied in an identical vial configuration. The placebo contains no preservatives and is suitable for single-use only. Placebo is formulated as 10 mM sodium succinate, 240 mM sucrose, and 0.02% polysorbate 20 at pH 5.5 in a total volume of 10 mL in a 15 mL forma vitrum (USP/PH. Eur. Type 1) glass vial.

MHAA4549A and placebo are supplied in identical blinded vials labeled with unique kit numbers. IxRS will assign kit numbers for each treatment arm; all treatment arms will be assigned the same total number of vials for each treatment, and the same preparation instructions. Placebo is identical to active MHAA4549A in formulation and appearance but does not contain active drug substance.

4.3.1.2 Oseltamivir (Tamiflu)

Oseltamivir (Tamiflu) is an influenza NAI indicated for treatment of acute, uncomplicated influenza. For information on the formulation, packaging, and handling of oseltamivir; see the local prescribing information for oseltamivir.

Storage: Capsules should be stored at 25°C (77.7°F); excursions permitted to 15° to 30°C (59° to 86°F).

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 MHAA4549A and Placebo

The randomization of patients will be managed by a central IxRS. All patients will be randomly assigned to receive either a single dose of MHAA4549A 3600 mg IV or placebo IV at a 1:1 ratio. Oseltamivir will be dispensed via IxRS. Oseltamivir dosing is described in Table 2.

Administration of MHAA4549A or placebo will be performed in a setting with emergency medical equipment and personnel who are trained to monitor for and respond to medical emergencies. A qualified physician will be on site during study drug administration for all patients.

A single dose of MHAA4549A or placebo will be delivered by IV infusion following dilution in 0.9% normal saline over approximately 60 minutes. Study drug should be delivered using a 0.22 μm in-line filter. Compatibility testing has shown that MHAA4549A is stable when diluted in 0.9% normal saline in a polyvinylchloride, polyolefin bag, or ethylene vinyl acetate bag (EVA), at or above a combined total concentration of 0.24 mg/mL up to 27.0 mg/mL. Study drug must be administered within the treatment window outlined in Section 3.1.1. Further detailed instructions for preparation of study drug can be found in the Pharmacy Manual.

There are no recommended dosage modifications for MHAA4549A since it is a single infusion. Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. General supportive measures will be taken to manage any AEs associated with overdose. Patients experiencing such AEs will be followed up clinically until the event has resolved.

Trained clinical site staff responsible for adequate and accurate study drug administration, accounting, and management will administer study drugs to patients. Study drug preparation and dosing instructions will be provided to each site. The exact times of study drug administration will be recorded in the relevant dispensing/administration logs and patient's source notes. Any noncompliance or problems with study drug administration will be recorded in the patient's source notes and reported to the Sponsor if appropriate.

4.3.2.2 Oseltamivir-Neuraminidase Inhibitor (NAI)

The Sponsor will be providing oseltamivir (Tamiflu®) for this study for up to a 10-day course. Dosage and administration should follow local prescribing information for oseltamivir. Either 75 mg or 150 mg of oseltamivir will be administered twice daily as described in Table 2. Capsules can be opened and the granules administered via nasogastric tube, if required.

Guidelines for dosage modification for renal dosing are presented in Table 2 .

Any overdose or incorrect administration of oseltamivir should be noted on the oseltamivir Administration eCRF. Adverse events associated with an overdose or incorrect administration of oseltamivir should be recorded on the Adverse Event eCRF.

4.3.3 Investigational Medicinal Product Accountability

Investigational medicinal products (IMPs) required for completion of this study (i.e., MHAA4549A and oseltamivir) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMP will be stored in a secure pharmacy or locked area with access limited to authorized personnel, in accordance with the details provided in the Investigator's Brochure and Pharmacy Manual. Upon receipt, MHAA4549A and placebo vials must be refrigerated at 2°C to 8°C until use. MHAA4549A does not contain antimicrobial preservatives; therefore, care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation. Dilute under appropriate aseptic conditions using 0.9% normal saline. The solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use should not exceed 24 hours at 2 to 8°C and/or 4 hours at ambient temperature (18°C – 24°C). If the dose solution is stored at 2°C – 8°C, it should be removed from refrigeration and allowed to reach room temperature prior to administration. If the infusion is interrupted and the combined ambient temperature storage and interruption time exceeds 4 hours, prepare a new dose solution to resume the infusion (see the Pharmacy Manual). Protect dose solutions from heat and intense light.

The total duration from the preparation of dose solutions to the end of infusion should not exceed 24 hours. Vials are intended for single use only; therefore, any remaining solution should be discarded (see the Pharmacy Manual).

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

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

4.4 POST-TRIAL ACCESS TO MHAA4549A

As this is single dose administration, Genentech does not intend to provide MHAA4549A to patients after the conclusion of the study or any earlier withdrawal. Patients may or may not be eligible for any potential subsequent trials of MHAA4549A under a separate protocol.

4.5 CONCOMITANT THERAPY AND FOOD

4.5.1 Permitted Therapy

Concomitant medication includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 30 days prior to screening to the study completion/discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. For any NAIs (e.g., oseltamivir, peramivir, zanamivir, laninimavir) that have been taken prior to study drug therapy, the number of doses and duration of therapy must be recorded.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

All therapies required for management of the patient's acute illness are permitted except for those listed below in Section 4.5.2.

4.5.2 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 7 days prior to study treatment, unless otherwise specified below: probenecid, amantadine, or rimantidine

Use of other NAIs, including but not limited to oral oseltamivir, inhaled zanamivir, oral ribavirin, laninimivir, and peramivir, are prohibited during the study, but allowed up to 3 days (6 doses) prior to study treatment as outlined in the exclusion criteria. If oseltamivir resistance is highly suspected or identified during treatment then, following discussion with the sponsor medical representative, an alternative NAI to oseltamivir may be used.

4.5.3 Prohibited Food

There are no prohibited foods for this study.

4.6 STUDY ASSESSMENTS

Please see Appendix 1a and Appendix 1b for the schedule of assessments performed during the study.

4.6.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed consent by authorized representatives may be obtained only if allowed by and in accordance with local regulations and Independent Review Board (IRB)/Independent Ethics Committee (IEC) policies and procedures. Informed Consent Forms (ICF) 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 randomization. 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.

4.6.2 Diagnostic Testing for Enrollment

All hospitalized patients with severe influenza A will be assessed for disease confirmation and enrollment into the study. A Sponsor-supplied rapid influenza test is required for the diagnosis of influenza A infection and uses an nasopharyngeal swab. When the Sponsor-supplied rapid influenza test is negative, the study inclusion criteria can be satisfied with a positive local molecular test (PCR) if the result is within the 48-hour screening window. Other tests may not be used for enrollment in the study unless the Sponsor has reviewed and approved the use of the diagnostic.

4.6.3 Medical History and Demographic Data

Medical history includes clinically significant diseases and procedures, including chronic respiratory disease, infections, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days prior to the screening visit. A careful assessment of the patient's baseline SpO_2 should be made especially if the patient has a history of severe chronic lung disease.

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

4.6.4 Priority of Assessments

When events warrant, or in the opinion of the investigator, safety issues become paramount, safety assessments will always have priority over all other measurements and procedures. Under routine circumstances, however, PK, nasal virological, and biomarker serum/plasma samples have priority over other measurements. The timing and number of safety measurements may be modified based on clinical evaluations.

4.6.5 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory,

gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At protocol designated visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed which includes, at a minimum, evaluation of general appearance, dermatological examination of the injection sites, evaluations directed by patient-reported symptoms, and any other evaluations that the investigator deems clinically relevant. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as AEs, if appropriate, on the AE eCRF.

4.6.6 Vital Signs

Vital signs will include measurements of resting SpO_2 (see Section 4.6.7 for measurement), respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressures after the patient has been in a seated or supine position for at least 10 minutes. Patients in intensive care may have vital signs assessed following local procedures, but those procedures should be captured in the eCRF in accordance with the eCRF instructions.

4.6.7 Oxygen Saturation Measurements

To ensure that the respiratory status is well recorded, the following daily measurements will be performed. Unless clinically contraindicated, all patients will have their SpO_2 recorded daily in the morning between 4 am – 10 am local time. Patients on low-flow O_2 will have a daily trial of their SpO_2 while on and off the supplementation, as outlined in Appendix 2, and both values will be recorded.

4.6.8 Laboratory, Biomarker, and Other Biological Samples

Samples for the laboratory tests listed in Table 3 and Table 4 will be sent to the study site's local laboratory for analysis at screening and during the study, respectively.

Table 3 Laboratory Tests at Screening

Hematology:	Serum Chemistry:
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Bicarbonate
Leukocytes (WBC)	Chloride
Neutrophils, segmented	Calcium
Lymphocytes	Phosphorus
Monocytes	Magnesium
Eosinophils	Glucose (fasting)
Basophils	Urea nitrogen (BUN)
Platelets	Creatinine
	Total cholesterol
Coagulation:	Total protein
Activated partial thromboplastin time (APTT)	Albumin
Prothrombin time (PT)	Total bilirubin
International Normalized Ratio (INR)	Alkaline phosphatase
	Aspartate aminotransferase (AST)
Urine Chemistry:	Alanine aminotransferase (ALT)
pH	Amylase
Specific gravity	
Glucose	Serology:
Creatinine	HIV Serology
Total protein to creatinine ratio	
Albumin	Misc:
Ketones	Thyroid stimulating hormone (optional)
Occult blood	Pregnancy Test (urine or serum; women of child-bearing potential)
Bilirubin	
Urobilinogen	
Nitrite	
Leukocyte esterase	
Microscopic examination (if clinically indicated)	

Note: Investigators must document their review of each laboratory report by signing (or initialing) and dating each report.

Table 4 Laboratory Tests During the Study

Hematology:	Clinical Chemistry (Blood):
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Bicarbonate
Leukocytes (WBC)	Chloride
Neutrophils, segmented	Calcium
Lymphocytes	Phosphorus
Monocytes	Magnesium
Eosinophils	Glucose (random)
Basophils	Urea nitrogen (BUN)
Platelets	Creatinine
Erythrocyte Sedimentation Rate (ESR)	Total cholesterol
	Total protein
Coagulation:	Albumin
Activated partial thromboplastin time (APTT)	Total bilirubin
Prothrombin time (PT)	Alkaline phosphatase
International Normalized Ratio (INR)	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
Urine Chemistry:	Amylase
pH	Gamma-glutamyl transpeptidase (GGT) (if clinically indicated)
Specific gravity	
Glucose	Misc:
Creatinine	C-reactive protein (CRP)
Total protein to creatinine ratio	Pregnancy Test (if clinically indicated)
Albumin	
Ketones	
Occult blood	
Bilirubin	
Urobilinogen	
Nitrite	
Leukocyte esterase	
Microscopic examination (if clinically indicated)	

Note: Investigators must document their review of each laboratory report by signing (or initialing) and dating each report.

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

- [redacted]

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

4.6.9 Electrocardiograms

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

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

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is > 500 ms and/or > 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QT interval corrected using Fridericia's formula (QTcF) has stabilized on two successive ECGs. The Medical Monitor should be notified. SOC treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 4.8.2. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.6.10 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.7 APACHE AND SOFA SCORES

Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) scores are for patients that are admitted into the ICU. These assessments are not required for study conduct or entry but should be collected if available. The initial scores for APACHE and SOFA should be taken within 24 hours of entry into the ICU and at specified time points as seen in Appendix 1a.

For the calculation of the initial APACHE and SOFA scores, the worst values in the first 24 hours of ICU admission should be used. SOFA scores are only for patients admitted into the ICU that have available data for calculation (i.e., particle pressure of oxygen/fraction of inspired oxygen [PaO_2/FiO_2] in mmHg). See Appendix 7 for SOFA score calculation.

4.8 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.8.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.8.2 Study Treatment Discontinuation

Patients must discontinue MHAA4549A infusion and therefore treatment if they experience any of the following:

- Infusion related reactions

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

- Pregnancy
- Serious skin/hypersensitivity reactions

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

4.8.3 Study Completion/Early Discontinuation Visit

Patients who complete all study visits through Day 30 are considered to have completed study. All patients who choose to discontinue from study early will be asked to complete the early discontinuation visit. Please see Schedule of Assessments provided in Appendix 1a for assessments performed at the Study Completion/Early Discontinuation visit.

4.8.4 Study and Site Discontinuation

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

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

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

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

MHAA4549A is not approved and is currently in clinical development. Thus, the entire safety profile is not known at this time. The safety plan for this study is based upon preclinical data and the previous Phase 1 and Phase 2a (interim) studies and is designed to ensure patient safety. It will include specific eligibility criteria and monitoring assessments as detailed below and above in Section 4.1.

The investigator, in consultation with the Sponsor, is responsible for assuring the safety of study participants who have entered this study and for taking appropriate action concerning any event that seems unusual, even if this event may be considered to be an unanticipated benefit to the study participant. The investigator will be responsible for a clinical assessment of the study participants before discharge from the study, and for the establishment of a discharge plan, if needed.

During the study, the incidence and nature of adverse events, serious adverse events, and laboratory abnormalities will be assessed. An ongoing review of safety will be performed by an internal Genentech Safety Review Committee, composed of the Medical Monitor, a drug safety scientist, and a biostatistician. External experts may be consulted as appropriate. An unblinded review of safety will be performed by an iDMC as described in Section 4.2 and the iDMC charter.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

Adverse events will be monitored throughout the entire study (enrollment through Day 30 or Early Discontinuation). If clinically significant signs or laboratory values are observed in a study participant, the investigator should repeat an assessment at the earliest opportunity. Only those events or laboratory values that exceed the level of clinical significance upon the repeat assessment will be considered an adverse event.

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug

- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS); see Section 5.3.3, Appendix 8, and Appendix 9); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Non-serious adverse events of special interest (AESI) are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study 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 (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Adverse events associated with suspected cases of infusion-related reactions (IRR) which occur within 24 hours of study drug administration and may show the following signs and symptoms (for guidance on reporting AEs associated with IRR, see Section 5.3.5.1 below):
  - Fever and/or shaking chills
  - Flushing and/or itching
  - Alterations in heart rate and blood pressure
  - Dyspnea or chest discomfort
  - Back or abdominal pain

  - Nausea, vomiting, and/or diarrhea
  - Various types of skin rashes
  - Anaphylaxis
- Anaphylaxis due to IV drugs most often presents with the following signs and symptoms:
  - Cutaneous symptoms: flushing, itching, urticaria, and/or angioedema (usually of face, eyelids, or lips)
  - Respiratory symptoms: repetitive cough, sudden nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and or change in voice quality due to laryngeal edema
  - Cardiovascular symptoms: faintness, tachycardia (or less often bradycardia), tunnel vision, chest pain, hypotension, sense of impending doom, and/or loss of consciousness
  - Gastrointestinal symptoms: such as nausea, vomiting, abdominal cramping, and diarrhea

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until the Day 30 visit or Early Discontinuation visit. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any death or other serious adverse event that occurs after discharge, regardless of causality. The Sponsor should also be notified if the investigator becomes aware of a congenital anomaly/birth

defect in a subsequently conceived offspring of a female patient exposed to study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

Investigators will seek information on adverse events and serious adverse events at each patient contact. All AEs, and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded.

The adverse event grading (severity) scale in the DAIDS v1.0 will be used for assessing AE severity (see Table 5).

Table 5 Adverse Event Grading (Severity) Scale

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical AE NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

- Temporal relationship of event onset to the initiation of study drug

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

Table 6 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Other Adverse Events

For adverse events other than infusion-related reactions, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated

transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF, unless the severity increases. If a persistent adverse event becomes more severe, it should be recorded as a separate event on the Adverse Event eCRF. The initial (less severe) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became more severe. If a persistent adverse event becomes serious, it should be recorded as a separate event on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The initial (non-serious) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became serious.

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

5.3.5.4 Abnormal Laboratory Values

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

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment (laboratory abnormalities should be repeated at the first opportunity and only considered clinically significant if they persist on repeat assessment)

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

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

- Accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment. Abnormal vital sign values should be repeated at the first opportunity and only considered clinically significant if they persist on repeat assessment)

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

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

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of severe influenza or any related co-morbidities should be recorded on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the

Adverse Event eCRF, and immediately reported to the Sponsor as an SAE (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

5.3.5.8 Pre-existing Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of Influenza A Infection

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

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care

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

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

  The patient has not experienced an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Adverse Events Associated with an Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No clinical safety data related to overdosing of MHAA4549A are available, however, overdoses with a monoclonal antibody theoretically could cause volume overload that can result in edema and/or heart failure.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

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

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results

- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/IEC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

[redacted] Medical Monitor contact information:

Primary Medical Monitor: [redacted]

Telephone Nos.: US Office: [redacted]

US Mobile: [redacted]

Secondary Medical Monitor: [redacted]

Telephone Nos.: US Office: [redacted]

US Mobile: [redacted]

Genentech Medical Monitor contact information for all sites if above medical monitor cannot be reached:

Medical Monitor: [redacted]

Telephone Nos.: US Mobile [redacted]

US Office [redacted]

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. A paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to the Sponsor's Safety Risk Management department or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided below per region:

Asia Pacific: [redacted]

Europe: [redacted]

Latin America: [redacted]

North America: [redacted]

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until the patient is at Day 30 or Early Discontinuation. Although the investigator is not required to actively monitor patients for adverse events after the patient has been discharged from the study, the Sponsor should be notified if the investigator becomes aware of any death or other serious adverse event that occurs after discharge, regardless of causality. The Sponsor should also be notified if the investigator becomes aware of a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug (see Section 5.4.3).

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

In the event that the EDC system is unavailable, a paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to investigators (see fax numbers provided in Section 5.4.2.1). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 120 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, a paper Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see fax numbers

provided in Section 5.4.2.1). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant within 30 days after the dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

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

5.4.4 Investigator Follow-Up

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

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF and the Investigator document a discharge plan.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.4.5 Sponsor Follow-Up

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

5.5 POSTSTUDY ADVERSE EVENTS

At the time of study completion or study discontinuation, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient or their personal physician believes could be related to prior study drug treatment or study procedures.

The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 30 days after the dose of study drug). However, the Sponsor should be notified if the investigator becomes aware of any death, other serious adverse event, or non-serious adverse event of special interest occurring after the end of the adverse event reporting period, regardless of causality. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient or a female partner of a male patient exposed to study drug.

The investigator should report these events by completing and faxing a paper Serious Adverse Event Reporting Form and fax cover sheet to Safety Risk Management using the fax numbers provided to investigators (see Section 5.4.2.1).

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

The Sponsor will promptly evaluate all serious adverse events including suspected unexpected serious adverse reactions (SUSARs) and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, IECs, and applicable health authorities based on applicable legislation.

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

- MHAA4549A Investigator's Brochure
- Local prescribing information for oseltamivir

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

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

Certain adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting. These anticipated events include, but are not limited to, the following:

- Elevations of ALT, AST, and or amylase that have been shown to be increased during influenza A infection (Polakos 2006)
- Influenza associated disease and or complications of influenza

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

All efficacy analyses will be conducted according to the intent-to-treat principle and will include all patients who meet the following condition with patients allocated to the treatment arm to which they were randomized:

- Randomized patients who have confirmed influenza A infection as confirmed by a central PCR test from Day 1 samples

Safety analyses will include all patients who were included in the randomization and who received at least one dose of study medication, with patients allocated to the treatment arm associated with the regimen actually received.

No formal hypothesis testing will be done in this study. As a result, no adjustment for a type 1 error will be made to account for the multiplicity of analyses.

Final efficacy and safety analyses of the total study population will be conducted at the end of the study after all patients have completed all study assessments and the database has been cleaned and closed. Further details of the analyses, including analysis of the exploratory endpoints, will be contained in the statistical analysis plan (SAP) which will be prepared and finalized before the optional interim analysis (see Section 6.7) or the final efficacy and safety analysis, if no interim analysis takes place.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is estimation of the effect size and hypothesis generation regarding the effect of MHAA4549A on the time to normalization of respiratory function relative to the standard of care rather than hypothesis testing. Point and interval

estimates will be obtained. A total of 334 patients will be enrolled in this study in order to obtain approximately 300 evaluable patients (an estimated dropout rate of 10%). It is assumed that the median time to normalization of respiratory function in the control arm is 5 days. Operating characteristics (power) for true differences of 1 to 2 days are provided in Table 7.

Table 7 Operating Characteristics for Proposed Study Design for Several Possible True Underlying Median Values

	True Underlying Median for MHAA4549A		
	3 days	3.5 days	4 days
Hazard Ratio	0.60	0.70	0.80
Power of log-rank test [a]	99%	86%	48%
95% confidence interval for true hazard ratio [b]	(0.48, 0.75)	(0.56, 0.88)	(0.64, 1.00)

Note: Operating characteristics are based on the following assumptions: 300 evaluable patients, event times are exponentially distributed, median time to normalization of respiratory function in the control arm is 5 days, and patients are followed for 30 days.

[a] Two-sided $\alpha = 0.05$.

[b] Confidence intervals are based on the assumption that the point estimate is equal to the true underlying value of the hazard ratio in each column.

It should be noted that the study is underpowered for detection of minimally clinically meaningful differences such as a true hazard ratio of 0.80 (see third column of Table 7).

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue (early discontinuation of treatment or early termination from the study), and complete the study will be tabulated by treatment group using descriptive statistics. Reasons for early discontinuation of treatment or early termination from the study will be listed and summarized by treatment group. Any eligibility criteria exceptions and other protocol deviations will also be summarized by treatment group.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics of the patient will be summarized for all randomized patients by treatment group by use of descriptive statistics. Baseline is defined as the last available value prior to study drug administration.

During the study; patient disposition, concurrent treatment, and compliance with study treatment and visits will be summarized on the safety analysis population using descriptive statistics.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized patients who are confirmed to be influenza A infected, with patients grouped according to the treatment assigned at randomization.

Time to event data will be computed using Kaplan-Meier methodology and stratified Cox proportional hazards models and will be summarized using n, median when estimable, hazard ratios, and 95% confidence intervals. Patients who are lost to follow-up (while event free) will be censored at the time that they are last known to be event free.

Estimation of the treatment difference of proportions and its 95% confidence interval will be calculated using stratum-adjusted Mantel-Haenszel methodology (Koch et al. 1989). For continuous endpoints, Analysis of Covariance methods (after appropriate transformation of data) will be used to estimate treatment differences and 95% confidence intervals.

Other than censoring in the time to event analyses, no other imputation for missing data will be performed.

6.4.1 Primary Efficacy Endpoint

- Median time to normalization of respiratory function

6.4.2 Secondary Efficacy Endpoints

- Proportion of patients with clinical failure 24 hours post-infusion of study drug
- Median time to clinical resolution of vital signs
- Hazard ratio for mortality at Day 14 and Day 30
- Mean and median AUC of viral load
- Mean and median peak viral load
- Median duration of viral shedding in upper respiratory samples
- Median duration of hospitalization
- Median duration of ICU stay
- Proportion of patients requiring antibiotics for respiratory indications during study
- Proportion of patients with influenza secondary complications
- Median duration of ventilation
- Proportion of patients who are readmitted by Day 30

6.4.3 Subgroup Analyses

Subgroup analyses will be performed to examine the consistency of the treatment estimates with use of the primary and selected secondary endpoints. Subgroups will include the stratification factors as well as patients who are identified at baseline as influenza A positive by the upper, lower, or both airways and by patients with bacterial

co-infections at admission. Additional subgroups may be added following assessment of baseline characteristics as exploratory analyses.

6.5 SAFETY ANALYSES

The safety analyses will include all randomized patients who received study drug, with patients grouped according to the treatment actually received. Safety parameters to be evaluated include adverse events (including deaths, serious adverse events, discontinuations due to adverse events, and the incidence and severity of adverse events), clinical laboratory tests, vital signs (including SpO_2 measurements), and ECGs.

All collected adverse event data will be listed by study site and patient number.
All adverse events that occur on or after treatment on Day 1 will be summarized for each treatment group by mapped term, appropriate thesaurus levels, body system, and event within each body system, and toxicity grade. In addition, all serious adverse events, including deaths, will be listed separately and summarized. SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) that occur between consent and first dose of study medication will be listed separately.

Laboratory data with values outside of the normal ranges will be identified. In addition, select laboratory data will be summarized by treatment group using descriptive summary statistics.

The absolute and percentage changes from baseline in vital sign parameters will be computed, and changes deemed clinically significant by the Investigator will be noted. Appropriate descriptive summary statistics will be provided for all vital sign parameters

6.6 PHARMACOKINETIC ANALYSES

Individual and mean serum MHAA4549A concentration versus time data will be tabulated and plotted. The serum pharmacokinetics of MHAA4549A will be summarized by estimating total serum drug exposure (i.e., AUC), C_{max}, C_{min}, total serum clearance, half-life, and volume of distribution, as data allow. Estimates for these parameters will be tabulated and summarized (e.g., mean, standard deviation, coefficient of variation). Inter-patient variability will be evaluated. MHAA4549A serum concentration–time data may be compared with available data from other MHAA4549A clinical studies.

[redacted]

[redacted]

[redacted]

6.7 OPTIONAL INTERIM ANALYSIS

To adapt to information that may emerge during the course of this study (e.g. additional results of competitor studies), the Sponsor may choose to conduct one interim efficacy analysis. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

The Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC charter will document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC charter will also be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied to determine the significance (α) level for the interim analysis (DeMets and Lan 1994). A statistically valid conclusion of positive efficacy based on an interim analysis of the specified endpoint would require a p-value below this α level. Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC charter. If the study continues beyond the interim analysis, the α level at the final analysis would be lowered accordingly to maintain the protocol-specified overall type I error rate.

If there is a potential for the study to be stopped for futility as a result of the interim analysis, the threshold for declaring futility will include an assessment of the predictive probability that the specified endpoint will achieve statistical significance. If the predictive probability is below 20%, the iDMC should consider recommending that the study be stopped for futility. Additional criteria for recommending that the study be stopped for futility may be added to the iDMC charter. An interim analysis that might lead to stopping the study for futility will not occur before at least 50% of the information has been accumulated.

If conducted, an interim analysis would be for administrative purposes only (i.e., internal planning or decision making) and would not impact the conduct of the current study in any way. A nominal type I error penalty of 0.0001 will be taken.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

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

The Consent Forms must be signed and dated by the patient or the patient's authorized representative as applicable and in accordance with local regulations, and IRB/IEC policies, before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments (see Section 9.5).

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

8.4 CONFIDENTIALITY

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

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

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate, financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the

course of the study and for 1 year after completion of the study (i.e., last patient, last visit [LPLV]).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/IEC in accordance with established IRB/IEC policies and procedures.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

Genentech, Inc., a member of the Roche group, is the Sponsor of this study. A clinical research organization (CRO) may provide clinical operations oversight, including but not limited to project management, clinical monitoring and site management, data quality support, medical monitoring, and some safety reporting and regulatory activities as specified in study management plans. Genentech will provide CRO oversight, develop the database and randomization scheme, and conduct statistical programming and analysis. An iDMC will provide an additional level of safety monitoring for the study.

EDC will be utilized for this study. An IxRS will be used to assign patient numbers, randomize patients into study, and manage site drug supply. A central laboratory will be used for sample management and storage until shipment to specialty laboratories or Genentech for analysis.

9.5 PROTOCOL AMENDMENTS

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

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

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APPENDIX 1a
Schedule of Assessments: Hospitalization Days

Notes: Unless otherwise indicated, all assessments should be performed prior to study drug administration; x's within parentheses, i.e., (x), indicate optional assessments. Please refer to Follow-up Period table for visits to be completed when patient is discharged from hospital prior to Day 30.

	Screening	Hospitalized Days (only to be completed while patients are hospitalized)													Hospital Discharge [a]	D30 Study Completion or Early Discontinuation while Hospitalized
Day (D)	D -2, -1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D14	D20	D25		
Confirm study drug administration can occur within 48 hours of hospital admission																
Informed consent [b]	x															
Rapid influenza A test [c]	x															
Local influenza A PCR test [d]	x															
Inclusion/exclusion criteria	x															
Demographic data	x															
Confirm onset of flu symptoms ($\leq$5 days prior to study drug administration on Day 1)	x															
Confirm history of baseline $SpO_2 > 92\%$	x															
Pregnancy screening [e]	x															
Confirm O_2 requirement [f]	x															
Resting oximetry reading [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
APACHE score [j]		(x^z)										(x)			(x)	(x)

APPENDIX 1a (cont'd)
Schedule of Assessments: Hospitalization Days

Day (D)	Screening	Hospitalized Days (only to be completed while patients are hospitalized)													Hospital Discharge [a]	D30 Study Completion or Early Discontinuation while Hospitalized
	D -2, -1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D14	D20	D25		
SOFA score [k]		(x^z)						(x)				(x)			(x)	(x)
Electrocardiogram (12-lead) [l]		x				x						x			x	x
Randomization		x														
MHAA4549A administration		x^m														
Oseltamivir administration [n]		x	x	x	x	x	(x)	(x)	(x)	(x)	(x)					
Complete physical examination [o]	x	(x)														
Limited, symptom-directed physical examination [p]			x	x	x	x						x			x	x
Weight & height, BMI [q]	x^q	x				x						x			x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [r]	x		x			x						x			x	x
Chemistry 20 panel [r]		x	x			x						x			x	x
Coagulation panel [r]		x				x						x			x	x
Urinalysis [r, s]		x	x			x						x			x	x
Serology (HIV)	x															
Upper respiratory tract sample (NP sample) [t]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
[redacted]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Flu antibodies (HAI)		x										x			x	x
[redacted]		x														x

APPENDIX 1a (cont'd)
Schedule of Assessments: Hospitalization Days

Day (D)	Screening	Hospitalized Days (only to be completed while patients are hospitalized)													Hospital Discharge [a]	D30 Study Completion or Early Discontinuation while Hospitalized
	D -2, -1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D14	D20	D25		
Serum for MHAA4549A PK measurements [v]		x	x	x		x		x				x			x	x
[redacted]		x				x									(x)[x]	
[redacted]		x	x	x		x		x			x	x	x	x	x	x
[redacted]		x	x	x		x		x			x	x	x	x	x	x
[redacted]		x													x	x
[redacted]		x														x
[redacted]		x													x	x
[redacted]		x													x	x
[redacted]															x	

[redacted]; APACHE = Acute Physiology and Chronic Health Evaluation; ATA = Anti-therapeutic antibodies; BMI = body mass index; D = day; Dx = diagnostics; eCFR = electronic Case Report Form; ECG = electrocardiogram; HAI = hemagglutinin inhibition; [redacted]; ICU = Intensive Care Unit; IRB/IEC = Independent Review Board/Independent Ethics Committee; NAI = neuraminidase inhibitor; NP = nasopharyngeal; O_2 = oxygen; PaO_2/FiO_2 = particle pressure of oxygen/fraction of inspired oxygen; PCR = polymerase chain reaction; PD = pharmacodynamics; PK = pharmacokinetic; PPV = positive pressure ventilation; qPCR = quantitative Polymerase Chain Reaction; RBCs = red blood cells; SOFA = Sequential Organ Failure Assessment; SpO_2 = oxygen saturation; WBCs = white blood cells.

[a] Assessments to be performed irrespective of day of discharge. Assessments on discharge day will supersede assessments for matching day except for the study completion/early term visit.

[b] Informed consent must be obtained from all patients. For patients who are unable to consent, an authorized representative may be used if allowed by local regulations and IRB/IEC policy.

[c] Sponsor-supplied rapid influenza test using nasopharyngeal swabs.

APPENDIX 1a (cont'd)
Schedule of Assessments: Hospitalization Days

[d] If the Sponsor-supplied rapid influenza test is negative, local influenza PCR testing can be used to confirm influenza A and satisfy entry criteria if results are received within screening/hospitalization window (48 hours)

[e] A urine pregnancy test should be sent only for women considered by the investigator to be of childbearing potential, see exclusion criteria. This result must be available prior to randomization. If urine testing is not available at the site, blood already collected from an existing sample may be tested for pregnancy.

[f] Confirm patient requires supplement O_2 or PPV with 24 hours of hospitalization. .

[g] All patients will have their on-study SpO_2 recorded daily in the morning between 4 am – 10 am local time; screening SpO_2 may be taken outside this window. Patients on low flow O_2 should have a daily trial of their SpO_2 while on and off the supplementation and both values will be recorded.

[h] Concomitant medications should be recorded for 30 days prior to screening, through the study completion/early discontinuation visit. See exclusion criteria in Section 4.5.2 for prohibited therapies.

[i] Vital signs will be collected within 1 hour before MHAA4549A infusion and within 1 hour after completion of MHAA4549A infusion include temperature, respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure. Temperature should be measured using the same methodology throughout the study and should be measured prior to administration of any antipyretic drugs. In patients who have multiple vital signs taken during any day, the most abnormal value should be recorded from that 24-hour period. Temperature, blood pressure, respiratory rate, and heart rate will be completed after the patient has been supine for > 5 minutes.

[j] APACHE scores are optional and only for patients that are in the ICU. For calculation of the screening APACHE score, the worst values in the preceding 24 hours should be used. APACHE scores are not required for study conduct or entry but should be collected if available.

[k] SOFA scores are only for patients in the ICU that have available data such as PaO_2/FiO_2 (mmHg). See Appendix 7 for SOFA score calculation.

[l] Patient should rest in a supine position for 10 minutes prior.

[m] Patient will be a resident for at least 24 hours following administration of MHAA4549A.

[n] Oseltamivir must be given for a minimum of 5 days. Treatment longer than 5 days is permitted based on the discretion of the investigator [indicated by (x)].

[o] Complete physical examination includes evaluations of general appearance of head, eye, ear, nose, and throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as adverse events, if appropriate.

[p] Limited, symptom-directed physical examination includes, at a minimum, evaluation of general appearance, dermatological examination of the injection sites, evaluations directed by patient-reported symptoms, and any other evaluations that the investigator deems clinically relevant. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as adverse events, if appropriate.

[q] Height will be obtained at screening only. Weight will be obtained at all indicated visits. Height and weight will be recorded in centimeters and kilograms, respectively. The eCRF will calculate BMI.

[r] Local laboratory measurements should be utilized.

[s] Urinalysis includes pH, specific gravity, glucose, creatinine, total protein to creatinine ratio, albumin, ketones, occult blood, bilirubin, urobilinogen, nitrite, and leukocyte esterase. Microscopic examination (e.g., sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) will be performed if clinically indicated.

[redacted]

[v] Day 1 serum PK samples are to be drawn 30 (± 5) minutes pre-dose of MHAA4549A, 60 (± 15) minutes after the end of infusion. PK samples will be drawn from the contralateral arm from that used for drug infusion and must be labeled with the exact time of draw.

[redacted]

[x] If patient is discharged on or before Day 5, the oseltamivir PK sample should be taken on the discharge day.

[redacted]

[z] Assessment to be conducted based on entry into ICU; may vary from patient to patient.

APPENDIX 1b
Schedule of Assessments: Follow-Up Period

- If a patient is discharged prior to Day 14, he/she will need to complete the following assessments for Day 14 and Day 30 below.
- If a patient is discharged prior to Day 30 and after Day 14, he/she will need to complete the following assessments for Day 30 below.
- If patient is hospitalized for Day 14, and/or Day 30, please refer to Appendix 1a.

Day (D)	D14 ± 1 (If Discharged BEFORE D14)	D30 ± 4 (Study Completion) or Early Discontinuation
Concomitant medications [a]	x	x
Vital signs [b]	x	x
Electrocardiogram (12-lead) [c]	x	x
Weight & height, BMI [d]	x	x
Adverse events	x	x
Hematology [e]	x	x
Chemistry 20 panel [e]	x	x
Coagulation panel [e]	x	x
Urinalysis [e]	x	x
Flu antibodies (HAI)	x	x
[redacted]		x
Serum for MHAA4549A PK measurements [f]	x	x
[redacted]	x	x
[redacted]	x	x
[redacted]		x
[redacted]		x
[redacted]		x
[redacted]		x

APPENDIX 1b (cont'd)
Schedule of Assessments: Follow-up Period

[redacted]; ATA = Anti-therapeutic antibodies; BMI = body mass index; D = day; Dx = diagnostics; eCFR = electronic Case Report Form; ECG = electrocardiogram; HAI = hemagglutinin inhibition; [redacted] PD = pharmacodynamics; PK = pharmacokinetic.

[a] Concomitant medications should be recorded for 30 days prior to screening, through the study completion/early discontinuation visit. See exclusion criteria in Section 4.5.2 for prohibited therapies.

[b] Vital signs include temperature, respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure. Temperature should be measured using the same methodology throughout the study and should be measured prior to study drug administration of any antipyretic drugs. In patients who have multiple vital signs taken during any day, the most abnormal value should be recorded from that 24-hour period. Temperature, blood pressure, respiratory rate, and heart rate will be completed after the patient has been supine for > 5 minutes.

[c] ECG should be recorded after the patient has rested in a supine position for 10 minutes.

[d] Height will be obtained at screening only. Weight will be obtained at all indicated visits. Height and weight will be recorded in meters and kg, respectively. The eCRF will calculate BMI.

[e] Local laboratory measurements should be used.

[f] PK samples should be drawn from the contralateral arm from the one used for drug infusion and must be labeled with the exact time of draw.

[redacted]

APPENDIX 2
Time to Normalization of Respiratory Function

For the purposes of this study, the time to normalization of respiratory function will be defined as the time to removal of the patient from O_2 supplementation in order to maintain an $SpO_2 > 95\%$.

Patients who are on low flow O_2 (2-6L/min) should receive a daily trial off O_2 in the morning between 4 am – 10 am as described below.

1. Patient should be resting or sitting.

2. Patient should be fitted with pulse oximeter, and their SpO_2 should be checked once while on O_2 and then again a minute after turning off O_2 supplementation.

3. If the $SpO_2 > 95\%$, then the time and reading should be recorded. Notify the study doctor so that he/she can make a clinical judgment to determine whether the O_2 can be removed.

4. If the patient is off O_2 for 24 hours and his/her reading the subsequent day is >95%, then the endpoint is considered satisfied. The recorded time for the endpoint corresponds with the initial discontinuation of O_2 and reading.

APPENDIX 3

[redacted]

APPENDIX 4

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX 5

[redacted]

APPENDIX 6

[redacted]

APPENDIX 7
SOFA Score Calculation

Administration of MHAA4549A will be performed in a setting with emergency medical equipment and personnel who are trained to monitor for and respond to medical emergencies. A qualified physician will be on site during study drug administration for all patients.

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Airway management equipment
- O_2
- Epinephrine 1:1000 solution for intravenous (IV) or endotracheal injection
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

1. Stop the study drug infusion.
2. Maintain an adequate airway.
3. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations.

APPENDIX 8
DAID Toxicity Grading Tables for Clinical Abnormalities

From the FDA Guidance document 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials' (September 2007)

Vital Signs [a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) [b] (°F)*	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40.0 102.1 – 104.0	>40 >104
Tachycardia – beats per minute	101- 115	116 – 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia – beats per minute [c]	50 – 54	45 – 49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) – mmHg	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mmHg	91 – 95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mmHg	85 – 89	80 – 84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	>25	Intubation

[a] Subject should be at rest for all vital sign measurements.

[b] Oral/tympanic temperature; no recent hot or cold beverages or smoking.

[c] When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

APPENDIX 8 (cont'd)
DAID Toxicity Grading Tables for Clinical Abnormalities

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/ vomiting	No interference with activity or 1 – 2 episodes/ 24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 g/ 24 hours	4 – 5 stools or 400 – 800 g/ 24 hours	5 or more watery stools or > 800 g/ 24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity no requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

APPENDIX 9
DAID Toxicity Grading Tables for Laboratory Abnormalities

Adapted from Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007 DRAFT and FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials

Abbreviations used in the table:
[redacted]; CPK = creatine phosphokinase; Dec = Decreased; IV = Intravenous; LLN = Lower limit of normal; Mod = Moderate; Req = Required; Rx = Therapy; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = Upper limit of normal.

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 – 10.5 g/dL	8.0 – 9.4 g/dL	6.5 – 7.9 g/dL	<6.5 gm/dL
Absolute Neutrophil Count	1,000 – 1,500/mm^3	750 – 999/mm^3	500 – 749/mm^3	<500/mm^3
*Platelets	125,000 – 140,000/mm^3	100,000 – 124,999/mm^3	25,000 – 99,999/mm^3	<25,000/mm^3
WBCs	11,000 – 13,000/mm^3	13,000 – 15,000/mm^3	15,000 – 30,000/mm^3	>30,000 or <1,000/mm^3
*Lymphocytes Decrease – cell/mm^3	750 – 1,000	500 – 749	250 – 499	<250
*Eosinophils – cell/mm^3	650 – 1500	1501 – 5000	>5000	Hypereosinophilic
Abnormal Fibrinogen	Low: 100 – 200 mg/dL High: 400 – 600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: <50 mg/dL	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20 – 40 mcg/mL	41 – 50 mcg/mL	51 – 60 mcg/mL	>60 mcg/mL
Prothrombin Time (PT)	1.01 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin Time (APTT)	1.01 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3 x ULN	>3 x ULN
Methemoglobin	5.0 – 9.9%	10.0 – 14.9%	15.0 – 19.9%	>20.0%

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

APPENDIX 9 (cont'd)
DAID Toxicity Grading Tables for Laboratory Abnormalities

CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130 – 135 mEq/L	123 – 129 mEq/L	116 – 122 mEq/L	<116 mEq/L or abnormal sodium with mental status changes or seizures
Hypernatremia	146 – 150 mEq/L	151 – 157 mEq/L	158 – 165 mEq/L	>165 mEq/L or abnormal sodium with mental status changes or seizures
Hypokalemia	3.0 – 3.4 mEq/L	2.5 – 2.9 mEq/L	2.0 – 2.4 mEq/L or intensive replacement therapy or hospitalization required	<2.0 mEq/L or abnormal potassium with paresis ileus or life-threatening arrhythmia
Hyperkalemia	5.6 – 6.0 mEq/L	6.1 – 6.5 mEq/L	6.6 – 7.0 mEq/L	>7.0 mEq/L or abnormal potassium with life-threatening arrhythmia
Hypoglycemia	55 – 64 mg/dL	40 – 54 mg/dL	30 – 39 mg/dL	<30 mg/dL or abnormal glucose with mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 – 160 mg/dL	161 – 250 mg/dL	251 – 500 mg/dL	>500 mg/dL or abnormal glucose with ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 – 7.8 mg/dL	7.7 – 7.0 mg/dL	6.9 – 6.1 mg/dL	<6.1 mg/dL or abnormal calcium with life threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6 – 11.5 mg/dL	11.6 – 12.5 mg/dL	12.6 – 13.5 mg/dL	>13.5 mg/dL or abnormal calcium with life-threatening arrhythmia
Hypomagnesemia	1.4 – 1.2 mEq/L	1.1 – 0.9 mEq/L	0.8 – 0.6 mEq/L	<0.6 mEq/L or abnormal magnesium with life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 – <1.25 x ULN	1.25 – <1.5 x ULN	1.5 – 1.75 x ULN	>1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 – <1.5 x ULN	1.5 – <2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

APPENDIX 9 (cont'd)
DAID Toxicity Grading Tables for Laboratory Abnormalities

ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 – 8.0 x ULN	>8.0 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 – 8.0 x ULN	>8.0 x ULN
GGT	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 – 8.0 x ULN	>8.0 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 – 8.0 x ULN	>8.0 x ULN
Amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	>5.1 x ULN
Lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	>5.1 x ULN
*CPK – mg/dL	1.25 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 10.0 x ULN	>10 x ULN

*From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg – 1 g loss/day	2-3+ or 1-2 g loss/day	4+ or 2-3.5 g loss/day	Nephrotic syndrome or >3.5 g loss/day
Hematuria	Microscopic only <10 rbc/hpf	Gross, no clots >10 rbc/hpf	Gross, with or without clots, OR red blood casts	Obstructive or required transfusion
*Glucose	Trace	1+	2+	Hospitalization for hyperglycemia

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

PROTOCOL

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY, IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION**
PROTOCOL NUMBER:	GV29216
VERSION NUMBER:	2
EUDRACT NUMBER:	2014-000461-43
IND NUMBER:	117,318
TEST PRODUCT:	MHAA4549A
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	30 May 2014
DATE AMENDED:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	14-Aug-2014 21:44:24

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PROTOCOL AMENDMENT RATIONALE:
VERSION 2 AMENDMENT

RATIONALE

Protocol GV29216 was amended in Version 2 to reflect the following changes:

- More frequent review of safety data will be facilitated by employing an Internal Monitoring Committee (IMC) in combination with a Scientific Oversight Committee (SOC) rather than a single Independent Data Monitoring Committee (iDMC)
- Allowing the inclusion of patients diagnosed with influenza A as determined by a Sponsor-supplied rapid influenza test and/or local molecular test (PCR) allows enrollment flexibility.
- Allowing the Sponsor to choose to conduct up to two interim analyses to assess safety and efficacy was for administrative purposes only.
- Adding a Day 60 timepoint allows for a longer follow up period.
- Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary as well as empty (used) oseltamivir packets and unused oseltamivir capsules to the study site at the next follow up visit. Patients will record the date and time when each oseltamivir capsule is administered. This allows the capture of oseltamivir administration after hospital discharge.
- Patients who are on low-flow oxygen should receive a daily trial off oxygen in the morning between 6 am and 12 pm. Patients should be fitted with pulse oximeter, and their SpO_2 should be checked once while on oxygen and then again 3-5 minutes after turning off oxygen supplementation. The time change will give a more accurate oximeter reading.
- Updated background clinical safety and efficacy data from the Phase 2a challenge study (GV28985) were added to provide investigators with the most current information concerning MHAA4549A.
- Updated Genentech Medical Monitor and contact information was added since the Medical Monitor has changed for this project.
- Updated randomization of patients will be managed by a central Interactive Voice and Web Response System through the use of a dynamic hierarchical algorithm.

The Sponsor considers that changes in this amendment will increase the safety monitoring in this Phase 2b study without any significant impact on the scientific value of the trial, nor will they have any significant impact on the safety or mental or physical integrity of study patients.

SUMMARY OF CHANGES:
VERSION 2 AMENDMENT

COVER PAGE

[redacted], M.D~~., Ph.D~~.

Genentech, Inc~~./Roche Registration Ltd.~~.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol.

GENERAL REVISIONS

The following changes were made consistently throughout the protocol:

- The meaning of the abbreviation "SOC" was changed from "standard of care" to "Scientific Oversight Committee." "Standard of care" was spelled out throughout the protocol.
- A Day 60 visit was added to the study. Text was revised or added, as appropriate, throughout the protocol to account for this addition.
- "DAID" was changed to "DAIDS" throughout the protocol.

SECTION 1.2: BACKGROUND ON MHAA4549A

This section was updated to include recently available data from Studies GV28916 and GV28985. Three subsection headers were added to organize the section. Data was also revised or added to Table 1.

SECTION 1.3.1: Study Rationale

~~Preliminary~~ Data from the Phase 2a study also provides evidence that the 3600 mg dose of MHAA4549A is effective in reducing viral titers in healthy volunteers inoculated with influenza A virus.

SECTION 1.3.2.1: Treatment in Combination with Oseltamivir

All patients in the study will receive *oseltamivir as* the current ~~SOC~~*standard of care* treatment ~~of oseltamivir~~ *,* either with or without MHAA4549A. Therefore, *at a minimum,* all patients ~~at minimum~~ will be treated with ~~SOC~~*standard of care* for influenza. Given that MHAA4549A is an antibody, the potential for *a drug-drug* interaction with oseltamivir is very low. In the ongoing Phase 2a challenge study (GV28985), ~~several~~ study subjects received MHAA4549A followed by oseltamivir with no AEs attributable to the combination therapy noted to date. In addition, *in this study* the PK profile of oseltamivir in concomitantly treated subjects will be assessed.

SECTION 1.3.2.3: Rational for Selection of Phase 2b Population

- Clinical safety data for MHAA4549A demonstrate a well-tolerated safety profile. ~~There were mild, related~~
    - AEs ~~observed~~ in the Phase 1 study (GV28916) *were mild* and ~~MHAA4549A was well tolerated.~~ *did not show a dose relationship; there were* no ATAs ~~were~~ detected~~. Safety data from~~ *in patients treated with MHAA4549A.*
    - *In* the ongoing Phase 2a ~~challenge~~ study (GV28985~~) was~~*), MHAA4549A was generally well tolerated. A few subjects in all treatment groups were* observed to have ~~mild and moderate~~ transient elevations in alanine transaminase (ALT), aspartate transaminase *(*AST*)*, and amylase *levels* ~~that may be related to either MHAA4549A or to influenza infection.~~*)*. There was no dose-dependent relationship of *the ALT/AST/amylase* elevations with MHAA4549A and the overall event rate was in line with ~~that of previous challenge studies (~~*published rates associated with the influenza challenge model regardless of treatment arm:* 27/100 [27%] in ~~the study~~*GV28985* vs. approximately 26~~%)~~ *(% in previous challenge studies (*Polakos 2006). *There were* no SAEs ~~that were~~ related to study drug were ~~observed. Testing for ATAs in Study GV28985 has not yet been concluded.~~ *There were a total of 3 SAEs unrelated to MHAA4549A in two subjects. One subject reported depressive psychosis associated with influenza. There were a total of 3 SAEs unrelated to MHAA4549A in two subjects. One subject reported depressive psychosis associated with influenza. The second subject reported a broken knee with a subsequent infection following a surgical procedure.*
- *Interim efficacy data in* the Phase 2a challenge study (GV28985) ~~interim efficacy data~~ demonstrated a significant decrease in viral shedding in the upper respiratory tract at the 3600 mg dose. There was a 97.5% (p=0.~~0092~~*0051*) decrease in the area under viral load–time curve (AUEC) and a 77% (p=0.~~0054~~*0024*) decrease in peak viral load by qPCR measurement in comparison to the placebo group, thus confirming proof of antiviral activity at the 3600 mg dose level. *Symptom data in the Phase 2a study showed a decrease in the AUC of symptoms scores for the 3600-mg dose that is consistent with the virological results as illustrated in Table 1.*

SECTION 1.3.2.4: Patient Monitoring and Supervision

~~An independent Data Monitoring Committee (iDMC) will evaluate the safety of MHAA4549A at a timepoint to be specified in the iDMC charter.~~*An internal monitoring committee (IMC) in combination with a scientific oversight committee (SOC) will provide safety monitoring for the study in addition to the ongoing review of safety by the Medical Monitor and Safety Scientist. See Section 3.1.2 for more information.*

The 120-day follow-up period in the Phase 1 and 2a studies allowed for monitoring of subjects for approximately 5 half-lives of ~~the study drug.~~*MHAA4549A.* No ATAs were detected in the Phase 1 study, ~~and the ATA testing for~~*while one subject in* the Phase 2a study ~~is ongoing.~~*tested positive for ATAs at baseline and post-baseline timepoints as described in Section 1.2.2.* The Phase 2b study will also include *a* safety follow-up

period of ~~up to 30~~ *60* days and an unlimited collection of all SAEs believed related to MHAA4549A.

SECTION 3.1.1: Overview of Study Design

At the time of randomization, patients who are eligible for enrollment*,* as described above, will be randomized to receive MHAA4549A at a dose of 3600 mg or placebo. Patients will be stratified by ~~country~~*site*, PPV versus supplemental O_2 ~~on the day of admission~~*at randomization*, and suspected or confirmed bacterial pneumonia versus no bacterial pneumonia based on the status ~~on the day of admission~~*at randomization*.

A follow-up study visit should occur on Day 14 ± 1 (if discharged before Day 14~~) and~~*);* Day 30 ± 4 days~~,~~ *(*if discharged before Day 30~~.~~*); and Day 60 ±4 days (if discharged before Day 60).*

Safety evaluations will be provided by an IMC and SOC, as defined in the IMC and SOC agreement (see Section 3.1.2)

SECTION 3.1.2: ~~Independent Data Monitoring Committee~~ *Independent Monitoring Committee and Scientific Oversight Committee*

Text describing the Independent Data Monitoring Committee and its function was replaced with text describing an Independent Monitoring Committee and a Scientific Oversight Committee and their respective functions.

~~An iDMC, which consists of two independent physicians and one independent biostatistician, will review safety data of the trial to ensure the safety of the patients enrolled. This should allow early detection of any potential safety concern and, thus, ensure the best possible protection of patients' safety. In addition, it includes a non-voting biostatistician from an independent data coordinating center (IDCC) who prepares the safety reports, including information on patient accrual and SAEs from the study. The iDMC reviews the safety reports, addresses any safety concerns, and informs the Sponsor whether or not to continue the study.~~

SECTION 3.2.2: Rationale for Patient Population and Primary Endpoint

Severe influenza, for the purpose of this study, is defined as requiring one of the following treatments: ~~PPV or~~ any supplemental O_2 to maintain an $SpO_2 > 92$~~%.~~*% or PPV.* PPV is defined as any mechanical positive pressure device to maintain oxygenation; this can include ~~mask ventilation~~ *positive pressure mask* and intubation.

SECTION 3.2.4: Rationale for MHAA4549A Dosage

~~The dose is adequately supported by safety data from the completed Phase 1 study and ongoing Phase 2a study in healthy volunteers, which has completed dosing..~~
MHAA4549A was shown to be safe and well-tolerated at all dose levels (ranging from

1.5 mg/kg to 45 mg/kg for Phase 1 and 400-3600 mg for Phase 2a) through a follow-up period of 120 days post-dose in the Phase 1 *and Phase 2a* study. The dose level used in this study was determined following ~~an interim~~ analysis of ~~the 1200-mg and 3600-mg doses in~~*data from* the Phase 2a study, GV28985, which demonstrated the following:

- The 3600-mg dose demonstrated a significant decrease in viral shedding in upper respiratory samples. Based on current interim analysis data, there was a 97.5% (p=0.~~0092~~*0051*) decrease in AUEC and a 77.3% decrease in peak viral load by qPCR measurement compared to the placebo group.
- *Symptom data in the Phase 2a study showed a decrease in the AUC of symptoms scores for the 3600-mg dose, as illustrated in Table 1, which is consistent with the virological results.*
- Hospitalized patients generally have a longer duration of viral shedding and significantly more viral burden in the lower lung compartments; therefore, high concentrations of mAb are likely needed to achieve sufficient occupancy of the virus binding sites in the upper and lower respiratory compartments. Furthermore, higher concentrations of mAb are necessary to mitigate the risk of resistance for MHAA4549A ~~and neuramin*i*dase inhibitors such as oseltamivir~~.

SECTION 3.3.3: Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- Clinical failure *after* 24 hours post-infusion of study drug; defined as:

SECTION 3.3.5: Secondary Efficacy Outcome Measures

The exploratory outcome measures for this study are as follows:

[redacted]

SECTION 4.1.1: Inclusion Criteria

- Diagnosis of influenza A *where one or both of the following are used as aid(s) in diagnosis:*~~as determined by the Sponsored-supplied rapid influenza test~~
  - ~~If negative~~*A Sponsor-supplied* rapid influenza ~~A~~ test~~, a positive~~
  - *A* local molecular ~~test~~ (PCR) ~~is required~~ *test*

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The randomization of patients will be managed by a central Interactive Voice and Web Response System (IxRS) *through use of a dynamic hierarchical algorithm. The treatment assignments will be unblinded to selected Sponsor personnel to facilitate ongoing monitoring of safety and tolerability, including members of the IMC and SOC.*

All patients will be randomly assigned to receive either MHAA4549A 3600 mg or placebo at a 1:1 ratio stratified by ~~country~~*site*, whether patient is on PPV vs supplemental O_2 ~~on the day of admission~~*at randomization*, and whether the patient has suspected or

confirmed bacterial pneumonia vs no bacterial pneumonia ~~on the day of admission.~~*at randomization.* All patients will receive oseltamivir (75 mg or 150 mg BID) for a minimum of 5 days. Treatment for longer than 5 days is permitted based on local investigator discretion.

~~The treatment assignments will be unblinded to an external IDCC to facilitate the iDMC assessment of safety.~~

SECTION 4.3.2.2: Oseltamivir-Neuraminidase Inhibitor (NAI)

Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary, empty (used) oseltamivir packets and unused oseltamivir capsules to the study site at the next follow up visit. Patients will record the date and time when each oseltamivir capsule is administered.

SECTION 4.6.2: Diagnostic Testing for Enrollment

Patients may be enrolled based on a positive local molecular test (PCR) result within the 48-hour screening window, but the rapid influenza test must still be conducted prior to randomization.

SECTION 4.6.7: Oxygen Saturation Measurements

Unless clinically contraindicated, all patients will have their SpO_2 *and corresponding respiratory assessments* recorded daily in the morning between ~~4~~ *6* am – ~~10 am~~*12 pm* local time.

If the patient is on oxygen supplementation, SpO2 measured by pulse oximetry and the corresponding respiratory assessments (e.g. FiO_2, flow rate) will be recorded. If the patient is on PPV, partial pressure of O2 (PaO_2) and the corresponding respiratory assessments (e.g. FiO_2, ventilator mode, ventilator respiratory rate, positive end-expiratory pressure) will be recorded.

SECTION 4.6.8: Laboratory, Biomarker, and Other Biological Samples

Table 3 (Laboratory Tests at Screening) was revised to remove the chemistry panel, coagulation tests, and the urinalysis at screening. "Bands" were added to the hematology tests. The table was reorganized because of the deletions.

Table 4 (Laboratory Tests During the Study) was revised to remove creatinine, total protein-to-creatinine ratio, albumin, and urobilinogen from the urinalysis. "Bands" were added to the hematology tests; "random" was removed from glucose; and "or urea" was added after urea nitrogen (BUN). The table was reorganized because of the deletions.

SECTION 4.6.9: Electrocardiograms

If QTcF is not available, QTcB may be recorded. ~~SOC~~*Standard of care* treatment may be instituted per the discretion of the investigator.

The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, ~~co~~ medications known to prolong the QT interval, severe bradycardia).

SECTION 4.6.10: [redacted]

SECTION 4.6.10.1: [redacted]

SECTION 4.6.10.2: [redacted]

SECTION 4.6.10.3: [redacted]

SECTION 4.8: *OSELTAMIVIR MEDICATION DIARY*

Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary, empty (used) oseltamivir packets, and unused oseltamivir capsules to the study site at the next follow up visit.

Patients will record the date and time when each oseltamivir capsule is administered.

SECTION 4.9.2: Study Treatment Discontinuation

The IMC and SOC may recommend permanently discontinuing dosing for all patients within one or both study arms in the event of a general safety concern.

SECTION 4.9.3: Study Completion/Early Discontinuation Visit

Patients who complete all study visits through Day ~~30~~*60* are considered to have completed study. All patients who ~~choose to~~ discontinue from *the* study early will be asked to complete *all assessments for the current visit day and for* the early discontinuation visit~~.~~ *without duplication.*

SECTION 5.1: STUDY PLAN

During the study, the incidence and nature of adverse events, serious adverse events, and laboratory abnormalities will be assessed. An ongoing *blinded* review of safety will be ~~performed~~*carried out* by ~~an internal Genentech Safety Review Committee, composed of~~ the Medical Monitor~~, a~~ *and a* drug safety scientist~~, and a biostatistician. External experts may be consulted as appropriate.~~. An unblinded review of safety will be performed ~~by an iDMC~~ *on an ongoing regular basis by the IMC and SOC* as described in ~~Section~~ *the IMC* and ~~the iDMC charter.~~ *SOC agreement.*

SECTION 5.3.5.6: Abnormal Liver Function Tests

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq$35% is direct bilirubin)

SECTION 5.4.2.2: Events That Occur after Study Drug Initiation

Although the investigator is not required to actively monitor patients for adverse events after the patient has been discharged from the study, the Sponsor should be notified if the investigator becomes aware of any death or other serious adverse event that occurs after discharge *from the study*, ~~regardless of causality~~ *if determined to be related to study drug by the investigator.*

SECTION 5.6: EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

- *Asymptomatic e*~~E~~levations of ALT, AST, and or amylase *without corresponding elevations of bilirubin* ~~that~~ have been shown to be increased during influenza A infection (Polakos 2006)

An ~~iDMC~~*IMC and SOC* will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

SECTION 6.1: DETERMINATION OF SAMPLE SIZE

This sample size provides 78% power to detect a treatment difference of 1 day for the primary endpoint assuming a 2-sided alpha of 0.2.

Operating characteristics (power) *under other possible assumptions for 2-sided alpha of 0.05 and* ~~for~~ true differences of 1 to 2 days are provided in Table 7.

It should be noted that the study is underpowered for detection of minimally clinically meaningful differences *at a 2-sided alpha of 0.05* such as a true hazard ratio of 0.80 (see third column of Table 7.

SECTION 6.7: OPTIONAL INTERIM ANALYSIS

~~To adapt to information that may emerge during~~*Given* the ~~course~~*hypothesis-generating nature* of this study ~~(e.g. additional results of competitor studies),~~ the Sponsor may choose to conduct ~~one~~*up to two* interim efficacy ~~analysis. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when~~ *analyses. The decision to conduct* an optional interim analysis ~~is executed.Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group~~ and ~~reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter.~~

~~The decision to conduct the optional interim analysis, along with the rationale,~~ *the* timing~~,~~ ~~and statistical details for~~ *of* the analysis~~,~~ will be documented in the ~~SAP, and the SAP will be submitted to relevant health authorities at least 2 months~~*Sponsor's trial master file* prior to the conduct of the interim analysis. ~~The iDMC charter will document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC charter will also be made available to relevant health authorities.~~

~~If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan DeMets α spending function that approximates the O'Brien Fleming boundary will be applied to determine the significance (α)~~ *The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel who will be unblinded at the treatment group* level ~~for the interim analysis (). A statistically valid conclusion of positive efficacy based on an interim analysis of the specified endpoint would require a p value below this α level. Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC charter. If the study continues beyond the interim analysis, the α level at the final analysis would be lowered accordingly to maintain the protocol specified overall type I error rate.~~

~~If there is a potential for the study to be stopped for futility as a result of the interim analysis, the threshold for declaring futility will include an assessment of the predictive probability that the specified endpoint will achieve statistical significance. If the predictive probability is below 20%, the iDMC should consider recommending that the study be stopped for futility. Additional criteria for recommending that the study be stopped for futility may be added to the iDMC charter. An interim analysis that might lead to stopping the study for futility will not occur before at least 50% of the information has been accumulated~~. *Access to treatment assignment information will follow the Sponsor's standard procedures.*

SECTION 9.4: ADMINISTRATIVE STRUCTURE

An ~~iDMC~~*IMC and SOC* will provide ~~an additional level of~~ safety monitoring for the study *in addition to the ongoing review of safety by the Medical Monitor and Safety Scientist.*

EDC will be utilized for this study. An IxRS will be used to assign patient numbers, randomize patients into study *through use of a dynamic hierarchical algorithm*, and manage site drug supply.

APPENDICES 1a and 1b: Schedule of Assessments

Tables and footnotes were revised to reflect the changes to the protocol. In addition, two rows were added to the table for the following optional tests: erythrocyte sedimentation rate and C-reactive protein.

APPENDIX 2: Time to Normalization of Respiratory Function

Patients who are on low flow O_2 (2-6L/min) should receive a daily trial off O_2 in the morning between ~~4~~ *6* am – ~~10 am~~*12 pm* as described below.

Patient should be resting or sitting.

Patient should be fitted with pulse oximeter, and their SpO_2 should be checked once while on O_2 and then again ~~a minute~~*3 – 5 minutes* after turning off O_2 supplementation.

APPENDIX 3: [redacted]

APPENDIX 4: [redacted]

[redacted]

APPENDIX 5: [redacted]

[redacted]

APPENDIX 7: SOFA Score Calculation

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- *Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice*
- ~~Epinephrine 1:1000 solution for intravenous (IV) or endotracheal injection~~

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

Additional minor changes have been made to improve clarity and consistency. The amendment number was updated throughout the protocol. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY, IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION**
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IND NUMBER:	117,318
TEST PRODUCT:	MHAA4549A
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND *PLACEBO-CONTROLLED* TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION**
PROTOCOL NUMBER:	GV29216
VERSION NUMBER:	*2*
EUDRACT NUMBER:	2014-000461-43
IND NUMBER:	117,318
TEST PRODUCT:	MHAA4549A
INDICATION:	INFLUENZA A
SPONSOR:	Genentech, Inc.

Objectives

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety of MHAA4549A in combination with oseltamivir compared with placebo and oseltamivir in patients with severe influenza A, focusing on the nature, frequency, and severity of serious and non-serious adverse events, as well as effects on laboratory values, vital signs, electrocardiogram (ECG) parameters, anti-therapeutic antibodies (ATA), or other safety biomarkers

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To determine the time to normalization of respiratory function of patients dosed with MHAA4549A in combination with oseltamivir compared to patients dosed with placebo and oseltamivir

The secondary efficacy objectives for this study are as follows:

- To measure clinical failure after 24 hours post-infusion of study drug
- To determine the time to clinical resolution of vital signs
- To measure mortality in patients
- To determine changes in the extent and duration of viral shedding in upper respiratory samples
- To measure the duration of hospital and/or intensive care unit (ICU) stay
- To measure antibiotic usage for respiratory indications
- To measure the frequency and severity of the following secondary complications of influenza:
  - Pneumonia (hospital acquired pneumonia [HAP]/ ventilator acquired pneumonia [VAP])
  - Exacerbations of chronic lung disease
  - Myocarditis
  - Acute respiratory distress syndrome (ARDS)

  - Otitis media
  - Other related complications
  - Readmission rates at 30 *and 60* days after study treatment
- To measure duration of positive pressure ventilation (PPV)
- To measure readmission rates

Pharmacokinetic Objectives

The major pharmacokinetic (PK) objective for this study is as follows:

- To characterize the PK profile of MHAA4549A in serum

The exploratory PK objectives for this study are as follows:

[redacted]

Exploratory Objectives

The exploratory objectives for this study are as follows:

[redacted]

Study Design

Description of Study

This is a Phase 2b randomized, double-blind, placebo-controlled study designed to assess the safety and clinical activity of a single IV dose of MHAA4549A in hospitalized patients with severe influenza A in combination with oseltamivir versus a comparator arm of oseltamivir with placebo.

Patients will be randomized 1:1 into two treatment groups: a single intravenous (IV) dose of 3600 mg of MHAA4549A with oseltamivir or a single IV dose of placebo with oseltamivir. All patients will receive oseltamivir, a NAI, as standard therapy for a minimum of 5 days, starting after study drug administration. Oseltamivir at doses of 75 mg twice daily (BID) or 150 mg BID is permitted in order to be consistent with local standard of care practice. Treatment for longer than 5 days is permitted based on local investigator discretion. The patients must start Sponsor-supplied oseltamivir within 8 hours of study drug administration.

Patients hospitalized with an oxygen (O_2) or PPV requirement will be evaluated for influenza A infection. Enrollment in this study requires ongoing treatment within 24 hours of hospital admission with one of the following: any PPV or any supplemental O_2 to maintain oxygen saturation (SpO_2) $>92\%$.

A Sponsor-supplied rapid influenza test and/or a local polymerase chain reaction (PCR) test must be used as an aid in the diagnosis of influenza A infection.

At the time of randomization, patients who are eligible for enrollment will be randomized to receive either a single IV infusion of MHAA4549A or a single IV infusion of placebo that will be administered on Day 1. All patients must have the study drug infused within 48 hours of hospital admission or sooner if possible; therefore, screening must be completed within this

window. All patients will receive oseltamivir for a minimum of 5 days (10 doses), starting on Day 1 beginning no later than 8 hours after study drug administration. All patients will be followed for *60* days from the time of study drug administration.

Number of Patients

The study has a planned enrollment of approximately 334 patients (adult men and women) globally. Patients will receive MHAA4549A or placebo in 1:1 ratio. The number of patients on PPV should not exceed 45% of the total enrolled patients.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Men or women ≥ 18 years of age on day of signing informed consent or obtaining surrogate consent from an authorized representative
- Diagnosis of influenza A as determined by *one or both of the following:*
  - *A Sponsor-supplied* rapid influenza test
  - *A* local molecular test (PCR)
- One of the following markers of severity within 24 hours of hospital admission:
  - Requirement for PPV, OR
  - Requirement for O_2 supplementation to maintain $SpO_2 > 92\%$
- A negative urine or serum pregnancy test for women of childbearing potential
- Patients of reproductive potential must agree to use reliable means of contraception as described below as a minimum (adherence to more stringent local requirements may be required):
  - For female patients: Use of two acceptable methods of contraception throughout the trial, including the active treatment phase AND for 24 weeks after the last dose of MHAA4549A. Acceptable methods of contraception include: intrauterine device, systemic hormonal contraception (oral or depot), vaginal ring, tubal ligation of the female partner, vasectomy of the male partner, use of latex condoms plus spermicide by the male partner, or cervical cap plus spermicide (where the spermicide could be foam, vaginal suppository, gel, cream, etc.).
  - For male patients: Use of condoms for 30 days after dosing when circulating drug levels remain high.
  - Non-reproductive potential is defined below (but could be superseded by local definitions, if they are more stringent):

    Women who are postmenopausal (i.e., spontaneous amenorrhea for the past year confirmed by an follicle stimulating hormone [FSH] level greater than 40 mIU/mL unless the patient is receiving a hormonal therapy for their menopause)

    Women who are surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)

    Men who are surgically sterile (castration)

Exclusion Criteria

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

- Pregnant or lactating, or intending to become pregnant during the study
  - Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or who are not surgically sterile must have a negative urine or serum pregnancy test result within 2 days prior to study treatment
- Hypersensitivity to monoclonal antibodies or any constituents of study drug
- Investigational therapy within the 30 days prior to study treatment

- Received prior therapy with any anti-influenza monoclonal antibody therapy including MHAA4549A 8 months prior to study treatment
- Current treatment (within 7 days of dosing) with amantadine or rimantidine
- Patients who have taken more than a total of 3 days (6 doses) of approved anti-influenza therapy (i.e., oral oseltamivir, inhaled zanamivir, or oral ribavirin) in the period from onset of symptoms and prior to enrollment
- Admission $>$ 48 hours prior to study treatment
- Onset of influenza symptoms $>$ 5 days prior to study treatment
- Positive influenza B or influenza A $+$ B infection within 2 weeks prior to study treatment
- High probability of mortality in the next 48 hours as determined by the investigator
- Patient requiring home or baseline oxygenation therapy
- Patient with history of chronic lung disease resulting in baseline $SpO_2 < 95\%$
- Patient on chronic dose of corticosteroids exceeding 10 mg/day of prednisone or equivalent steroid dose for a duration of greater than 14 days within 30 days of entry into study
- Patients with the following significant immune suppression:
  - Bone marrow or solid organ transplant in the previous 12 months
  - Cancer chemotherapy in the previous 12 month
  - HIV infection with most recent CD4 $<$ 200 cells/mL
  - Other significant immune suppression as determined by the investigator in discussion with the Sponsor Medical Monitor or representative
- Patient on extracorporeal membrane oxygenation (ECMO) at time of randomization
- Any disease or condition that would, in the opinion of the site investigator or Sponsor, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol

Length of Study

This study will consist of the following study periods:

- A screening period of 48 hours, beginning at time of hospital submission
- A treatment period of 1 day, during which patients will receive a single dose of MHAA4549A or placebo and $a\ minimum\ of\ 5$ days of oseltamivir.
- A follow-up period beginning at hospital discharge through 60 days post study drug (MHAA4594A/placebo) administration

End of Study

The end of the study is defined as the first day when all patients have had a study completion visit or early termination visit or have otherwise been discontinued from the study.

Outcome Measures

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Adverse events and clinical laboratory abnormalities
- Vital signs, physical findings, ATAs, and clinical laboratory results during and following administration of MHAA4549A

Efficacy Outcome Measures

The primary outcome measure for this study is as follows:

- Time to normalization of respiratory function defined as:
  - The time to cessation of O_2 support resulting in a stable $SpO_2 > 95\%$ for at least 24 hours

The secondary efficacy outcome measures for this study are as follows:

- Clinical failure $after$ 24 hours post-infusion of study drug defined as:

  - Progression to increased O_2 requirement defined by an increase in oxygen supplementation from low flow oxygen (2 – 6 L/min) to high flow oxygen (> 6 L/min) or from oxygen supplementation alone to any PPV
  - Progression to ICU
  - Prolonged ventilation or O_2 support defined by > 2 weeks, or
  - Death
- Time to clinical normalization of vital signs (3/5 criteria must be met):
  - SpO_2 > 95% without supplemental O_2 for at least 24 hours
  - Respiratory rate < 24 *breaths per minute* without supplemental O_2 for at least 24 hours
  - Core temperature < 37.2°C immediately prior to receipt of any antipyretic drug, and at least 6-8 hours from the last dose of antipyretic or core temperature > 36°C in patients who are initially hypothermic
  - Heart rate (HR) < 100/minute
  - Systolic blood pressure (SBP) > 90 mmHg
- All-cause mortality at Day 14, *Day 30,* and Day *60*
- Influenza A viral load in nasopharyngeal samples
  - Area under viral load–time curve (AUEC)
  - Peak viral load
  - Time to resolution of infection
- Duration of hospitalization
- Duration of ICU stay
- Antibiotic usage for respiratory infections
- Complications of influenza:
  - Pneumonia (HAP/VAP)
  - Exacerbations of chronic lung disease
  - Myocarditis
  - Acute respiratory distress syndrome (ARDS)
  - Otitis media
  - Other related complications
- All-cause readmission at Day 30 *and Day 60*
- Duration of ventilation

Pharmacokinetic Outcome Measures

The primary PK outcome measures for this study are as follows:

- PK parameters for MHAA4549A in serum including total exposure (i.e., AUC), maximum observed concentration (C_{max}), clearance, half-life, and volume of distribution, when appropriate, as data allow

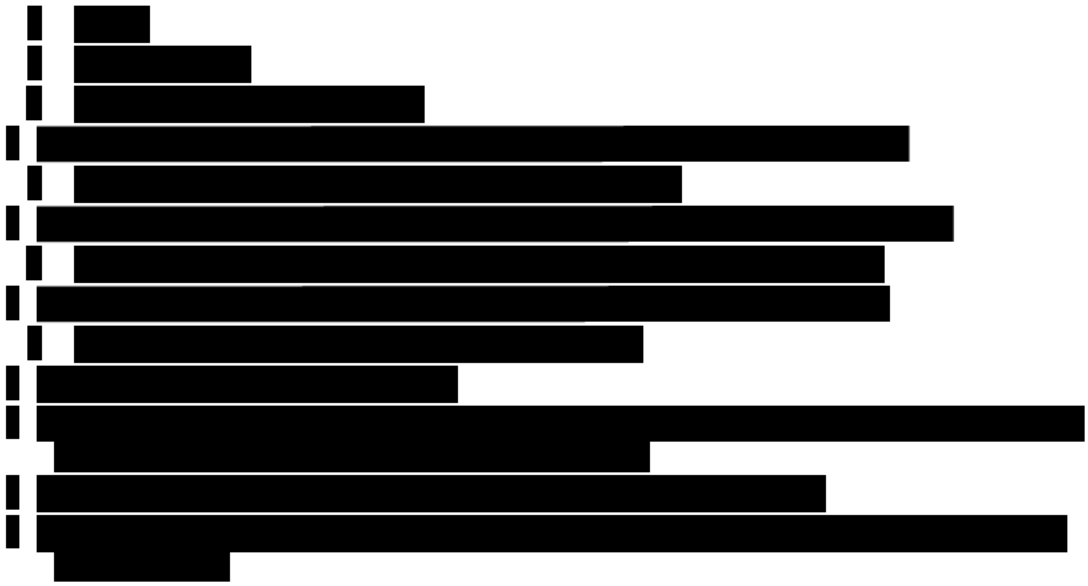
The exploratory PK outcome measures for this study are as follows:

[redacted]

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

[redacted]



Investigational Medicinal Products

An investigational medicinal product (IMP) is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, excluding marketed products unless the product is 1) used or assembled (formulated or packaged) differently than the authorized form, 2) used for an unauthorized indication, or 3) used to gain further information about the authorized form (Directive 2001/20/EC Article 2[d]). A non-investigational medicinal product (NIMP) is a medicinal product that is intended for use in a clinical trial per the protocol but does not fall under the definition of IMP. Further details can be found in the following EU guidance: Guidance on Investigational Medicinal Products and Non-Investigational Medicinal Products (effective March 2011).

MHAA4549A and Placebo

A single 3600-mg dose of MHAA4549A or dose of placebo will be delivered by IV infusion following dilution in 0.9% normal saline over approximately 60 minutes. Study drug should be delivered using a 0.22 μm in-line filter. Placebo will be identical to active MHAA4549A in formulation and appearance, but will not contain active drug substance.

Oseltamivir (Tamiflu®)

Sponsor-supplied oseltamivir (Tamiflu) 75 mg or 150 mg will be administered BID for *a minimum of 5 days*. Dosage and administration should follow local prescribing information for oseltamivir. Capsules can be opened and the granules administered via nasogastric tube, if required.

Statistical Methods

Primary Analysis

All efficacy analyses will be conducted according to the intent-to-treat principle and will include all patients who meet the following condition with patients allocated to the treatment arm to which they were randomized:

- Randomized patients who have confirmed influenza A infection by a central PCR test from Day 1 samples.

The primary and secondary efficacy analyses will include all randomized patients who are confirmed to be influenza A infected, with patients grouped according to the treatment assigned at randomization.

Time to event data will be computed using Kaplan-Meier methodology and stratified Cox proportional hazards models and will be summarized using n, median when estimable, hazard ratios, and 95% confidence intervals. Patients who are lost to follow-up (while event free) will be censored at the time that they are last known to be event free.

Estimation of the treatment difference of proportions and its 95% confidence interval will be calculated using stratum-adjusted Mantel-Haenszel methodology. For continuous endpoints, Analysis of Covariance methods (after appropriate transformation of data) will be used to estimate treatment differences at 95% confidence intervals.

Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

If conducted, an interim analysis would be for administrative purposes only (i.e., internal planning or decision making) and would not impact the conduct of the current study in any way. A nominal type I error penalty of 0.0001 will be taken. *In addition, as discussed below, the Sponsor will conduct interim safety analyses separate from and in conjunction with the above.*

Determination of Sample Size

A total of 334 patients will be enrolled in this study in order to obtain approximately 300 evaluable patients (an estimated dropout rate of 10%). It is assumed that the median time to normalization of respiratory function in the control arm is 5 days

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
[redacted]	[redacted]
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
ATA	Anti-therapeutic antibody
AUC	Area under serum concentration–time curve
AUEC	Area under viral load–time curve
BID	Twice a day
°C	Celsius
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CPK	Creatine phosphokinase
CRO	Contract (or Clinical) Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECMO	Extracorporeal membrane oxygenation
EDC	Electronic data capture
FDA	Food and Drug Administration
FiO_2	*Fraction of inspired oxygen*
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HA	Hemagglutinin
HAI	Hemagglutinin inhibition
HAP	Hospital Acquired Pneumonia
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart rate
[redacted]	[redacted]
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee

Abbreviation	Definition
IMC	*Internal Monitoring Committee*
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRR	Infusion-related reactions
IV	Intravenous
LFTs	Liver function tests
mAB	Monoclonal antibody
NAI	Neuraminidase inhibitor
NP	Nasopharyngeal
PaO_2	*Partial pressure of arterial oxygen*
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
PPV	Positive pressure ventilation
qPCR	Quantitative Polymerase Chain Reaction
QTcB	*QT interval corrected using Bazett's formula*
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SOC	*Scientific Oversight Committee*
SpO_2	Oxygen saturation *by pulse oximetry*
SUSAR	Suspected unexpected serious adverse reactions
ULN	Upper limit of normal
VAP	Ventilation Acquired Pneumonia

1. BACKGROUND

1.1 BACKGROUND ON INFLUENZA

Influenza A is a membrane-enveloped RNA virus that causes significant morbidity and mortality. Currently, there is a great need in hospitalized influenza patients for a parenteral therapeutic option that is well tolerated, can rapidly resolve influenza-related signs and symptoms, decrease mortality, reduce hospital and intensive care unit (ICU) stays, as well as have a prolonged window for initiation of treatment beyond the current standard of care (i.e., within 48 hours of the onset of flu symptoms).

Approximately 200,000 to 278,000 patients are hospitalized with severe influenza infections annually in the United States (U.S.) (Thompson et al. 2004; Zhou et al. 2012), and assuming the same rate reported in the U.S., an estimated 319,000 to 445,000 patients are hospitalized in the European Union (E.U.). Hospitalization due to severe influenza is associated with high mortality (4%–8%), ICU admission (5%–17%; Lee and Ison 2012), mechanical ventilation support in an ICU setting (7%–11%; Doshi et al. 2011), and prolonged hospital stays (5−9 days; Lee and Ison 2012). 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).

Influenza infection is an upper and lower respiratory disease with a broad spectrum of presentations that can result in fever, shortness-of-breath, pneumonia, respiratory failure, secondary respiratory infections, and even death. The *standard of care* therapy for patients hospitalized with influenza consists of supportive measures and administration of available antiviral agents, primarily neuraminidase inhibitors (NAI) that include but are not limited to oseltamivir, zanamivir, and peramivir. However, a significant unmet medical need still exists in the severely ill patient population, as evidenced by the considerable degree of morbidity and mortality in this setting. To address this need, Genentech Inc. /F.Hoffmann-La Roche Ltd. (Genentech) is developing a highly-specific anti-influenza A (MHAA4549A) antibody therapy for treatment of hospitalized patients with severe influenza.

1.2 BACKGROUND ON MHAA4549A

1.2.1 *Nonclinical Background*

MHAA4549A is a human monoclonal IgG1 antibody (mAb) that binds to the influenza A virus and is cloned from a single-human plasmablast cell isolated from an influenza vaccinated donor (Nakamura et al. 2013). This antibody binds to a highly conserved epitope on the influenza A hemagglutinin stalk region, which allows broad neutralization of the influenza A virus by blocking the hemagglutinin-mediated, membrane-fusion event in the late endosome.

In vitro, MHAA4549A is capable of neutralizing all current clinically relevant influenza A strains. In vivo, efficacy of MHAA4549A has been demonstrated in mouse models of influenza A infection, both as a single agent and in combination with oseltamivir.

MHAA4549A specifically targets an epitope on the human influenza A hemagglutinin glycoprotein, which does not appear to be endogenously expressed on human or rat tissues and, therefore, is unlikely to be present in the absence of viral infection. Weekly administration of MHAA4549A (total of 5 doses) in Sprague-Dawley rats was well tolerated up to the maximum feasible dose of 150 mg/kg. *Ex* vivo tissue cross-reactivity study *data showed* no specific binding of MHAA4549A to any of the human or rat tissues examined.

1.2.2 Clinical *Safety Background*

To date, MHAA4549A has been shown to be safe and well tolerated *in two clinical studies, which altogether enrolled 122 healthy volunteers.* The first study was a Phase 1 study (GV28916) in 21 healthy volunteers where single doses of 1.5 mg/kg, 5 mg/kg, 15 mg/kg, and 45 mg/kg were tested with an extended follow-up period of 120 days. MHAA4549A was safe and well tolerated with no serious adverse events (SAEs). All adverse events (AEs) were mild or mild-to-moderate and resolved fully *before the end of the study's follow-up period. No anti-therapeutic antibodies (ATAs) were detected in this study.* In addition, the *MHAA4549A* pharmacokinetics were generally dose proportional, *and* appeared to have a pharmacokinetic (PK) profile consistent with that of a human *IgG1* antibody that *lacks* known endogenous host targets.

The second study was a Phase 2a challenge study *(GV28985)* in 101 healthy volunteers infected with a H3N2 *(A/Wisconsin/67/2005)* strain of influenza virus. Fixed dosing was selected for this study and is further described in Section 1.3.2.3. *Sixty subjects received* doses *of* 400 mg, 1200 mg, *or* 3600 mg *MHAA4549A and 41 subjects received placebo following nasal inoculation of influenza A virus one day earlier. The interim efficacy analysis in Table 1 includes the Intent-to-Treat (ITT) infected population who received placebo (N =21), 400 mg MHAA4549A (N =11), 1200 mg MHAA4549A (N =13), 3600 mg MHAA4549A (N=14), and oseltamivir (N =2).* All subjects have completed dosing, and interim PK and efficacy data are available *in* the *Investigator's Brochure* and *upon request.* During *this* study, elevated *ALT, AST,* and amylase levels *were observed within the first 2 weeks after inoculation with A/Wisconsin/67/2005 and dosing with MHAA4549A. Previous experience with this challenge model has shown ALT/AST/amylase elevations to be associated with the influenza infection itself (Polakos 2006). Consistent with previous trials, in GV28985, there was no* relationship *of elevations in AST, ALT, or amylase with either dose or exposure (*e.*g.*, placebo*: 22.0%, 400 mg: 35.0%,*1200 *mg: 25.0%, 3600* mg*: 20.0%).*

In GV28985, most AEs were Grade 1 or Grade 2 (mild or moderate) and appeared to reflect the symptoms of the influenza infection. In the 400 mg group, 15 (75.0%), 1 (5.0%), and 2 (10.0%) subjects reported Grade 1, 2, and 3 AEs respectively. In the 1200-mg group, 9 (45.0%), 6 (30.0%), and 1 (5.0%) subjects reported Grade 1, 2, and 3 AEs, respectively. In the 3600-mg group, 10 (50.0%), 5 (25.0%), 1 (5.0%) subjects reported Grade 1, 2, and 3 AEs, respectively. One (5.0%) subject reported a Grade 4

AE in the 3600-mg group, which was a lower limb fracture, not related to MHAA4549A. Subjects in the placebo group reported 18 (56.3%) Grade 1 AEs, 8 (25.0%) Grade 2 AEs, and 2 (6.3%) Grade 3 AEs. In addition, there were no drug related SAEs, deaths, or discontinuations due to AEs. There were a total of 3 SAEs unrelated to MHAA4549A in two subjects. One subject reported depressive psychosis associated with influenza. There were a total of 3 SAEs unrelated to MHAA4549A in two subjects. One subject reported depressive psychosis associated with influenza. The second subject reported a broken knee with a subsequent infection following a surgical procedure.

In GV28985, 1 patient tested positive for anti-therapeutic antibodies (ATAs). This patient tested positive for ATA at baseline and post baseline. This patient was in the placebo group, which included 32 other subjects, resulting in an immunogenicity prevalence rate (ATA-positive rate at baseline) of 3.1% and an immunogenicity incidence rate (ATA titers post-baseline) of 3.1%, as well, within the placebo group. Overall, study GV28985 had an immunogenicity prevalence rate of 1%. The immunogenicity incidence rate amongst the 60 subjects who received MHAA4549A was 0%.

Based on this data, MHAA4549A is considered generally safe and well tolerated to date at all doses tested, including the 3600 mg dose.

1.2.3 *Clinical Efficacy Background*

Analysis of efficacy from the 3600-mg dose level demonstrated a statistically significant decrease in viral shedding from upper respiratory tract as measured by *the* area under the curve (97% reduction by quantitative polymerase chain reaction [qPCR]) and peak viral load (77% reduction by qPCR) as *shown* in Table 1.

In this study, oseltamivir was started on Day 7 for a 5-day course, and there were no observed AEs or imbalances in safety events that were considered attributable to interactions between oseltamivir and MHAA4549A. The PK profile of MHAA4549A and oseltamivir *in GV28985* are being analyzed to exclude potential drug-drug interactions and will be available before the start of this study *GV29216.*

Table 1 Interim Efficacy Results from Phase 2a Challenge Study (GV28985)

Endpoint	Placebo *(N=21)*	MHAA4549A *400 mg (N=11) % reduction (p-value)*[a]	MHAA4549A *1200* mg *(N=13)* % reduction (p-value)[a]	MHAA4549A *3600 mg (N=14) % reduction (p-value)*[a]	*Oseltamivir* 75 mg BID (N=2) % reduction (p-value)[a]
Median qPCR Viral AUEC (log_{10} vc/mL x hour)	458.1	*247.2 46.0% (0.0455)*	444.4 3.0% (0.9020)	11.3 97.5% (0.0051)	57.4 87.5% (0.0558)
Median qPCR Peak Viral Load (log_{10} vc/mL)	6.38	5.08 20.4% (0.0187)	6.36 0.3% (1.0000)	1.45 77.3% (0.0024)	2.30 63.9% (0.0947)
Median Total Clinical Symptom AUEC	207.7	87.5 57.9% (0.2000)	192.1 7.5% (0.8743)	37.7 81.8% (0.2887)	8.1 96.1% (0.0855)

AUEC = area under viral load–time curve; qPCR = quantitative polymerase chain reaction.

[a] Comparison of *active and* placebo using nonparametric Wilcoxon rank-sum test. All p-values are unadjusted for multiple testing.

The *A/Wisconsin/67/2005 virus induced mild symptoms that were predominantly captured in the upper respiratory tract symptoms that included runny nose, stuffy nose and sneezing.*

The Symptom Diary Cards used a scale of 0-3, where Grade 0 is absence, Grade 1 is just noticeable, Grade 2 is bothersome but does not prevent participation in activities, and Grade 3 is bothersome and interferes with activities. Composite clinical symptom scores from Study GV28985 for the Intent-to-Treat (ITT) infected population who received placebo (N =21), 400 mg MHAA4549A (N =11), 1200 mg MHAA4549A (N =13), 3600 mg MHAA4549A (N =14), and oseltamivir (N =2) are shown in Table 1.

Given the variability of the symptom scores the results were not statistically significant. However, there was a decrease in the AUEC of symptoms scores for the 3600 mg dose, which is consistent with the virological results described in the Table 1 above. Data from the oseltamivir treated group is also shown but it should be noted that only 2 subjects were in the ITT infected population.

See the MHAA4549A Investigator's Brochure for additional details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

The Phase 1 and Phase 2a studies have demonstrated that MHAA4549A is safe and well tolerated to date in healthy volunteers including those who were inoculated with influenza A virus. Data from the Phase 2a study also provides evidence that the 3600 mg dose of MHAA4549A is effective in reducing viral titers in healthy volunteers inoculated with influenza A virus. These findings, when combined with previous nonclinical studies showing MHAA4549A to have in vitro and in vivo efficacy, a well-tolerated safety profile, and anti-viral activity, support further clinical development of MHAA4549A.

In this Phase 2b study (GV29216), MHAA4549A is being evaluated in combination with the current *standard of care* (oseltamivir), to decrease the severity and duration of viral infection with influenza A virus with the ultimate goal of reducing the clinical symptoms of infection as compared to oseltamivir with placebo. There are three primary goals for this Phase 2b study:

- Demonstrate the safety and efficacy of MHAA4549A in combination with oseltamivir in hospitalized influenza A patients
- [redacted]
- Demonstrate and evaluate the optimal endpoints for study in hospitalized patients with influenza A, given the lack of precedence for approval in patients hospitalized with influenza infection, an area of high unmet medical need

This Phase 2b study has been designed to estimate the improvement in outcome of a combination therapy of MHAA4549A 3600 mg with oseltamivir versus placebo with oseltamivir. All patients will be on oseltamivir*,* which is part of the recommended *standard of care.* In addition, and as discussed above, MHAA4549A is a human monoclonal antibody that has, to date, shown an acceptable safety profile, a PK profile consistent with that of a IgG1 human antibody that lacks known endogenous host targets, and a demonstrated antiviral activity at the planned dose level of 3600 mg.

1.3.2 Benefit-Risk Assessment

1.3.2.1 Treatment in Combination with Oseltamivir

All patients in the study will receive *oseltamivir as* the current *standard of care* treatment*,* either with or without MHAA4549A. Therefore, *at a minimum,* all patients will be treated with *standard of care* for influenza. Given that MHAA4549A is an antibody, the potential for *a drug-drug* interaction with oseltamivir is very low. In the ongoing Phase 2a challenge study (GV28985), study subjects received MHAA4549A followed by oseltamivir with no AEs attributable to the combination therapy noted to date. In addition,

in this study the PK profile of oseltamivir in concomitantly treated subjects will be assessed.

1.3.2.2 Drug Mechanism and Preclinical Studies

The available pre-clinical data suggest that there is low risk for drug target-related safety events in healthy humans since MHAA4549A specifically targets an epitope on a viral protein (i.e., the human influenza A virus hemagglutinin glycoprotein), which is not endogenously expressed in human tissues. Furthermore, there were no adverse MHAA4549A-related findings demonstrated in nonclinical studies at doses up to 150 mg/kg administered weekly for 5 weeks and no evidence of target present in host tissues.

1.3.2.3 Rationale for Selection of Phase 2b Study Population

The target patient population of hospitalized patients with severe influenza A requiring oxygen (O_2) or positive pressure ventilation (PPV) is considered an appropriate population to test MHAA4549A for the following reasons:

- Nonclinical safety data does not show any expected or unexpected toxicity.
- Clinical safety data for MHAA4549A demonstrate a well-tolerated safety profile:
  - AEs in the Phase 1 study (GV28916) *were mild* and *did not show a dose relationship; there were* no ATAs detected *in patients treated with MHAA4549A.*
  - *In* the ongoing Phase 2a study (GV28985*), MHAA4549A was generally well tolerated. A few subjects in all treatment groups were* observed to have transient elevations in alanine transaminase (ALT), aspartate transaminase *(*AST*)*, and amylase *levels.* There was no dose-dependent relationship of *the ALT/AST/amylase* elevations with MHAA4549A and the overall event rate was in line with *published rates associated with the influenza challenge model regardless of treatment arm:* 27/100 [27%] in *GV28985* vs. approximately 26*% in previous challenge studies (*Polakos 2006). *There were* no SAEs related to study drug. *There were a total of 3 SAEs unrelated to MHAA4549A in two subjects. One subject reported depressive psychosis associated with influenza. The second subject reported a broken knee with a subsequent infection following a surgical procedure.*
- *Interim efficacy data in* the Phase 2a challenge study (GV28985) demonstrated a significant decrease in viral shedding in the upper respiratory tract at the 3600 mg dose. There was a 97.5% (p=0.*0051*) decrease in the area under viral load–time curve (AUEC) and a 77% (p=0.*0024*) decrease in peak viral load by qPCR measurement in comparison to the placebo group, thus confirming proof of antiviral activity at the 3600 mg dose level. *Symptom data in the Phase 2a study showed a decrease in the AUC of symptoms scores for the 3600-mg dose that is consistent with the virological results as illustrated in Table 1.*

1.3.2.4 Patient Monitoring and Supervision

MHAA4549A will be administered to enrolled patients in a hospital environment under close medical supervision by physician investigators. Medical staff will be available for prompt evaluation and treatment of any adverse events. Emergency resuscitation equipment and emergency facilities will be readily available. Patients will undergo screening assessments to confirm eligibility, will be closely monitored during the administration of MHAA4549A, and will be resident for at least 24 hours following the administration of MHAA4549A. Furthermore, safety laboratory tests relating to the blood chemistries, including liver function tests, will be conducted.

.An internal monitoring committee (IMC) in combination with a scientific oversight committee (SOC) will provide safety monitoring for the study in addition to the ongoing review of safety by the Medical Monitor and Safety Scientist. See Section 3.1.2 for more information.

The 120-day follow-up period in the Phase 1 and 2a studies allowed for monitoring of subjects for approximately 5 half-lives of *MHAA4549A*. No ATAs were detected in the Phase 1 study, *while one subject in* the Phase 2a study *tested positive for ATAs at baseline and post-baseline timepoints as described in Section 1.2.2.* The Phase 2b study will also include *a* safety follow-up period of *60* days and an unlimited collection of all SAEs believed related to MHAA4549A.

Based on the above data and design of this study, the Sponsor concludes that the benefit−risk profile of MHAA4549A in the population with severe influenza is favorable.

2. OBJECTIVES

2.1 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety of MHAA4549A in combination with oseltamivir compared with placebo and oseltamivir in patients with severe influenza A, focusing on the nature, frequency, and severity of serious and non-serious adverse events as well as effects on laboratory values, vital signs, electrocardiogram (ECG) parameters, ATAs, or other safety biomarkers

2.2 PRIMARY EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To determine the time to normalization of respiratory function of patients dosed with MHAA4549A in combination with oseltamivir compared to patients dosed with placebo and oseltamivir.

2.3 SECONDARY EFFICACY OBJECTIVES

The secondary efficacy objectives for this study are as follows:

- To measure clinical failure, as defined in Section 3.3.3, after 24 hours post-infusion of study drug
- To determine the time to clinical resolution of vital signs
- To measure mortality in patients
- To determine changes in the extent and duration of viral shedding in upper respiratory samples
- To measure the duration of hospital and/or ICU stay
- To measure antibiotic usage for respiratory indications
- To measure the frequency and severity of the following secondary complications of influenza:
  - Pneumonia (hospital acquired pneumonia [HAP]/ ventilator acquired pneumonia [VAP])
  - Exacerbations of chronic lung disease
  - Myocarditis
  - Acute respiratory distress syndrome (ARDS)
  - Otitis media
  - Other related complications
  - Readmission rates at 30 $and\ 60$ days after study treatment
- To measure duration of PPV
- To measure readmission rates

2.4 PHARMACOKINETIC OBJECTIVES

The major PK objective for this study is as follows:

- To characterize the PK profile of MHAA4549A in serum

The exploratory PK objectives for this study are as follows:

- [redacted]
- [redacted]

2.5 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are as follows:

- [redacted]

[redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase 2b, randomized, double-blind, placebo-controlled study designed to assess the safety and clinical activity of a single intravenous (IV) dose of MHAA4549A in hospitalized patients with severe influenza A in combination with oseltamivir versus a comparator arm of placebo with oseltamivir. This study is planned to take place in approximately 170 study centers globally.

Patients will be randomized 1:1 into two treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir or a single IV dose of placebo with oseltamivir. All patients will receive oseltamivir, a NAI, as standard therapy for a minimum of 5 days after study drug administration. Oseltamivir at doses of 75 mg BID or 150 mg BID is permitted in order to be consistent with local $standard\ of\ care$ practice. Treatment for longer than 5 days is permitted based on local investigator discretion. The patient must start Sponsor-supplied oseltamivir within 8 hours of study drug administration. The study has a planned enrollment of approximately 334 patients globally.

Hospitalized patients with an O_2 or PPV requirement will be evaluated for influenza A infection. Enrollment in this study requires ongoing treatment within 24 hours of hospital admission with one of the following:

- any PPV or
- any supplemental O_2 to maintain oxygen saturation (SpO_2) >92% (see Section 3.3.2)

Patients on PPV should not exceed 45% of the total patients enrolled.

A Sponsor-supplied rapid influenza test and/or a local polymerase chain reaction (PCR) test must be used as an aid in the diagnosis of influenza A infection.

[redacted]

At the time of randomization, patients who are eligible for enrollment, as described above, will be randomized to receive MHAA4549A at a dose of 3600 mg or placebo. Patients will be stratified by *site*, PPV versus supplemental O_2 *at randomization*, and suspected or confirmed bacterial pneumonia versus no bacterial pneumonia based on the status *at randomization*.

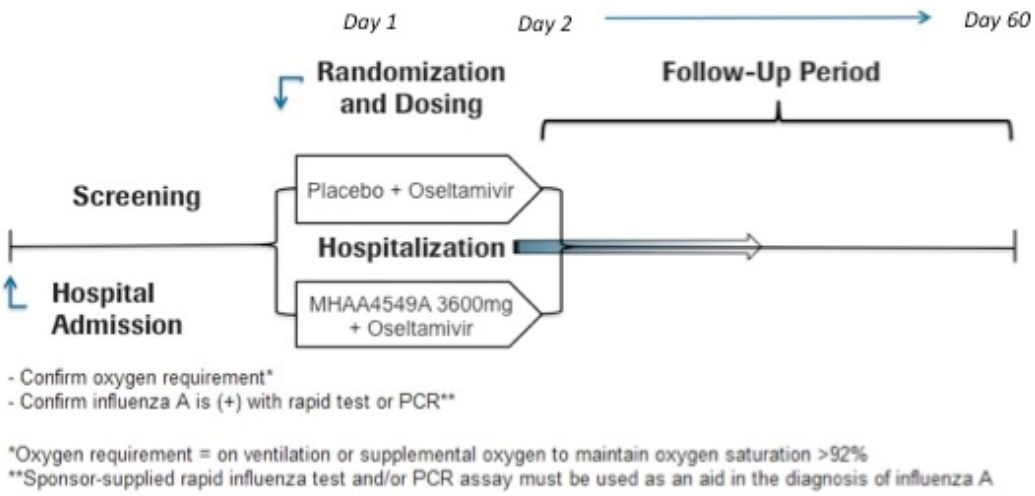
Eligible patients who are enrolled into the study will receive either a single IV infusion of MHAA4549A or a single IV infusion of placebo on Day 1. All patients must have the study drug infused within 48 hours of hospital admission or sooner if possible. All patients will receive oseltamivir for a minimum of 5 days (10 doses), starting on Day 1, beginning no later than 8 hours after study drug administration.

All patients will be followed and evaluated at minimum on a daily basis for the duration of their hospital stay consistent with the planned schedule of assessments. Any suspicion of bacterial superinfection should be thoroughly evaluated including microbiological confirmation, if possible. A follow-up study visit should occur on Day 14 ± 1 (if discharged before Day 14); Day 30 ± 4 days (if discharged before Day 30); *and Day 60 ±4 days (if discharged before Day 60).*

Safety evaluations will be provided by an IMC and SOC, as defined in the IMC and SOC agreement (see Section 3.1.2)

A schedule of assessments is provided in Appendix 1a and Appendix 1b. A diagram of the study design is presented in Figure 1.

Figure 1 Phase 2b Study Design (GV29216)



3.1.2 Independent Monitoring Committee and Scientific Oversight Committee

A combined approach with both an IMC and a SOC is proposed to enhance patient safety. The IMC consists of Sponsor representatives from the following functions: Clinical Science, Drug Safety, Biostatistics, and Statistical Programming and Analysis. The IMC members will be unblinded to patient treatment and assignment. The Clinical Science representative on the IMC (IMC Chair) will be a person other than the Study Medical Monitor and will not be involved in the conduct of the study or have any contact with study investigators or site staff. The Study Medical Monitor will remain blinded to individual treatment assignments, unless, in exceptional cases, specific circumstances require Study Medical Monitor unblinding after IMC Chair approval. The Drug Safety Scientist on the IMC will also not be involved in the conduct of the study or have any contact with the study investigators. The Biostatistician and Statistical Programmer are the only IMC members involved in the conduct of the study; however, they do not have any contact with study investigators, and all discussion within the IMC are kept confidential. All other Sponsor and Contract Research Organization personnel involved in the conduct of the study will remain blinded to individual treatment assignments.

The two SOC members are external experts in the field and will be unblinded to treatment allocation. The SOC may be further expanded by the IMC during the course of the study to include additional external experts if the need arises.

A detailed description of the procedures, data flow, and meeting schedule of the *IMC and SOC* will be provided in a separate *IMC and SOC agreement*.

3.1.3 End of Study

The end of study is defined as the first day when all patients have had a study completion visit or early termination visit or have otherwise been discontinued from the study.

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Study Design

Hospitalized influenza A infection represents a high unmet need, which, when left untreated, may progress to a more serious disease that may result in significant morbidity and mortality in otherwise healthy adults as well as in vulnerable populations.

This study is designed to estimate the improvement in outcome of a combination regimen of MHAA4549A with oseltamivir compared to a *standard of care* arm of placebo with oseltamivir. The study population will include hospitalized patients with influenza A requiring O_2 support and/or PPV support within 24 hours of hospital admission.

Study GV29216 will be a Phase 2b study involving approximately 334 patients. The sample size was determined based on an expected clinically meaningful difference of $1-2$ days improvement in time to normalization of respiratory function between the control and treatment arms, assuming a 5-day median time to the time to normalization of respiratory function in the *standard of care* arm (Blackwood 2011; PREMIER® database).

This design ensures that all patients in the trial will receive the current NAI treatment, oseltamivir, as *standard of care* at a minimum, and will evaluate the clinical benefit of combining MHAA4549A with this *standard of care* regimen. Therefore, this study aims to identify a regimen that could deliver maximum benefit in this high unmet need disease, while still treating all enrolled patients with the currently accepted *standard of care*.

3.2.2 Rationale for Patient Population and Primary Endpoint

Severe influenza, for the purpose of this study, is defined as requiring one of the following treatments: any supplemental O_2 to maintain an $SpO_2 > 92\%$ *or PPV*. PPV is defined as any mechanical positive pressure device to maintain oxygenation; this can include *positive pressure mask* and intubation. A Sponsor-supplied rapid influenza test and/or a local PCR must be used as an aid in the diagnosis of influenza A infection.

This patient population was chosen based on the rationale that respiratory failure is a hallmark of influenza and a major driver of morbidity and mortality, as well as hospitalization. The recovery from ventilator support has been shown to be directly proportional to time spent in the ICU (Blackwood 2011; PREMIER® database). Based upon an analysis of morbidity and mortality, the patient population that requires supplemental O_2 or ventilation on their first day of admission was determined to have a high unmet medical need as they have an estimated mortality of 9%–32%, and 27%

require admission to the ICU, according to analysis of a database of over 70,000 hospitalized patients in the US from 2005–2012 (PREMIER® database).

Support for use of the respiratory endpoint in this population comes from recently published data demonstrating that a composite endpoint that captured respiratory rate, fever, heart rate, and blood pressure resolution was primarily driven by the respiratory component of the endpoint (Marty et al. 2014).

3.2.3 Rationale for Control Group and Treatment Window

In this study, the *standard of care* regimen for the control or comparator group is oseltamivir, an NAI. In the treatment groups, MHAA4549A will be dosed in addition to an oseltamivir *standard of care* regimen. The oseltamivir dose will be consistent with the local investigator practice at each site where the study will be conducted. Either 75 mg or 150 mg orally BID oseltamivir for a minimum of 5 days is permitted following treatment with MHAA4549A. Treatment for longer than 5 days is permitted based on local investigator discretion. The oseltamivir dosing regimen, including the renal dosing adjustment, is listed in Table 2. This control treatment was based on consideration of safety, ethics, and efficacy for treatment of severe influenza and is consistent with guidelines for antiviral treatment of hospitalized patients with influenza (Harper et al. 2009, Fiore 2011).

Table 2 Oseltamivir Dosing Regimen

Neuraminidase Inhibitor	Dosing Regimen	Duration of Therapy
Oseltamivir	75 mg or 150 mg orally BID [a] 75 mg oral once daily for adult patients with creatinine clearance (CrCL) between 10 and 30 mL/min [b]	5 days [c]

[a] 75 mg or 150 mg dose at the discretion of the investigator, and dose must be documented. Capsules can be opened and the granules administered via nasogastric tube, if required.

[b] No recommended dosing regimens are available for patients with end-stage renal disease undergoing routine hemodialysis or continuous peritoneal dialysis treatment.

[c] Longer treatment times are at the discretion of the investigator.

From a safety standpoint there are no expected drug interactions between MHAA4549A, a monoclonal antibody, and any NAI, which are small molecule drugs that bind to a different viral protein than MHAA4549A. In the Phase 2a challenge study, all subjects that were dosed with MHAA4549A also received a 5-day course of oseltamivir starting on Day 7. There were no safety effects attributable to the combination when the drugs were present concurrently. The pharmacokinetics of oseltamivir and its potential interaction with MHAA4549A are being assessed from this Phase 2a.

For this Phase 2b study, a combination of MHAA4549A and oseltamivir was determined to be the most clinically feasible treatment regimen, both from an ethical as well as a

practical perspective. The treatment of all patients with oseltamivir ensures that all patients will receive *standard of care* given the high morbidity and mortality of hospitalized patients with influenza A along with guidelines from Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) stating NAIs are the *standard of care* for hospitalized patients with influenza A (Harper et al. 2009 and CDC Website). Further, pre-clinical efficacy data from a study using MHAA4549A and oseltamivir in combination, showed a potential synergistic effect of both compounds which may be due to the different and potentially complementary mechanisms of action, i.e. targeting viral hemagglutinin and neuramin*i*dase.

Dosing of MHAA4549A is confined to a treatment window designed for best expected treatment success and to ensure that any observed effects can be attributed to the study drug with high confidence. MHAA4549A shall only be dosed within 5 days of symptom onset, within 3 days of initial treatment with a NAI, and no later than 48 hours after admission to the hospital. This proposed window is supported by data demonstrating that hospitalized influenza patients benefit from NAI treatment even at 5 days from symptom onset (Louie et al. 2012).

3.2.4 Rationale for MHAA4549A Dosage

A single IV dose of 3600 mg of MHAA4549A was selected to assess the efficacy of MHAA4549A and to provide data for further clinical development. The selection of dose in this study for severely ill patients was based on the observed human pharmacokinetics in Phase 1 and the relationship between the pharmacokinetics, pharmacodynamics, and efficacy observed in a Phase 2a human challenge model of influenza. MHAA4549A was shown to be safe and well-tolerated at all dose levels (ranging from 1.5 mg/kg to 45 mg/kg for Phase 1 and 400-3600 mg for Phase 2a) through a follow-up period of 120 days post-dose in the Phase 1 *and Phase 2a* study. The dose level used in this study was determined following analysis of *data from* the Phase 2a study, GV28985, which demonstrated the following:

- The 3600-mg dose demonstrated a significant decrease in viral shedding in upper respiratory samples. Based on current interim analysis data, there was a 97.5% ($p = 0.0051$) decrease in AUEC and a 77.3% decrease in peak viral load by qPCR measurement compared to the placebo group.
- *Symptom data in the Phase 2a study showed a decrease in the AUC of symptoms scores for the 3600-mg dose, as illustrated in Table 1, which is consistent with the virological results.*
- The 1200-mg dose level was not efficacious
- There are no safety concerns at the 3600-mg dose level to date.
- Hospitalized patients generally have a longer duration of viral shedding and significantly more viral burden in the lower lung compartments; therefore, high concentrations of mAb are likely needed to achieve sufficient occupancy of the virus binding sites in the upper and lower respiratory compartments. Furthermore, higher

concentrations of mAb are necessary to mitigate the risk of resistance for MHAA4549A .

The Phase 1 study was conducted using body-weight based dosing followed by a fixed dosing strategy that was used in the Phase 2*a* study. Thus, the fixed dosing regimen that was used in the Phase 2a study will be used for this study, given the practical advantages and positive safety profile of MHAA4549A to date. Further, fixed dosing is generally recommended with monoclonal antibodies, due to their minimal PK variability (Bai et al. 2012). The PK variability introduced by different dosing regimens (i.e., body-weight based dosing versus fixed dosing) is moderate relative to the variability generally observed in pharmacodynamics, efficacy, and safety and would not be expected to be clinically meaningful.

3.2.5 Rationale for Biomarker Assessments

[redacted]

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Adverse events and clinical laboratory abnormalities
- Vital signs, physical findings, ATAs, and clinical laboratory results during and following administration of MHAA4549A

3.3.2 Primary Efficacy Outcome Measure

The primary outcome measure for this study is as follows:

- Time to normalization of respiratory function defined as:
  - The time to cessation of O_2 support resulting in a stable $SpO_2 > 95\%$ for at least 24 hours (see Appendix 2 for details)

3.3.3 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- Clinical failure *after* 24 hours post-infusion of study drug; defined as:

- Progression to increased O_2 requirement defined by an increase in oxygen supplementation from low flow oxygen (2 – 6 L/min) to high flow oxygen (> 6 L/min) or from oxygen supplementation alone to any PPV
- Progression to ICU
- Prolonged ventilation or O_2 support defined by > 2 weeks, or
- Death

- Time to clinical normalization of vital signs (3/5 criteria must be met):
  - SpO_2 > 95% without supplemental O_2 for at least 24 hours
  - Core temperature < 37.2°C immediately prior to receipt of any antipyretic drug, and at least 6-8 hours from the last dose of antipyretic or core temperature > 36°C in patients who are initially hypothermic
  - Heart rate (HR) < 100/minute
  - Systolic blood pressure (SBP) > 90 mmHg
- All-cause mortality at Day 14*, Day 30,* and Day *60*
- Influenza A viral load in nasopharyngeal samples
  - AUEC
  - Peak viral load
  - Time to resolution of infection
- Duration of hospitalization
- Duration of ICU stay
- Antibiotic usage for respiratory infections
- Complications of influenza:
  - Pneumonia (HAP/VAP)
  - Exacerbations of chronic lung disease
  - Myocarditis
  - ARDS
  - Otitis media
  - Other related complications
- All-cause readmission at Day 30 *and Day 60*
- Duration of ventilation

3.3.4 Pharmacokinetic Outcome Measures

The primary PK outcome measures for this study are as follows:

- PK parameters for MHAA4549A in serum including total exposure (i.e., AUC), maximum observed concentration (C_{max}), clearance, half-life, and volume of distribution, when appropriate, as data allow

The exploratory PK outcome measures for this study are as follows:

[redacted]

3.3.5 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

This study aims to enroll approximately 334 men and women and is designed to assess the safety and clinical activity of a single IV administration of MHAA4549A in adult patients hospitalized with severe influenza A.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Hospitalized men or women ≥ 18 years of age on the day of signing the informed consent or obtaining surrogate consent from an authorized representative
- Diagnosis of influenza A *where one or both of the following are used as aid(s) in diagnosis:*
  - *A Sponsor-supplied* rapid influenza test
  - *A* local molecular (PCR) *test*
- One of the following markers of severity within 24 hours of hospital admission:
  - Requirement for PPV –or–
  - Requirement for O_2 supplementation to maintain $SpO_2 > 92\%$
- A negative urine or serum pregnancy test for women of child-bearing potential
- Patients of reproductive potential must agree to use reliable means of contraception as described below as a minimum (adherence to more stringent local requirements may be required):
  - For female patients: Use of two acceptable methods of contraception throughout the trial, including the active treatment phase AND for 24 weeks after the last dose of MHAA4549A. Acceptable methods of contraception include: intrauterine device, systemic hormonal contraception (oral or depot), vaginal ring, tubal ligation of the female partner, vasectomy of the male partner, use of latex condoms plus spermicide by the male partner, or cervical cap plus spermicide (where the spermicide could be foam, vaginal suppository, gel, cream, etc.).
  - For male patients: Use of condoms for 30 days after dosing when circulating drug levels remain high.
  - Non-reproductive potential is defined below (but could be superseded by local definitions, if they are more stringent):

    Women who are postmenopausal (i.e., spontaneous amenorrhea for the past year confirmed by an FSH level greater than 40 mIU/mL unless the patient is receiving a hormonal therapy for their menopause)

    Women who are surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)

    Men who are surgically sterile (castration)

4.1.2 Exclusion Criteria

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

- Pregnant or lactating or intending to become pregnant during the study
  - Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or who are not surgically sterile must have a negative urine or serum pregnancy test result within 2 days prior to study treatment.

- Hypersensitivity to mABs or any constituents of study drug
- Investigational therapy within the 30 days prior to study treatment
- Received prior therapy with any anti-influenza monoclonal antibody therapy including MHAA4549A 8 months prior to study treatment
- Current treatment (within 7 days of dosing) with amantadine or rimantidine
- Patients who have taken more than a total of 3 days (6 doses) of approved anti-influenza therapy (e.g., oral oseltamivir, inhaled zanamivir, or oral ribavirin) in the period from onset of symptoms and prior to enrollment
- Admission $>$ 48 hours prior to study treatment
- Onset of influenza symptoms $>$ 5 days prior to study treatment
- Positive influenza B or influenza A $+$ B infection within 2 weeks prior to study treatment
- High probability of mortality in the next 48 hours as determined by the investigator
- Patient requiring home or baseline oxygenation therapy
- Patient with history of chronic lung disease resulting in baseline $SpO_2 < 95\%$
- Patient on a chronic dose of corticosteroids exceeding 10 mg/day of prednisone or equivalent steroid dose for a duration of greater than 14 days within 30 days of entry into study
- Patients with the following significant immune suppression:
  - Bone marrow or solid organ transplant in the previous 12 months
  - Cancer chemotherapy in the previous 12 month
  - HIV infection with most recent CD4 $<$ 200 cells/mL
  - Other significant immune suppression as determined by the investigator in discussion with the Sponsor Medical Monitor or representative
- Patient on extracorporeal membrane oxygenation (ECMO) at time of randomization
- Any disease or condition that would, in the opinion of the site investigator or Sponsor, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The randomization of patients will be managed by a central Interactive Voice and Web Response System (IxRS) *through use of a dynamic hierarchical algorithm. The treatment assignments will be unblinded to selected Sponsor personnel to facilitate ongoing monitoring of safety and tolerability, including members of the IMC and SOC.*

All patients will be randomly assigned to receive either MHAA4549A 3600 mg or placebo at a 1:1 ratio stratified by *site*, whether patient is on PPV vs supplemental O_2 *at randomization*, and whether the patient has suspected or confirmed bacterial pneumonia vs no bacterial pneumonia *at randomization.* All patients will receive

oseltamivir (75 mg or 150 mg BID) for a minimum of 5 days. Treatment for longer than 5 days is permitted based on local investigator discretion.

Blinded personnel at each study site will make appropriate preparations and perform the IV infusions of study drug, as described in Section 4.3.3. The other parties who are involved in the conduct of the study (i.e., patients and blinded site personnel) will remain blinded to patient-specific treatment assignments until the final database lock after the completion of the study.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this trial. Bioanalytical laboratory personnel responsible for performing PK assays will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed. Samples from patients assigned to the comparator arm will not be analyzed except by request (e.g., to evaluate a possible error in study drug administration).

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code in IxRS. Treatment codes should not be broken except in emergency situations. *If the investigator wishes to know the identity of the study drug for any other reason, they should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event)*.

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all suspected unexpected serious adverse reactions (SUSAR)(see Section 5.6) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 MHAA4549A and Placebo

MHAA4549A, matching placebo, and up to 10-day supply of oseltamivir (Tamiflu®) will be supplied by the Sponsor. For information on the formulation, packaging, and handling of MHAA4549A and placebo; see the Pharmacy Manual and the MHAA4549A Investigator's Brochure.

The MHAA4549A vial delivers 10 mL (500 mg) of drug product solution, but may contain more (approximately 10.3 mL) than the stated volume to enable delivery of the entire 10 mL volume. MHAA4549A is formulated as 50 mg/mL in 10 mM sodium succinate, 240 mM sucrose, and 0.02% (w/v) polysorbate 20 at pH 5.5 and is contained in a 15 mL

forma vitrum (USP/PH. Eur. Type 1) glass vial. The drug product is suitable for single use only and contains no preservatives.

Placebo for MHAA4549A has the same composition as the drug product (without MHAA4549A) and is supplied in an identical vial configuration. The placebo contains no preservatives and is suitable for single-use only. Placebo is formulated as 10 mM sodium succinate, 240 mM sucrose, and 0.02% polysorbate 20 at pH 5.5 in a total volume of 10 mL in a 15 mL forma vitrum (USP/PH. Eur. Type 1) glass vial.

MHAA4549A and placebo are supplied in identical blinded vials labeled with unique kit numbers. IxRS will assign kit numbers for each treatment arm; all treatment arms will be assigned the same total number of vials for each treatment, and the same preparation instructions. Placebo is identical to active MHAA4549A in formulation and appearance but does not contain active drug substance.

4.3.1.2 Oseltamivir (Tamiflu)

Oseltamivir (Tamiflu) is an influenza NAI indicated for treatment of acute, uncomplicated influenza. For information on the formulation, packaging, and handling of oseltamivir; see the local prescribing information for oseltamivir.

Storage: Capsules should be stored at 25°C (77.7°F); excursions permitted to 15° to 30°C (59° to 86°F).

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 MHAA4549A and Placebo

The randomization of patients will be managed by a central IxRS. All patients will be randomly assigned to receive either a single dose of MHAA4549A 3600 mg IV or placebo IV at a 1:1 ratio. Oseltamivir will be dispensed via IxRS. Oseltamivir dosing is described in Table 2.

Administration of MHAA4549A or placebo will be performed in a setting with emergency medical equipment and personnel who are trained to monitor for and respond to medical emergencies. A qualified physician will be on site during study drug administration for all patients.

A single dose of MHAA4549A or placebo will be delivered by IV infusion following dilution in 0.9% normal saline over approximately 60 minutes. Study drug should be delivered using a 0.22 μm in-line filter. Compatibility testing has shown that MHAA4549A is stable when diluted in 0.9% normal saline in a polyvinylchloride, polyolefin bag, or ethylene vinyl acetate bag (EVA), at or above a combined total concentration of 0.24 mg/mL up to 27.0 mg/mL. Study drug must be administered within the treatment window outlined in Section 3.1.1. Further detailed instructions for preparation of study drug can be found in the Pharmacy Manual.

There are no recommended dosage modifications for MHAA4549A since it is a single infusion. Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. General supportive measures will be taken to manage any AEs associated with overdose. Patients experiencing such AEs will be followed up clinically until the event has resolved.

Trained clinical site staff responsible for adequate and accurate study drug administration, accounting, and management will administer study drugs to patients. Study drug preparation and dosing instructions will be provided to each site. The exact times of study drug administration will be recorded in the relevant dispensing/administration logs and patient's source notes. Any noncompliance or problems with study drug administration will be recorded in the patient's source notes and reported to the Sponsor if appropriate.

4.3.2.2 Oseltamivir-Neuraminidase Inhibitor (NAI)

The Sponsor will be providing oseltamivir (Tamiflu®) for this study for up to a 10-day course. Dosage and administration should follow local prescribing information for oseltamivir. Either 75 mg or 150 mg of oseltamivir will be administered twice daily as described in Table 2. Capsules can be opened and the granules administered via nasogastric tube, if required.

Guidelines for dosage modification for renal dosing are presented in Table 2.

Any overdose or incorrect administration of oseltamivir should be noted on the oseltamivir Administration eCRF. Adverse events associated with an overdose or incorrect administration of oseltamivir should be recorded on the Adverse Event eCRF.

Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary, empty (used) oseltamivir packets and unused oseltamivir capsules to the study site at the next follow up visit. Patients will record the date and time when each oseltamivir capsule is administered.

4.3.3 Investigational Medicinal Product Accountability

Investigational medicinal products (IMPs) required for completion of this study (i.e., MHAA4549A and oseltamivir) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMP will be stored in a secure pharmacy or locked area with access limited to authorized personnel, in accordance with the details provided in the Investigator's Brochure and Pharmacy Manual. Upon receipt, MHAA4549A and placebo vials must be refrigerated at 2°C to 8°C until use. MHAA4549A does not contain antimicrobial

preservatives; therefore, care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation. Dilute under appropriate aseptic conditions using 0.9% normal saline. The solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use should not exceed 24 hours at 2 to 8°C and/or 4 hours at ambient temperature (18°C – 24°C). If the dose solution is stored at 2°C – 8°C, it should be removed from refrigeration and allowed to reach room temperature prior to administration. If the infusion is interrupted and the combined ambient temperature storage and interruption time exceeds 4 hours, prepare a new dose solution to resume the infusion (see the Pharmacy Manual). Protect dose solutions from heat and intense light.

The total duration from the preparation of dose solutions to the end of infusion should not exceed 24 hours. Vials are intended for single use only; therefore, any remaining solution should be discarded (see the Pharmacy Manual).

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

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

4.4 POST-TRIAL ACCESS TO MHAA4549A

As this is single dose administration, Genentech does not intend to provide MHAA4549A to patients after the conclusion of the study or any earlier withdrawal. Patients may or may not be eligible for any potential subsequent trials of MHAA4549A under a separate protocol.

4.5 CONCOMITANT THERAPY AND FOOD

4.5.1 Permitted Therapy

Concomitant medication includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 30 days prior to screening to the study completion/discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. For any NAIs (e.g., oseltamivir, peramivir, zanamivir, laninimavir) that have been taken prior to study drug therapy, the number of doses and duration of therapy must be recorded.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

All therapies required for management of the patient's acute illness are permitted except for those listed below in Section 4.5.2.

4.5.2 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 7 days prior to study treatment, unless otherwise specified below: probenecid, amantadine, or rimantidine

Use of other NAIs, including but not limited to oral oseltamivir, inhaled zanamivir, oral ribavirin, laninimivir, and peramivir, are prohibited during the study, but allowed up to 3 days (6 doses) prior to study treatment as outlined in the exclusion criteria. If oseltamivir resistance is highly suspected or identified during treatment then, following discussion with the sponsor medical representative, an alternative NAI to oseltamivir may be used.

4.5.3 Prohibited Food

There are no prohibited foods for this study.

4.6 STUDY ASSESSMENTS

Please see Appendix 1a and Appendix 1b for the schedule of assessments performed during the study.

4.6.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed consent by authorized representatives may be obtained only if allowed by and in accordance with local regulations and Independent Review Board (IRB)/Independent Ethics Committee (IEC) policies and procedures. Informed Consent Forms (ICF) 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 randomization. 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.

4.6.2 Diagnostic Testing for Enrollment

All hospitalized patients with severe influenza A will be assessed for disease confirmation and enrollment into the study. A Sponsor-supplied rapid influenza test is required for the diagnosis of influenza A infection and uses *a* nasopharyngeal swab. When the Sponsor-supplied rapid influenza test is negative, the study inclusion criteria can be satisfied with a positive local molecular test (PCR) if the result is within the 48-hour screening window. *Patients may be enrolled based on a positive local molecular test (PCR) result within the 48-hour screening window, but the rapid influenza test*

must still be conducted prior to randomization. Other tests may not be used for enrollment in the study unless the Sponsor has reviewed and approved the use of the diagnostic.

4.6.3 Medical History and Demographic Data

Medical history includes clinically significant diseases and procedures, including chronic respiratory disease, infections, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days prior to the screening visit. A careful assessment of the patient's baseline SpO_2 should be made especially if the patient has a history of severe chronic lung disease.

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

4.6.4 Priority of Assessments

When events warrant, or in the opinion of the investigator, safety issues become paramount, safety assessments will always have priority over all other measurements and procedures. Under routine circumstances, however, PK, nasal virological, and biomarker serum/plasma samples have priority over other measurements. The timing and number of safety measurements may be modified based on clinical evaluations.

4.6.5 Physical Examinations

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

At protocol designated visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed which includes, at a minimum, evaluation of general appearance, dermatological examination of the injection sites, evaluations directed by patient-reported symptoms, and any other evaluations that the investigator deems clinically relevant. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as AEs, if appropriate, on the AE eCRF.

4.6.6 Vital Signs

Vital signs will include measurements of resting SpO_2 (see Section 4.6.7 for measurement), respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressures after the patient has been in a seated or supine position for at least 10 minutes. Patients in intensive care may have vital signs assessed following local procedures, but those procedures should be captured in the eCRF in accordance with the eCRF instructions.

4.6.7 Oxygen Saturation Measurements

To ensure that the respiratory status is well recorded, the following daily measurements will be performed. Unless clinically contraindicated, all patients will have their SpO_2 *and corresponding respiratory assessments* recorded daily in the morning between *6* am – *12 pm* local time. Patients on low-flow O_2 will have a daily trial of their SpO_2 while on and off the supplementation, as outlined in Appendix 2, and both values will be recorded.

If the patient is on oxygen supplementation, SpO_2 measured by pulse oximetry and the corresponding respiratory assessments (e.g. FiO_2, flow rate) will be recorded. If the patient is on PPV, partial pressure of O_2 (PaO_2) and the corresponding respiratory assessments (e.g. FiO_2, ventilator mode, ventilator respiratory rate, positive end-expiratory pressure) will be recorded.

4.6.8 Laboratory, Biomarker, and Other Biological Samples

Samples for the laboratory tests listed in Table 3 and Table 4 will be sent to the study site's local laboratory for analysis at screening and during the study, respectively.

Table 3 Laboratory Tests at Screening

Hematology:	***Clinical* Chemistry:**
Hemoglobin	Thyroid stimulating hormone (optional)
Hematocrit	
Erythrocyte count (RBC)	**Serology:**
Leukocytes (WBC)	HIV Serology
Neutrophils, segmented & bands	
Lymphocytes	**Misc:**
Monocytes	Pregnancy Test (urine or serum; women of child-bearing potential)
Eosinophils	
Basophils	
Platelets	

Note: Investigators must document their review of each laboratory report by signing (or initialing) and dating each report.

Table 4 Laboratory Tests During the Study

Hematology:	**Clinical Chemistry (Blood):**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Bicarbonate
Leukocytes (WBC)	Chloride
Neutrophils, segmented *& bands*	Calcium
Lymphocytes	Phosphorus
Monocytes	Magnesium
Eosinophils	Glucose
Basophils	Urea nitrogen (BUN) *or urea*
Platelets	Creatinine
Erythrocyte Sedimentation Rate (ESR) *(optional)*	Total cholesterol
	Total protein
Coagulation:	Albumin
Activated partial thromboplastin time (APTT)	Total bilirubin
Prothrombin time (PT)	Alkaline phosphatase
International Normalized Ratio (INR)	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
Urinalysis:	Amylase
pH	Gamma-glutamyl transpeptidase (GGT) (if clinically indicated)
Specific gravity	
Glucose	C-reactive protein (CRP) *(optional)*
Protein	
Ketones	**Misc:**
Blood	Pregnancy Test (if clinically indicated)
Bilirubin	
Nitrite	
Leukocyte esterase	
Microscopic examination (if clinically indicated)	

Note: Investigators must document their review of each laboratory report by signing (or initialing) and dating each report.

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

- [redacted]
- [redacted]

- [redacted]

[redacted]

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

4.6.9 Electrocardiograms

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

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

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is $>$ 500 ms and/or $>$ 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QT interval corrected using Fridericia's formula (QTcF) has stabilized on two successive ECGs. The Medical Monitor should be notified. *If QTcF is not available, QTcB may be recorded. Standard of care* treatment may be instituted per the discretion of the investigator. If a PK sample

is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 4.9.2. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, medications known to prolong the QT interval, severe bradycardia).

4.6.10 [redacted]

[redacted]

[redacted]

4.7 APACHE AND SOFA SCORES

Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) scores are for patients that are admitted into the ICU. These assessments are not required for study conduct or entry but should be collected if available. The initial scores for APACHE and SOFA should be taken within 24 hours of entry into the ICU and at specified time points as seen in Appendix 1a.

For the calculation of the initial APACHE and SOFA scores, the worst values in the first 24 hours of ICU admission should be used. SOFA scores are only for patients admitted into the ICU that have available data for calculation (i.e., *partial* pressure of *arterial* oxygen/fraction of inspired oxygen [PaO_2/FiO_2] in mmHg). See Appendix 7 for SOFA score calculation.

4.8 *OSELTAMIVIR MEDICATION DIARY*

Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary, empty (used) oseltamivir packets, and unused oseltamivir capsules to the study site at the next follow up visit.

Patients will record the date and time when each oseltamivir capsule is administered.

4.9 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.9.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.9.2 Study Treatment Discontinuation

Patients must discontinue MHAA4549A infusion and therefore treatment if they experience any of the following:

- Infusion related reactions

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

- Pregnancy
- Serious skin/hypersensitivity reactions

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

The IMC and SOC may recommend to permanently discontinue dosing for all patients within one or both study arms in the event of a general safety concern.

4.9.3 Study Completion/Early Discontinuation Visit

Patients who complete all study visits through Day *60* are considered to have completed study. All patients who discontinue from *the* study early will be asked to complete *all assessments for the current visit day and for* the early discontinuation visit *without duplication.* Please see Schedule of Assessments provided in Appendix 1a for assessments performed at the Study Completion/Early Discontinuation visit.

4.9.4 Study and Site Discontinuation

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

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

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

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

MHAA4549A is not approved and is currently in clinical development. Thus, the entire safety profile is not known at this time. The safety plan for this study is based upon preclinical data and the previous Phase 1 and Phase 2a (interim) studies and is designed to ensure patient safety. It will include specific eligibility criteria and monitoring assessments as detailed below and above in Section 4.1.

The investigator, in consultation with the Sponsor, is responsible for assuring the safety of study participants who have entered this study and for taking appropriate action concerning any event that seems unusual, even if this event may be considered to be an unanticipated benefit to the study participant. The investigator will be responsible for a clinical assessment of the study participants before discharge from the study, and for the establishment of a discharge plan, if needed.

During the study, the incidence and nature of adverse events, serious adverse events, and laboratory abnormalities will be assessed. An ongoing *blinded* review of safety will be *carried out* by the Medical Monitor *and a* drug safety scientist. An unblinded review of safety will be performed *on an ongoing regular basis by the IMC and SOC* as described in *the IMC* and *SOC agreement*.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

Adverse events will be monitored throughout the entire study (enrollment through Day *60* or Early Discontinuation). If clinically significant signs or laboratory values are observed in a study participant, the investigator should repeat an assessment at the earliest opportunity. Only those events or laboratory values that exceed the level of clinical significance upon the repeat assessment will be considered an adverse event.

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Fatal (i.e., the adverse event actually causes or leads to death)

- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS); see Section 5.3.3, Appendix 8, and Appendix 9); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Non-serious adverse events of special interest (AESI) are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study 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 (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

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

- Adverse events associated with suspected cases of infusion-related reactions (IRR) which occur within 24 hours of study drug administration and may show the following signs and symptoms (for guidance on reporting AEs associated with IRR, see Section 5.3.5.1 below):
  - Fever and/or shaking chills
  - Flushing and/or itching
  - Alterations in heart rate and blood pressure
  - Dyspnea or chest discomfort
  - Back or abdominal pain
  - Nausea, vomiting, and/or diarrhea
  - Various types of skin rashes
  - Anaphylaxis
- Anaphylaxis due to IV drugs most often presents with the following signs and symptoms:
  - Cutaneous symptoms: flushing, itching, urticaria, and/or angioedema (usually of face, eyelids, or lips)
  - Respiratory symptoms: repetitive cough, sudden nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and or change in voice quality due to laryngeal edema
  - Cardiovascular symptoms: faintness, tachycardia (or less often bradycardia), tunnel vision, chest pain, hypotension, sense of impending doom, and/or loss of consciousness
  - Gastrointestinal symptoms: such as nausea, vomiting, abdominal cramping, and diarrhea

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until the Day *60* visit or Early Discontinuation visit. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any death or other serious adverse event that occurs after discharge, regardless of causality. The Sponsor should also be notified if the investigator becomes aware of a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

Investigators will seek information on adverse events and serious adverse events at each patient contact. All AEs, and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded.

The adverse event grading (severity) scale in the DAIDS v1.0 will be used for assessing AE severity (see Table 5).

Table 5 Adverse Event Grading (Severity) Scale

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical AE NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

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

Table 6 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Other Adverse Events

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF, unless the severity increases. If a persistent adverse event becomes more severe, it should be recorded as a separate event on the Adverse Event

eCRF. The initial (less severe) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became more severe. If a persistent adverse event becomes serious, it should be recorded as a separate event on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The initial (non-serious) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became serious.

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

5.3.5.4 Abnormal Laboratory Values

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

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment (laboratory abnormalities should be repeated at the first opportunity and only considered clinically significant if they persist on repeat assessment)

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

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

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment. Abnormal vital sign values should be repeated at the first opportunity and only considered clinically significant if they persist on repeat assessment)

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq$35% is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

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

the event) either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of severe influenza or any related co-morbidities should be recorded on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF, and immediately reported to the Sponsor as an SAE (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

5.3.5.8 Pre-existing Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of Influenza A Infection

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

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Adverse Events Associated with an Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No clinical safety data related to overdosing of MHAA4549A are available, however, overdoses with a monoclonal antibody theoretically could cause volume overload that can result in edema and/or heart failure.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

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

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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/IEC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

[redacted] Medical Monitor contact information:

Primary Medical Monitor: [redacted]

Telephone Nos.: US Office: [redacted]

US Mobile: [redacted]

Secondary Medical Monitor: [redacted]

Telephone Nos.: US Office: [redacted]

US Mobile: [redacted]

Genentech Medical Monitor contact information for all sites if above medical monitor cannot be reached:

Medical Monitor: [redacted]

Telephone Nos.: US Mobile [redacted]

US Office [redacted]

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. A paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to the Sponsor's Safety Risk Management department or its

designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided below per region:

Asia Pacific: [redacted]

Europe: [redacted]

Latin America: [redacted]

North America: [redacted]

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until the patient is at Day *60* or Early Discontinuation. Although the investigator is not required to actively monitor patients for adverse events after the patient has been discharged from the study, the Sponsor should be notified if the investigator becomes aware of any death or other serious adverse event that occurs after discharge *from the study, if determined to be related to study drug by the investigator*. The Sponsor should also be notified if the investigator becomes aware of a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug (see Section 5.4.3).

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

In the event that the EDC system is unavailable, a paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to investigators (see fax numbers provided in Section 5.4.2.1). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 120 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should

continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, a paper Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see fax numbers provided in Section 5.4.2.1). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant within 30 days after the dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

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

5.4.4 Investigator Follow-Up

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

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF and the Investigator document a discharge plan.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.4.5 Sponsor Follow-Up

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

5.5 POSTSTUDY ADVERSE EVENTS

At the time of study completion or study discontinuation, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient or their personal physician believes could be related to prior study drug treatment or study procedures.

The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as *60* days after the dose of study drug). However, the Sponsor should be notified if the investigator becomes aware of any death, other serious adverse event, or non-serious adverse event of special interest occurring after the end of the adverse event reporting period, regardless of causality. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient or a female partner of a male patient exposed to study drug.

The investigator should report these events by completing and faxing a paper Serious Adverse Event Reporting Form and fax cover sheet to Safety Risk Management using the fax numbers provided to investigators (see Section 5.4.2.1).

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

The Sponsor will promptly evaluate all serious adverse events including suspected unexpected serious adverse reactions (SUSARs) and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, IECs, and applicable health authorities based on applicable legislation.

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

- MHAA4549A Investigator's Brochure
- Local prescribing information for oseltamivir

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

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

Certain adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting. These anticipated events include, but are not limited to, the following:

- *Asymptomatic e*levations of ALT, AST, and or amylase *without corresponding elevations of bilirubin* have been shown to be increased during influenza A infection (Polakos 2006)
- Influenza associated disease and or complications of influenza

An *IMC and SOC* will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

All efficacy analyses will be conducted according to the intent-to-treat principle and will include all patients who meet the following condition with patients allocated to the treatment arm to which they were randomized:

- Randomized patients who have confirmed influenza A infection as confirmed by a central PCR test from Day 1 samples

Safety analyses will include all patients who were included in the randomization and who received at least one dose of study medication, with patients allocated to the treatment arm associated with the regimen actually received.

No formal hypothesis testing will be done in this study. As a result, no adjustment for a type 1 error will be made to account for the multiplicity of analyses.

Final efficacy and safety analyses of the total study population will be conducted at the end of the study after all patients have completed all study assessments and the database has been cleaned and closed. Further details of the analyses, including analysis of the exploratory endpoints, will be contained in the statistical analysis plan

(SAP) which will be prepared and finalized before the *first* optional interim analysis (see Section 6.7) or the final efficacy and safety analysis, if no interim analysis takes place.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is estimation of the effect size and hypothesis generation regarding the effect of MHAA4549A on the time to normalization of respiratory function relative to the standard of care rather than hypothesis testing. Point and interval estimates will be obtained. A total of 334 patients will be enrolled in this study in order to obtain approximately 300 evaluable patients (an estimated dropout rate of 10%). It is assumed that the median time to normalization of respiratory function in the control arm is 5 days. *This sample size (approximately 150 patients per arm) provides 75% power to detect a treatment difference of 1 day for the primary endpoint assuming a 2-sided alpha of 0.2.*

Operating characteristics (power) *under other possible assumptions for 2-sided alpha of 0.05 and* true differences of 1 to 2 days are provided in Table 7.

Table 7 Operating Characteristics for Proposed Study Design for Several Possible True Underlying Median Values

	True Underlying Median for MHAA4549A		
	3 days	3.5 days	4 days
Hazard Ratio	0.60	0.70	0.80
Power of log-rank test [a]	99%	86%	48%
95% confidence interval for true hazard ratio [b]	(0.48, 0.75)	(0.56, 0.88)	(0.64, 1.00)

Note: Operating characteristics are based on the following assumptions: 300 evaluable patients, event times are exponentially distributed, median time to normalization of respiratory function in the control arm is 5 days, and patients are followed for *60* days.

[a] Two-sided $\alpha = 0.05$.

[b] Confidence intervals are based on the assumption that the point estimate is equal to the true underlying value of the hazard ratio in each column.

It should be noted that the study is underpowered for detection of minimally clinically meaningful differences *at a 2-sided alpha of 0.05* such as a true hazard ratio of 0.80 (see third column of Table 7.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue (early discontinuation of treatment or early termination from the study), and complete the study will be tabulated by treatment group using descriptive statistics. Reasons for early discontinuation of treatment or early termination from the study will be listed and summarized by treatment group. Any eligibility criteria exceptions and other protocol deviations will also be summarized by treatment group.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics of the patient will be summarized for all randomized patients by treatment group by use of descriptive statistics. Baseline is defined as the last available value prior to study drug administration.

During the study; patient disposition, concurrent treatment, and compliance with study treatment and visits will be summarized on the safety analysis population using descriptive statistics.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized patients who are confirmed to be influenza A infected, with patients grouped according to the treatment assigned at randomization.

Time to event data will be computed using Kaplan-Meier methodology and stratified Cox proportional hazards models and will be summarized using n, median when estimable, hazard ratios, and 95% confidence intervals. Patients who are lost to follow-up (while event free) will be censored at the time that they are last known to be event free.

Estimation of the treatment difference of proportions and its 95% confidence interval will be calculated using stratum-adjusted Mantel-Haenszel methodology (Koch et al. 1989). For continuous endpoints, Analysis of Covariance methods (after appropriate transformation of data) will be used to estimate treatment differences and 95% confidence intervals.

Other than censoring in the time to event analyses, no other imputation for missing data will be performed.

6.4.1 Primary Efficacy Endpoint

- Median time to normalization of respiratory function

6.4.2 Secondary Efficacy Endpoints

- Proportion of patients with clinical failure *after* 24 hours post-infusion of study drug
- Median time to clinical resolution of vital signs
- Hazard ratio for mortality at Day 14*, Day 30,* and Day *60*
- Mean and median AUC of viral load
- Mean and median peak viral load
- Median duration of viral shedding in upper respiratory samples
- Median duration of hospitalization
- Median duration of ICU stay
- Proportion of patients requiring antibiotics for respiratory indications during study

- Proportion of patients with influenza secondary complications
- Median duration of ventilation
- Proportion of patients who are readmitted by Day 30 *and Day 60*

6.4.3 Subgroup Analyses

Subgroup analyses will be performed to examine the consistency of the treatment estimates with use of the primary and selected secondary endpoints. Subgroups will include the stratification factors as well as patients who are identified at baseline as influenza A positive by the upper, lower, or both airways and by patients with bacterial co-infections at admission. Additional subgroups may be added following assessment of baseline characteristics as exploratory analyses.

6.5 SAFETY ANALYSES

The safety analyses will include all randomized patients who received study drug, with patients grouped according to the treatment actually received. Safety parameters to be evaluated include adverse events (including deaths, serious adverse events, discontinuations due to adverse events, and the incidence and severity of adverse events), clinical laboratory tests, vital signs (including SpO_2 measurements), and ECGs.

All collected adverse event data will be listed by study site and patient number.
All adverse events that occur on or after treatment on Day 1 will be summarized for each treatment group by mapped term, appropriate thesaurus levels, body system, and event within each body system, and toxicity grade. In addition, all serious adverse events, including deaths, will be listed separately and summarized. SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) that occur between consent and first dose of study medication will be listed separately.

Laboratory data with values outside of the normal ranges will be identified. In addition, select laboratory data will be summarized by treatment group using descriptive summary statistics.

The absolute and percentage changes from baseline in vital sign parameters will be computed, and changes deemed clinically significant by the Investigator will be noted. Appropriate descriptive summary statistics will be provided for all vital sign parameters

6.6 PHARMACOKINETIC ANALYSES

Individual and mean serum MHAA4549A concentration versus time data will be tabulated and plotted. The serum pharmacokinetics of MHAA4549A will be summarized by estimating total serum drug exposure (i.e., AUC), C_{max}, C_{min}, total serum clearance, half-life, and volume of distribution, as data allow. Estimates for these parameters will be tabulated and summarized (e.g., mean, standard deviation, coefficient of variation).

Inter-patient variability will be evaluated. MHAA4549A serum concentration–time data may be compared with available data from other MHAA4549A clinical studies.

[redacted]

[redacted]

6.7 OPTIONAL INTERIM ANALYSIS

Given the *hypothesis-generating nature* of this study*,* the Sponsor may choose to conduct *up to two* interim efficacy *analyses. The decision to conduct* an optional interim analysis and *the* timing *of* the analysis will be documented in the *Sponsor's trial master file* prior to the conduct of the interim analysis. *The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel who will be unblinded at the treatment group* level*. Access to treatment assignment information will follow the Sponsor's standard procedures.*

If conducted, an interim analysis would be for administrative purposes only (i.e., internal planning or decision making) and would not impact the conduct of the current study in any way. A nominal type I error penalty of 0.0001 will be taken.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

The Consent Forms must be signed and dated by the patient or the patient’s authorized representative as applicable and in accordance with local regulations, and IRB/IEC policies, before his or her participation in the study. The case history or clinical records

for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments (see Section 9.1).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/IEC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible

for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC, and archived in the site's study file.

8.4 CONFIDENTIALITY

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

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

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate, financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient, last visit [LPLV]).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and

data integrity to the Sponsor and to the IRB/IEC in accordance with established IRB/IEC policies and procedures.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

Genentech, Inc., a member of the Roche group, is the Sponsor of this study. A clinical research organization (CRO) may provide clinical operations oversight, including but not limited to project management, clinical monitoring and site management, data quality support, medical monitoring, and some safety reporting and regulatory activities as specified in study management plans. Genentech will provide CRO oversight, develop the database and randomization scheme, and conduct statistical programming and analysis. An *IMC and SOC* will provide safety monitoring for the study *in addition to the ongoing review of safety by the Medical Monitor and Safety Scientist*.

EDC will be utilized for this study. An IxRS will be used to assign patient numbers, randomize patients into study *through use of a dynamic hierarchical algorithm*, and manage site drug supply. A central laboratory will be used for sample management and storage until shipment to specialty laboratories or Genentech for analysis.

9.5 PROTOCOL AMENDMENTS

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

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

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APPENDIX 1a
Schedule of Assessments: Hospitalization Days

Notes: Unless otherwise indicated, all assessments on Day 1 should be performed prior to study drug administration; x's within parentheses, i.e., (x), indicate optional assessments. Please refer to Follow-up Period table for visits to be completed *after* patient is discharged from hospital prior to Day *60*.

	Screening	Hospitalized Days (only to be completed while patients are hospitalized)															*D60*
Day (D)	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D14	D20	D25	Hospital Discharge [a]	D30	Study Completion or Early Discontinuation while Hospitalized
Confirm study drug administration can occur within 48 hours of hospital admission																	
Informed consent [b]	x																
Rapid influenza A test [c]	x																
Local influenza A PCR test [d]	x																
Inclusion/exclusion criteria	x																
Medical history and demographic data	x																
Confirm onset of flu symptoms (≤ 5 days prior to study drug administration on Day 1)	x																
Confirm history of baseline $SpO_2 > 92\%$	x																
Pregnancy screening [e]	x																
Confirm O_2 requirement [f]	x																
Respiratory Assessment [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
APACHE score [j]		(x^z)										(x)			(x)	(x)	(x)
SOFA score [k]		(x^z)						(x)				(x)			(x)	(x)	(x)

APPENDIX 1a (cont'd)
Schedule of Assessments: Hospitalization Days

	Screening	Hospitalized Days (only to be completed while patients are hospitalized)															*D60*
Day (D)	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D14	D20	D25	Hospital Discharge [a]	D30	Study Completion or Early Discontinuation while Hospitalized
Electrocardiogram (12-lead) [l]		x				x						x			x	x	x
Randomization		x															
MHAA4549A administration		x[m]															
Oseltamivir administration [n]		x	x	x	x	x	(x)	(x)	(x)	(x)	(x)						
Complete physical examination [o]	x	(x)															
Limited, symptom-directed physical examination [p]			x	x	x	x						x			x	x	x
Weight & height, BMI [q]	x[q]	x				x						x			x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [r]	x		x			x						x			x	x	x
Chemistry panel [r]	*(x)*[aa]	x	x			x						x			x	x	x
Coagulation panel [r]		x				x						x			x	x	x
Erythrocyte sedimentation rate		*(x)*	*(x)*			*(x)*						*(x)*			*(x)*	*(x)*	*(x)*
C-reactive protein		*(x)*	*(x)*			*(x)*						*(x)*			*(x)*	*(x)*	*(x)*
Urinalysis [r, s]		x	x			x						x			x	x	x
Serology (HIV) [bb, r]	x																
Upper respiratory tract sample (NP sample) [t]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
[redacted]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Flu antibodies (HAI)		x										x			x	x	x

APPENDIX 1a (cont'd)
Schedule of Assessments: Hospitalization Days

Day (D)	Screening	Hospitalized Days (only to be completed while patients are hospitalized)													Hospital Discharge [a]	D30	*D60* Study Completion or Early Discontinuation while Hospitalized
	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D14	D20	D25			
[redacted]		x														x	x
Serum for MHAA4549A PK measurements [v]		x	x	x		x		x				x			x	x	x
[redacted]		x				x									(x)[x]		
[redacted]		x	x	x		x		x			x	x	x	x	x	x	x
[redacted]		x	x	x		x		x			x	x	x	x	x	x	x
[redacted]		x													x	x	x
[redacted]		x														x	x
[redacted]		x													x	x	x
[redacted]		x													x	x	x
[redacted]															x		
Oseltamivir medication diary[cc]															*x*		

[redacted]; APACHE = Acute Physiology and Chronic Health Evaluation; ATA = Anti-therapeutic antibodies; BMI = body mass index; D = day; Dx = diagnostics; eCFR = electronic Case Report Form; ECG = electrocardiogram; HAI = hemagglutinin inhibition; [redacted]; ICU = Intensive Care Unit; IRB/IEC = Independent Review Board/Independent Ethics Committee; NAI = neuraminidase inhibitor; NP = nasopharyngeal; O_2 = oxygen; PaO_2/FiO_2 = *partial* pressure of oxygen/fraction of inspired oxygen; PCR = polymerase chain reaction; PD = pharmacodynamics; PK = pharmacokinetic; PPV = positive pressure ventilation; qPCR = quantitative Polymerase Chain Reaction; RBCs = red blood cells; SOFA = Sequential Organ Failure Assessment; SpO_2 = oxygen saturation *measured by pulse oximetry*; WBCs = white blood cells.

APPENDIX 1a (cont'd)
Schedule of Assessments: Hospitalization Days

[a] Assessments to be performed irrespective of day of discharge. Assessments on discharge day will supersede assessments for matching day except for the study completion/early *discontinuation visit (e.g., If a patient is discharged from the hospital on Day X, use assessments under "hospital discharge" column instead of the Day X column and record under the hospital discharge folder in the eCRF. If a patient discontinues from the study early on Day X, complete all assessments under the Day X column and "early discontinuation" column without duplication, and record under the early discontinuation folder in the eCRF).*

[b] Informed consent must be obtained from all patients. For patients who are unable to consent, an authorized representative may be used if allowed by local regulations and IRB/IEC policy.

[c] Sponsor-supplied rapid influenza test using nasopharyngeal swabs.

[d] If the Sponsor-supplied rapid influenza test is negative, local influenza PCR testing can be used to confirm influenza A and satisfy entry criteria if results are received within screening/hospitalization window (48 hours). *Patients can be enrolled based on a positive local influenza PCR test result within the 48 hour screening window, but the rapid influenza test must still be conducted prior to randomization.*

[e] A urine pregnancy test should be sent only for women considered by the investigator to be of childbearing potential, see exclusion criteria. This result must be available prior to randomization. If urine testing is not available at the site, blood already collected from an existing sample may be tested for pregnancy.

[f] Confirm patient requires *supplemental* O_2 or PPV with*in* 24 hours of *hospital admission*.

[g] All patients will have their on-study SpO_2 *and corresponding respiratory assessments* recorded daily in the morning between *6* am*–12 pm* local time; screening SpO_2 may be taken outside this window. Patients on low flow O_2 should have a daily trial of their SpO_2 while on and off the supplementation and both values will be recorded. *If the patient is on oxygen supplementation, SpO_2 measured by pulse oximetry and the corresponding respiratory assessments (e.g. FiO_2, flow rate) will be recorded. If the patient is on PPV, PaO_2 and the corresponding respiratory assessments (e.g. FiO_2, ventilator mode, ventilator respiratory rate, positive end-expiratory pressure) will be recorded.*

[h] Concomitant medications should be recorded for 30 days prior to screening, through the study completion/early discontinuation visit. See exclusion criteria in Section 4.5.2 for prohibited therapies.

[i] Vital signs will be collected within 1 hour before MHAA4549A infusion and within 1 hour after completion of MHAA4549A infusion include temperature, respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure. Temperature should be measured using the same methodology throughout the study and should be measured prior to administration of any antipyretic drugs. In patients who have multiple vital signs taken during any day, the most abnormal value should be recorded from that 24-hour period. Temperature, blood pressure, respiratory rate, and heart rate will be completed after the patient has been supine for > 5 minutes. *The worst/most abnormal value from the last 24-hour period should be recorded for patients who are in the ICU.*

[j] APACHE scores are optional and only for patients that are in the ICU. For calculation of the screening APACHE score, the worst values in the preceding 24 hours should be used. APACHE scores are not required for study conduct or entry but should be collected if available.

[k] SOFA scores are only for patients in the ICU that have available data such as PaO_2/FiO_2 (mmHg). See Appendix 7 for SOFA score calculation.

[l] Patient should rest in a supine position for 10 minutes prior.

[m] Patient will be a resident for at least 24 hours following administration of MHAA4549A.

[n] Oseltamivir must be given for a minimum of 5 days. Treatment longer than 5 days is permitted based on the discretion of the investigator [indicated by (x)].

[o] Complete physical examination includes evaluations of general appearance of head, eye, ear, nose, and throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as adverse events, if appropriate.

[p] Limited, symptom-directed physical examination includes, at a minimum, evaluation of general appearance, dermatological examination of the injection sites, evaluations directed by patient-reported symptoms, and any other evaluations that the investigator deems clinically relevant. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as adverse events, if appropriate.

[q] Height will be obtained at screening only. Weight will be obtained at all indicated visits. Height and weight will be recorded in centimeters and kilograms, respectively.

[r] Local laboratory measurements should be utilized.

[s] Urinalysis includes pH, specific gravity, glucose, protein, ketones, blood, bilirubin, nitrite, and leukocyte esterase. Microscopic examination (e.g., sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) will be performed if clinically indicated.

[redacted]

[v] Day 1 serum PK samples are to be drawn 30 (± 5) minutes pre-dose of MHAA4549A, 60 (± 15) minutes after the end of infusion. PK samples will be drawn from the contralateral arm from that used for drug infusion and must be labeled with the exact time of draw.

[redacted]

[x] If patient is discharged on or before Day 5, the oseltamivir PK sample should be taken on the discharge day.

[redacted]

[z] Assessment to be conducted based on entry into ICU; may vary from patient to patient.

[aa] *For optional thyroid stimulating hormone test*

[bb] *HIV serology result not needed for randomization*

APPENDIX 1a (cont'd)
Schedule of Assessments: Hospitalization Days

[cc] *Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary, empty (used) oseltamivir packets and unused oseltamivir capsules to the study site at the next follow up visit. Patients will record the date and time when each oseltamivir capsule is administered.*

APPENDIX 1b
Schedule of Assessments: Follow-Up Period

- If a patient is discharged prior to Day 14, he/she will need to complete the following assessments for Day 14 ,Day 30, *and Day 60* below.
- If a patient is discharged prior to Day 30 and after Day 14, he/she will need to complete the following assessments for Day 30 *and Day 60* below.
- *If a patient is discharged prior to Day 60 but after Day 30, he/she will need to complete the following assessments for Day 60 below.*
- If patient is hospitalized for Day 14, *Day 30,* and/or Day *60*, please refer to Appendix 1a.

Day (D)	D14 ± 1 (If discharged BEFORE D14)	*D30 ± 4 (If discharged BEFORE D30)*	*Day 60* ± 4 (Study Completion) or Early Discontinuation
Concomitant medications [a]	x	x	*x*
Vital signs [b]	x	x	x
Electrocardiogram (12-lead) [c]	x	x	x
Weight & height, BMI [d]	x	x	x
Adverse events	x	x	x
Hematology [e]	x	x	x
Chemistry panel [e]	x	x	x
Coagulation panel [e]	x	x	x
Urinalysis [e]	x	x	x
Flu antibodies (HAI)	x	x	x
[redacted]		x	x
Serum for MHAA4549A PK measurements [f]	x	x	x
[redacted]	x	x	x
[redacted]	x	x	x
[redacted]		x	x
[redacted]		x	x
[redacted]		x	x
[redacted]		x	x

[redacted]; ATA = Anti-therapeutic antibodies; BMI = body mass index; D = day; Dx = diagnostics; eCFR = electronic Case Report Form; ECG = electrocardiogram; HAI = hemagglutinin inhibition; [redacted]; PD = pharmacodynamics; PK = pharmacokinetic.

APPENDIX 1b (cont'd)
Schedule of Assessments: Follow-up Period

[a] Concomitant medications should be recorded for 30 days prior to screening, through the study completion/early discontinuation visit. See exclusion criteria in Section 4.5.2 for prohibited therapies.

[b] Vital signs include temperature, respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure. Temperature should be measured using the same methodology throughout the study and should be measured prior to study drug administration of any antipyretic drugs. In patients who have multiple vital signs taken during any day, the most abnormal value should be recorded from that 24-hour period. Temperature, blood pressure, respiratory rate, and heart rate will be completed after the patient has been supine for > 5 minutes.

[c] ECG should be recorded after the patient has rested in a supine position for 10 minutes.

[d] Height will be obtained at screening only. Weight will be obtained at all indicated visits. Height and weight will be recorded in meters and kg, respectively.

[e] Local laboratory measurements should be used.

[f] PK samples should be drawn from the *opposite* arm from the one used for drug infusion and must be labeled with the exact time of draw.

[redacted]

APPENDIX 2
Time to Normalization of Respiratory Function

For the purposes of this study, the time to normalization of respiratory function will be defined as the time to removal of the patient from O_2 supplementation in order to maintain an $SpO_2 > 95\%$.

Patients who are on low flow O_2 (2-6L/min) should receive a daily trial off O_2 in the morning between 6 am $- 12\ pm$ as described below.

1. Patient should be resting or sitting.

2. Patient should be fitted with pulse oximeter, and their SpO_2 should be checked once while on O_2 and then again $3 - 5\ minutes$ after turning off O_2 supplementation.

3. If the $SpO_2 > 95\%$, then the time and reading should be recorded. Notify the study doctor so that he/she can make a clinical judgment to determine whether the O_2 can be removed.

4. If the patient is off O_2 for 24 hours and his/her reading the subsequent day is >95%, then the endpoint is considered satisfied. The recorded time for the endpoint corresponds with the initial discontinuation of O_2 and reading.

APPENDIX 3

[redacted]

APPENDIX 4

[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX 5

[redacted]

APPENDIX 6

[redacted]

APPENDIX 7
SOFA Score Calculation

Administration of MHAA4549A will be performed in a setting with emergency medical equipment and personnel who are trained to monitor for and respond to medical emergencies. A qualified physician will be on site during study drug administration for all patients.

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Airway management equipment
- O_2
- *Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice*
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

Stop the study drug infusion.

Maintain an adequate airway.

Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.

Continue to observe the patient and document observations.

APPENDIX 8
DAID*S* Toxicity Grading Tables for Clinical Abnormalities

From the FDA Guidance document 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials' (September 2007)

Vital Signs [a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) [b] (°F)*	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40.0 102.1 – 104.0	>40 >104
Tachycardia – beats per minute	101- 115	116 – 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia – beats per minute [c]	50 – 54	45 – 49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) – mmHg	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mmHg	91 – 95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mmHg	85 – 89	80 – 84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	>25	Intubation

[a] Subject should be at rest for all vital sign measurements.

[b] Oral/tympanic temperature; no recent hot or cold beverages or smoking.

[c] When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

APPENDIX 8 (cont'd)
DAID*S* Toxicity Grading Tables for Clinical Abnormalities

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/ vomiting	No interference with activity or 1 – 2 episodes/ 24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 g/ 24 hours	4 – 5 stools or 400 – 800 g/ 24 hours	5 or more watery stools or > 800 g/ 24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity no requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

APPENDIX 9
DAIDS Toxicity Grading Tables for Laboratory Abnormalities

Adapted from Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007 DRAFT and FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials

Abbreviations used in the table:
[redacted]; CPK = creatine phosphokinase; Dec = Decreased; IV = Intravenous; LLN = Lower limit of normal; Mod = Moderate; Req = Required; Rx = Therapy; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = Upper limit of normal.

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 – 10.5 g/dL	8.0 – 9.4 g/dL	6.5 – 7.9 g/dL	<6.5 gm/dL
Absolute Neutrophil Count	1,000 – 1,500/mm^3	750 – 999/mm^3	500 – 749/mm^3	<500/mm^3
*Platelets	125,000 – 140,000/mm^3	100,000 – 124,999/mm^3	25,000 – 99,999/mm^3	<25,000/mm^3
WBCs	11,000 – 13,000/mm^3	13,000 – 15,000/mm^3	15,000 – 30,000/mm^3	>30,000 or <1,000/mm^3
*Lymphocytes Decrease – cell/mm^3	750 – 1,000	500 – 749	250 – 499	<250
*Eosinophils – cell/mm^3	650 – 1500	1501 – 5000	>5000	Hypereosinophilic
Abnormal Fibrinogen	Low: 100 – 200 mg/dL High: 400 – 600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: <50 mg/dL	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20 – 40 mcg/mL	41 – 50 mcg/mL	51 – 60 mcg/mL	>60 mcg/mL
Prothrombin Time (PT)	1.01 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin Time (APTT)	1.01 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3 x ULN	>3 x ULN
Methemoglobin	5.0 – 9.9%	10.0 – 14.9%	15.0 – 19.9%	>20.0%

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

APPENDIX 9 (cont'd)
DAIDS Toxicity Grading Tables for Laboratory Abnormalities

CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130 – 135 mEq/L	123 – 129 mEq/L	116 – 122 mEq/L	<116 mEq/L or abnormal sodium with mental status changes or seizures
Hypernatremia	146 – 150 mEq/L	151 – 157 mEq/L	158 – 165 mEq/L	>165 mEq/L or abnormal sodium with mental status changes or seizures
Hypokalemia	3.0 – 3.4 mEq/L	2.5 – 2.9 mEq/L	2.0 – 2.4 mEq/L or intensive replacement therapy or hospitalization required	<2.0 mEq/L or abnormal potassium with paresis ileus or life-threatening arrhythmia
Hyperkalemia	5.6 – 6.0 mEq/L	6.1 – 6.5 mEq/L	6.6 – 7.0 mEq/L	>7.0 mEq/L or abnormal potassium with life-threatening arrhythmia
Hypoglycemia	55 – 64 mg/dL	40 – 54 mg/dL	30 – 39 mg/dL	<30 mg/dL or abnormal glucose with mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 – 160 mg/dL	161 – 250 mg/dL	251 – 500 mg/dL	>500 mg/dL or abnormal glucose with ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 – 7.8 mg/dL	7.7 – 7.0 mg/dL	6.9 – 6.1 mg/dL	<6.1 mg/dL or abnormal calcium with life threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6 – 11.5 mg/dL	11.6 – 12.5 mg/dL	12.6 – 13.5 mg/dL	>13.5 mg/dL or abnormal calcium with life-threatening arrhythmia
Hypomagnesemia	1.4 – 1.2 mEq/L	1.1 – 0.9 mEq/L	0.8 – 0.6 mEq/L	<0.6 mEq/L or abnormal magnesium with life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 – <1.25 x ULN	1.25 – <1.5 x ULN	1.5 – 1.75 x ULN	>1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 – <1.5 x ULN	1.5 – <2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 – 8.0 x ULN	>8.0 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 – 8.0 x ULN	>8.0 x ULN
GGT	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 – 8.0 x ULN	>8.0 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 – 8.0 x ULN	>8.0 x ULN
Amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	>5.1 x ULN
Lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	>5.1 x ULN
*CPK – mg/dL	1.25 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 10.0 x ULN	>10 x ULN

*From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg – 1 g loss/day	2-3+ or 1-2 g loss/day	4+ or 2-3.5 g loss/day	Nephrotic syndrome or >3.5 g loss/day
Hematuria	Microscopic only <10 rbc/hpf	Gross, no clots >10 rbc/hpf	Gross, with or without clots, OR red blood casts	Obstructive or required transfusion
*Glucose	Trace	1+	2+	Hospitalization for hyperglycemia

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

PROTOCOL

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY, IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION**
PROTOCOL NUMBER:	GV29216
VERSION NUMBER:	*3 (VHP Only)*
EUDRACT NUMBER:	2014-000461-43
IND NUMBER:	117,318
TEST PRODUCT:	MHAA4549A
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	30 May 2014
DATE AMENDED:	Version 2: 14 August 2014 Version 3 (VHP Only): See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	25-Sep-2014 21:28:53

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PROTOCOL AMENDMENT RATIONALE:
VERSION 3 (VHP ONLY) AMENDMENT

RATIONALE

Protocol GV29216 was amended in Version 3 was revised to incorporate VHP feedback and reflects the following changes:

- Male partners of female patients who have had a vasectomy should have appropriate post-vasectomy documentation available of the absence of sperm in the ejaculate (see Section 4.1.1).
- Female patients should use two acceptable methods of contraception throughout the trial, including the active treatment phase AND for 120 days after the last dose of MHAA4549A (see Section 4.1.1).
- Male patients should use condoms and refrain from donating sperm until 30 days after dosing (see Section 4.1.1).
- Exclusion criteria “hypersensitivity to monoclonal antibodies or to the active substance or any excipients of MHAA4549A study drug” and “hypersensitivity to the active substance or to any excipients of oseltamivir” (see Section 4.1.2)

SUMMARY OF CHANGES:
VERSION 3 (VHP ONLY) AMENDMENT

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol.

SECTION 4.1.1: Inclusion Criteria

- Patients of reproductive potential must agree to use reliable means of contraception as described below as a minimum (adherence to more stringent local requirements may be required):
  - For female patients: Use of two acceptable methods of contraception throughout the trial, including the active treatment phase AND for *120 days* ~~24 weeks~~ after the last dose of MHAA4549A. Acceptable methods of contraception include: intrauterine device, systemic hormonal contraception (oral or depot), vaginal ring, tubal ligation of the female partner, vasectomy of the male partner, use of latex condoms plus spermicide by the male partner, or cervical cap plus spermicide (where the spermicide could be foam, vaginal suppository, gel, cream, etc.). *Male partners who have had a vasectomy should have the appropriate post-vasectomy documentation available of the absence of sperm in the ejaculate. The vasectomized male partner should be the sole partner for that patient.*
  - For male patients: Use ~~of~~ condoms *and refrain from sperm donation until* ~~for~~ 30 days after dosing ~~when circulating drug levels remain high~~.

SECTION 4.1.2: Exclusion Criteria

- *Hypersensitivity to monoclonal antibodies or to the active substance or any excipients of MHAA4549A study drug*
- *Hypersensitivity to the active substance or to any excipients of oseltamivir*
- ~~Hypersensitivity to mABs or any constituents of study drug~~

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY, IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION**
PROTOCOL NUMBER:	GV29216
VERSION NUMBER:	*3 (VHP Only)*
EUDRACT NUMBER:	2014-000461-43
IND NUMBER:	117,318
TEST PRODUCT:	MHAA4549A
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION**
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EUDRACT NUMBER:	2014-000461-43
IND NUMBER:	117,318
TEST PRODUCT:	MHAA4549A
INDICATION:	Influenza A
SPONSOR:	Genentech, Inc.

Objectives

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety of MHAA4549A in combination with oseltamivir compared with placebo and oseltamivir in patients with severe influenza A, focusing on the nature, frequency, and severity of serious and non-serious adverse events, as well as effects on laboratory values, vital signs, electrocardiogram (ECG) parameters, anti-therapeutic antibodies (ATA), or other safety biomarkers

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To determine the time to normalization of respiratory function of patients dosed with MHAA4549A in combination with oseltamivir compared to patients dosed with placebo and oseltamivir

The secondary efficacy objectives for this study are as follows:

- To measure clinical failure after 24 hours post-infusion of study drug
- To determine the time to clinical resolution of vital signs
- To measure mortality in patients
- To determine changes in the extent and duration of viral shedding in upper respiratory samples
- To measure the duration of hospital and/or intensive care unit (ICU) stay
- To measure antibiotic usage for respiratory indications
- To measure the frequency and severity of the following secondary complications of influenza:
  - Pneumonia (hospital acquired pneumonia [HAP]/ ventilator acquired pneumonia [VAP])
  - Exacerbations of chronic lung disease
  - Myocarditis
  - Acute respiratory distress syndrome (ARDS)

  - Otitis media
  - Other related complications
  - Readmission rates at 30 and 60 days after study treatment
- To measure duration of positive pressure ventilation (PPV)
- To measure readmission rates

Pharmacokinetic Objectives

The major pharmacokinetic (PK) objective for this study is as follows:

- To characterize the PK profile of MHAA4549A in serum

The exploratory PK objectives for this study are as follows:

[redacted]

Exploratory Objectives

The exploratory objectives for this study are as follows:

[redacted]

Study Design

Description of Study

This is a Phase 2b randomized, double-blind, placebo-controlled study designed to assess the safety and clinical activity of a single IV dose of MHAA4549A in hospitalized patients with severe influenza A in combination with oseltamivir versus a comparator arm of oseltamivir with placebo.

Patients will be randomized 1:1 into two treatment groups: a single intravenous (IV) dose of 3600 mg of MHAA4549A with oseltamivir or a single IV dose of placebo with oseltamivir. All patients will receive oseltamivir, a NAI, as standard therapy for a minimum of 5 days, starting after study drug administration. Oseltamivir at doses of 75 mg twice daily (BID) or 150 mg BID is permitted in order to be consistent with local standard of care practice. Treatment for longer than 5 days is permitted based on local investigator discretion. The patients must start Sponsor-supplied oseltamivir within 8 hours of study drug administration.

Patients hospitalized with an oxygen (O_2) or PPV requirement will be evaluated for influenza A infection. Enrollment in this study requires ongoing treatment within 24 hours of hospital admission with one of the following: any PPV or any supplemental O_2 to maintain oxygen saturation (SpO_2) $>92\%$.

A Sponsor-supplied rapid influenza test and/or a local polymerase chain reaction (PCR) test must be used as an aid in the diagnosis of influenza A infection.

At the time of randomization, patients who are eligible for enrollment will be randomized to receive either a single IV infusion of MHAA4549A or a single IV infusion of placebo that will be administered on Day 1. All patients must have the study drug infused within 48 hours of hospital admission or sooner if possible; therefore, screening must be completed within this

window. All patients will receive oseltamivir for a minimum of 5 days (10 doses), starting on Day 1 beginning no later than 8 hours after study drug administration. All patients will be followed for 60 days from the time of study drug administration.

Number of Patients

The study has a planned enrollment of approximately 334 patients (adult men and women) globally. Patients will receive MHAA4549A or placebo in 1:1 ratio. The number of patients on PPV should not exceed 45% of the total enrolled patients.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Men or women ≥ 18 years of age on day of signing informed consent or obtaining surrogate consent from an authorized representative
- Diagnosis of influenza A as determined by one or both of the following:
  - A Sponsor-supplied rapid influenza test
  - *A* local molecular test (PCR)
- One of the following markers of severity within 24 hours of hospital admission:
  - Requirement for PPV, OR
  - Requirement for O_2 supplementation to maintain $SpO_2 > 92\%$
- A negative urine or serum pregnancy test for women of childbearing potential
- Patients of reproductive potential must agree to use reliable means of contraception as described below as a minimum (adherence to more stringent local requirements may be required):
  - For female patients: Use of two acceptable methods of contraception throughout the trial, including the active treatment phase AND for *120 days* after the last dose of MHAA4549A. Acceptable methods of contraception include: intrauterine device, systemic hormonal contraception (oral or depot), vaginal ring, tubal ligation of the female partner, vasectomy of the male partner, use of latex condoms plus spermicide by the male partner, or cervical cap plus spermicide (where the spermicide could be foam, vaginal suppository, gel, cream, etc.). *Male partners who have had a vasectomy should have the appropriate post-vasectomy documentation available of the absence of sperm in the ejaculate. The vasectomized male partner should be the sole partner for that subject.*
  - For male patients: Use of condoms *and refrain from sperm donation until* 30 days after dosing.
  - Non-reproductive potential is defined below (but could be superseded by local definitions, if they are more stringent):

    Women who are postmenopausal (i.e., spontaneous amenorrhea for the past year confirmed by an follicle stimulating hormone [FSH] level greater than 40 mIU/mL unless the patient is receiving a hormonal therapy for their menopause)

    Women who are surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)

    Men who are surgically sterile (castration)

Exclusion Criteria

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

- Pregnant or lactating, or intending to become pregnant during the study
  - Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or who are not surgically sterile must have a negative urine or serum pregnancy test result within 2 days prior to study treatment

- *Hypersensitivity to monoclonal antibodies or to the active substance or any excipients of MHAA4549Astudy drug*
- *Hypersensitivity to the active substance or to any excipients of oseltamivir*
- Investigational therapy within the 30 days prior to study treatment
- Received prior therapy with any anti-influenza monoclonal antibody therapy including MHAA4549A 8 months prior to study treatment
- Current treatment (within 7 days of dosing) with amantadine or rimantidine
- Patients who have taken more than a total of 3 days (6 doses) of approved anti-influenza therapy (i.e., oral oseltamivir, inhaled zanamivir, or oral ribavirin) in the period from onset of symptoms and prior to enrollment
- Admission $>$ 48 hours prior to study treatment
- Onset of influenza symptoms $>$ 5 days prior to study treatment
- Positive influenza B or influenza A + B infection within 2 weeks prior to study treatment
- High probability of mortality in the next 48 hours as determined by the investigator
- Patient requiring home or baseline oxygenation therapy
- Patient with history of chronic lung disease resulting in baseline $SpO_2 < 95\%$
- Patient on chronic dose of corticosteroids exceeding 10 mg/day of prednisone or equivalent steroid dose for a duration of greater than 14 days within 30 days of entry into study
- Patients with the following significant immune suppression:
  - Bone marrow or solid organ transplant in the previous 12 months
  - Cancer chemotherapy in the previous 12 month
  - HIV infection with most recent CD4 $<$ 200 cells/mL
  - Other significant immune suppression as determined by the investigator in discussion with the Sponsor Medical Monitor or representative
- Patient on extracorporeal membrane oxygenation (ECMO) at time of randomization
- Any disease or condition that would, in the opinion of the site investigator or Sponsor, place the patient at an unacceptable risk of injury or render the patient unable to meet the requirements of the protocol

Length of Study

This study will consist of the following study periods:

- A screening period of 48 hours, beginning at time of hospital submission
- A treatment period of 1 day, during which patients will receive a single dose of MHAA4549A or placebo and a minimum of 5 days of oseltamivir.
- A follow-up period beginning at hospital discharge through 60 days post study drug (MHAA4594A/placebo) administration

End of Study

The end of the study is defined as the first day when all patients have had a study completion visit or early termination visit or have otherwise been discontinued from the study.

Outcome Measures

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Adverse events and clinical laboratory abnormalities
- Vital signs, physical findings, ATAs, and clinical laboratory results during and following administration of MHAA4549A

Efficacy Outcome Measures

The primary outcome measure for this study is as follows:

- Time to normalization of respiratory function defined as:

  - The time to cessation of O_2 support resulting in a stable $SpO_2 > 95\%$ for at least 24 hours

The secondary efficacy outcome measures for this study are as follows:

- Clinical failure after 24 hours post-infusion of study drug defined as:
  - Progression to increased O_2 requirement defined by an increase in oxygen supplementation from low flow oxygen (2 – 6 L/min) to high flow oxygen (> 6 L/min) or from oxygen supplementation alone to any PPV
  - Progression to ICU
  - Prolonged ventilation or O_2 support defined by > 2 weeks, or
  - Death
- Time to clinical normalization of vital signs (3/5 criteria must be met):
  - $SpO_2 > 95\%$ without supplemental O_2 for at least 24 hours
  - Respiratory rate < 24 breaths per minute without supplemental O_2 for at least 24 hours
  - Core temperature < 37.2°C immediately prior to receipt of any antipyretic drug, and at least 6-8 hours from the last dose of antipyretic or core temperature > 36°C in patients who are initially hypothermic
  - Heart rate (HR) < 100/minute
  - Systolic blood pressure (SBP) > 90 mmHg
- All-cause mortality at Day 14, Day 30, and Day 60
- Influenza A viral load in nasopharyngeal samples
  - Area under viral load–time curve (AUEC)
  - Peak viral load
  - Time to resolution of infection
- Duration of hospitalization
- Duration of ICU stay
- Antibiotic usage for respiratory infections
- Complications of influenza:
  - Pneumonia (HAP/VAP)
  - Exacerbations of chronic lung disease
  - Myocarditis
  - Acute respiratory distress syndrome (ARDS)
  - Otitis media
  - Other related complications
- All-cause readmission at Day 30 and Day 60
- Duration of ventilation

Pharmacokinetic Outcome Measures

The primary PK outcome measures for this study are as follows:

- PK parameters for MHAA4549A in serum including total exposure (i.e., AUC), maximum observed concentration (C_{max}), clearance, half-life, and volume of distribution, when appropriate, as data allow

The exploratory PK outcome measures for this study are as follows:

- [redacted]

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

Investigational Medicinal Products

An investigational medicinal product (IMP) is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, excluding marketed products unless the product is 1) used or assembled (formulated or packaged) differently than the authorized form, 2) used for an unauthorized indication, or 3) used to gain further information about the authorized form (Directive 2001/20/EC Article 2[d]). A non-investigational medicinal product (NIMP) is a medicinal product that is intended for use in a clinical trial per the protocol but does not fall under the definition of IMP. Further details can be found in the following EU guidance: Guidance on Investigational Medicinal Products and Non-Investigational Medicinal Products (effective March 2011).

MHAA4549A and Placebo

A single 3600-mg dose of MHAA4549A or dose of placebo will be delivered by IV infusion following dilution in 0.9% normal saline over approximately 60 minutes. Study drug should be delivered using a 0.22 μm in-line filter. Placebo will be identical to active MHAA4549A in formulation and appearance, but will not contain active drug substance.

Oseltamivir (Tamiflu®)

Sponsor-supplied oseltamivir (Tamiflu) 75 mg or 150 mg will be administered BID for a minimum of 5 days. Dosage and administration should follow local prescribing information for oseltamivir. Capsules can be opened and the granules administered via nasogastric tube, if required.

Statistical Methods

Primary Analysis

All efficacy analyses will be conducted according to the intent-to-treat principle and will include all patients who meet the following condition with patients allocated to the treatment arm to which they were randomized:

- Randomized patients who have confirmed influenza A infection by a central PCR test from Day 1 samples.

The primary and secondary efficacy analyses will include all randomized patients who are confirmed to be influenza A infected, with patients grouped according to the treatment assigned at randomization.

Time to event data will be computed using Kaplan-Meier methodology and stratified Cox proportional hazards models and will be summarized using n, median when estimable, hazard ratios, and 95% confidence intervals. Patients who are lost to follow-up (while event free) will be censored at the time that they are last known to be event free.

Estimation of the treatment difference of proportions and its 95% confidence interval will be calculated using stratum-adjusted Mantel-Haenszel methodology. For continuous endpoints, Analysis of Covariance methods (after appropriate transformation of data) will be used to estimate treatment differences at 95% confidence intervals.

Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

If conducted, an interim analysis would be for administrative purposes only (i.e., internal planning or decision making) and would not impact the conduct of the current study in any way. A nominal type I error penalty of 0.0001 will be taken. In addition, as discussed below, the Sponsor will conduct interim safety analyses separate from and in conjunction with the above.

Determination of Sample Size

A total of 334 patients will be enrolled in this study in order to obtain approximately 300 evaluable patients (an estimated dropout rate of 10%). It is assumed that the median time to normalization of respiratory function in the control arm is 5 days

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
[redacted]	[redacted]
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
ATA	Anti-therapeutic antibody
AUC	Area under serum concentration–time curve
AUEC	Area under viral load–time curve
BID	Twice a day
°C	Celsius
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CPK	Creatine phosphokinase
CRO	Contract (or Clinical) Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECMO	Extracorporeal membrane oxygenation
EDC	Electronic data capture
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HA	Hemagglutinin
HAI	Hemagglutinin inhibition
HAP	Hospital Acquired Pneumonia
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart rate
[redacted]	[redacted]
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee

Abbreviation	Definition
IMC	Internal Monitoring Committee
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRR	Infusion-related reactions
IV	Intravenous
LFTs	Liver function tests
mAB	Monoclonal antibody
NAI	Neuraminidase inhibitor
NP	Nasopharyngeal
PaO_2	Partial pressure of arterial oxygen
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
PPV	Positive pressure ventilation
qPCR	Quantitative Polymerase Chain Reaction
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SOC	Scientific Oversight Committee
SpO_2	Oxygen saturation by pulse oximetry
SUSAR	Suspected unexpected serious adverse reactions
ULN	Upper limit of normal
VAP	Ventilation Acquired Pneumonia

1. BACKGROUND

1.1 BACKGROUND ON INFLUENZA

Influenza A is a membrane-enveloped RNA virus that causes significant morbidity and mortality. Currently, there is a great need in hospitalized influenza patients for a parenteral therapeutic option that is well tolerated, can rapidly resolve influenza-related signs and symptoms, decrease mortality, reduce hospital and intensive care unit (ICU) stays, as well as have a prolonged window for initiation of treatment beyond the current standard of care (i.e., within 48 hours of the onset of flu symptoms).

Approximately 200,000 to 278,000 patients are hospitalized with severe influenza infections annually in the United States (U.S.) (Thompson et al. 2004; Zhou et al. 2012), and assuming the same rate reported in the U.S., an estimated 319,000 to 445,000 patients are hospitalized in the European Union (E.U.). Hospitalization due to severe influenza is associated with high mortality (4%–8%), ICU admission (5%–17%; Lee and Ison 2012), mechanical ventilation support in an ICU setting (7%–11%; Doshi et al. 2011), and prolonged hospital stays (5−9 days; Lee and Ison 2012). 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).

Influenza infection is an upper and lower respiratory disease with a broad spectrum of presentations that can result in fever, shortness-of-breath, pneumonia, respiratory failure, secondary respiratory infections, and even death. The standard of care therapy for patients hospitalized with influenza consists of supportive measures and administration of available antiviral agents, primarily neuraminidase inhibitors (NAI) that include but are not limited to oseltamivir, zanamivir, and peramivir. However, a significant unmet medical need still exists in the severely ill patient population, as evidenced by the considerable degree of morbidity and mortality in this setting. To address this need, Genentech Inc. /F.Hoffmann-La Roche Ltd. (Genentech) is developing a highly-specific anti-influenza A (MHAA4549A) antibody therapy for treatment of hospitalized patients with severe influenza.

1.2 BACKGROUND ON MHAA4549A

1.2.1 Nonclinical Background

MHAA4549A is a human monoclonal IgG1 antibody (mAb) that binds to the influenza A virus and is cloned from a single-human plasmablast cell isolated from an influenza vaccinated donor (Nakamura et al. 2013). This antibody binds to a highly conserved epitope on the influenza A hemagglutinin stalk region, which allows broad neutralization of the influenza A virus by blocking the hemagglutinin-mediated, membrane-fusion event in the late endosome.

In vitro, MHAA4549A is capable of neutralizing all current clinically relevant influenza A strains. In vivo, efficacy of MHAA4549A has been demonstrated in mouse models of influenza A infection, both as a single agent and in combination with oseltamivir.

MHAA4549A specifically targets an epitope on the human influenza A hemagglutinin glycoprotein, which does not appear to be endogenously expressed on human or rat tissues and, therefore, is unlikely to be present in the absence of viral infection. Weekly administration of MHAA4549A (total of 5 doses) in Sprague-Dawley rats was well tolerated up to the maximum feasible dose of 150 mg/kg. Ex vivo tissue cross-reactivity study data showed no specific binding of MHAA4549A to any of the human or rat tissues examined.

1.2.2 Clinical Safety Background

To date, MHAA4549A has been shown to be safe and well tolerated in two clinical studies, which altogether enrolled 122 healthy volunteers. The first study was a Phase 1 study (GV28916) in 21 healthy volunteers where single doses of 1.5 mg/kg, 5 mg/kg, 15 mg/kg, and 45 mg/kg were tested with an extended follow-up period of 120 days. MHAA4549A was safe and well tolerated with no serious adverse events (SAEs). All adverse events (AEs) were mild or mild-to-moderate and resolved fully before the end of the study's follow-up period. No anti-therapeutic antibodies (ATAs) were detected in this study. In addition, the MHAA4549A pharmacokinetics were generally dose proportional, and appeared to have a pharmacokinetic (PK) profile consistent with that of a human IgG1 antibody that lacks known endogenous host targets.

The second study was a Phase 2a challenge study (GV28985) in 101 healthy volunteers infected with a H3N2 (A/Wisconsin/67/2005) strain of influenza virus. Fixed dosing was selected for this study and is further described in Section 1.3.2.3. Sixty subjects received doses of 400 mg, 1200 mg, or 3600 mg MHAA4549A and 41 subjects received placebo following nasal inoculation of influenza A virus one day earlier. The interim efficacy analysis in Table 1 includes the Intent-to-Treat (ITT) infected population who received placebo (N = 21), 400 mg MHAA4549A (N = 11), 1200 mg MHAA4549A (N = 13), 3600 mg MHAA4549A (N=14), and oseltamivir (N = 2). All subjects have completed dosing, and interim PK and efficacy data are available in the Investigator's Brochure and upon request. During this study, elevated ALT, AST, and amylase levels were observed within the first 2 weeks after inoculation with A/Wisconsin/67/2005 and dosing with MHAA4549A. Previous experience with this challenge model has shown ALT/AST/amylase elevations to be associated with the influenza infection itself (Polakos 2006). Consistent with previous trials, in GV28985, there was no relationship of elevations in AST, ALT, or amylase with either dose or exposure (e.g., placebo: 22.0%, 400 mg: 35.0%,1200 mg: 25.0%, 3600 mg: 20.0%).

In GV28985, most AEs were Grade 1 or Grade 2 (mild or moderate) and appeared to reflect the symptoms of the influenza infection. In the 400 mg group, 15 (75.0%), 1 (5.0%), and 2 (10.0%) subjects reported Grade 1, 2, and 3 AEs respectively. In the 1200-mg group, 9 (45.0%), 6 (30.0%), and 1 (5.0%) subjects reported Grade 1, 2, and 3 AEs, respectively. In the 3600-mg group, 10 (50.0%), 5 (25.0%), 1 (5.0%) subjects reported Grade 1, 2, and 3 AEs, respectively. One (5.0%) subject reported a Grade 4

AE in the 3600-mg group, which was a lower limb fracture, not related to MHAA4549A. Subjects in the placebo group reported 18 (56.3%) Grade 1 AEs, 8 (25.0%) Grade 2 AEs, and 2 (6.3%) Grade 3 AEs. In addition, there were no drug related SAEs, deaths, or discontinuations due to AEs. There were a total of 3 SAEs unrelated to MHAA4549A in two subjects. One subject reported depressive psychosis associated with influenza. There were a total of 3 SAEs unrelated to MHAA4549A in two subjects. One subject reported depressive psychosis associated with influenza. The second subject reported a broken knee with a subsequent infection following a surgical procedure.

In GV28985, 1 patient tested positive for anti-therapeutic antibodies (ATAs). This patient tested positive for ATA at baseline and post baseline. This patient was in the placebo group, which included 32 other subjects, resulting in an immunogenicity prevalence rate (ATA-positive rate at baseline) of 3.1% and an immunogenicity incidence rate (ATA titers post-baseline) of 3.1%, as well, within the placebo group. Overall, study GV28985 had an immunogenicity prevalence rate of 1%. The immunogenicity incidence rate amongst the 60 subjects who received MHAA4549A was 0%.

Based on this data, MHAA4549A is considered generally safe and well tolerated to date at all doses tested, including the 3600 mg dose.

1.2.3 Clinical Efficacy Background

Analysis of efficacy from the 3600-mg dose level demonstrated a statistically significant decrease in viral shedding from upper respiratory tract as measured by the area under the curve (97% reduction by quantitative polymerase chain reaction [qPCR]) and peak viral load (77% reduction by qPCR) as shown in Table 1.

In this study, oseltamivir was started on Day 7 for a 5-day course, and there were no observed AEs or imbalances in safety events that were considered attributable to interactions between oseltamivir and MHAA4549A. The PK profile of MHAA4549A and oseltamivir in GV28985 are being analyzed to exclude potential drug-drug interactions and will be available before the start of this study GV29216.

Table 1 Interim Efficacy Results from Phase 2a Challenge Study (GV28985)

Endpoint	Placebo (N=21)	MHAA4549A 400 mg (N=11) % reduction (p-value)a	MHAA4549A 1200 mg (N=13) % reduction (p-value)a	MHAA4549A 3600 mg (N=14) % reduction (p-value)a	Oseltamivir 75 mg BID (N=2) % reduction (p-value)a
Median qPCR Viral AUEC (log_{10} vc/mL x hour)	458.1	247.2 46.0% (0.0455)	444.4 3.0% (0.9020)	11.3 97.5% (0.0051)	57.4 87.5% (0.0558)
Median qPCR Peak Viral Load (log_{10} vc/mL)	6.38	5.08 20.4% (0.0187)	6.36 0.3% (1.0000)	1.45 77.3% (0.0024)	2.30 63.9% (0.0947)
Median Total Clinical Symptom AUEC	207.7	87.5 57.9% (0.2000)	192.1 7.5% (0.8743)	37.7 81.8% (0.2887)	8.1 96.1% (0.0855)

AUEC = area under viral load–time curve; qPCR = quantitative polymerase chain reaction.

[a] Comparison of active and placebo using nonparametric Wilcoxon rank-sum test. All p-values are unadjusted for multiple testing.

The A/Wisconsin/67/2005 virus induced mild symptoms that were predominantly captured in the upper respiratory tract symptoms that included runny nose, stuffy nose and sneezing.

The Symptom Diary Cards used a scale of 0-3, where Grade 0 is absence, Grade 1 is just noticeable, Grade 2 is bothersome but does not prevent participation in activities, and Grade 3 is bothersome and interferes with activities. Composite clinical symptom scores from Study GV28985 for the Intent-to-Treat (ITT) infected population who received placebo (N = 21), 400 mg MHAA4549A (N = 11), 1200 mg MHAA4549A (N = 13), 3600 mg MHAA4549A (N = 14), and oseltamivir (N = 2) are shown in Table 1.

Given the variability of the symptom scores the results were not statistically significant. However, there was a decrease in the AUEC of symptoms scores for the 3600 mg dose, which is consistent with the virological results described in the Table 1 above. Data from the oseltamivir treated group is also shown but it should be noted that only 2 subjects were in the ITT infected population.

See the MHAA4549A Investigator's Brochure for additional details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

The Phase 1 and Phase 2a studies have demonstrated that MHAA4549A is safe and well tolerated to date in healthy volunteers including those who were inoculated with influenza A virus. Data from the Phase 2a study also provides evidence that the

3600 mg dose of MHAA4549A is effective in reducing viral titers in healthy volunteers inoculated with influenza A virus. These findings, when combined with previous nonclinical studies showing MHAA4549A to have in vitro and in vivo efficacy, a well-tolerated safety profile, and anti-viral activity, support further clinical development of MHAA4549A.

In this Phase 2b study (GV29216), MHAA4549A is being evaluated in combination with the current standard of care (oseltamivir), to decrease the severity and duration of viral infection with influenza A virus with the ultimate goal of reducing the clinical symptoms of infection as compared to oseltamivir with placebo. There are three primary goals for this Phase 2b study:

- Demonstrate the safety and efficacy of MHAA4549A in combination with oseltamivir in hospitalized influenza A patients
- [redacted]
- Demonstrate and evaluate the optimal endpoints for study in hospitalized patients with influenza A, given the lack of precedence for approval in patients hospitalized with influenza infection, an area of high unmet medical need

This Phase 2b study has been designed to estimate the improvement in outcome of a combination therapy of MHAA4549A 3600 mg with oseltamivir versus placebo with oseltamivir. All patients will be on oseltamivir, which is part of the recommended standard of care. In addition, and as discussed above, MHAA4549A is a human monoclonal antibody that has, to date, shown an acceptable safety profile, a PK profile consistent with that of a IgG1 human antibody that lacks known endogenous host targets, and a demonstrated antiviral activity at the planned dose level of 3600 mg.

1.3.2 Benefit-Risk Assessment

1.3.2.1 Treatment in Combination with Oseltamivir

All patients in the study will receive oseltamivir as the current standard of care treatment, either with or without MHAA4549A. Therefore, at a minimum, all patients will be treated with standard of care for influenza. Given that MHAA4549A is an antibody, the potential for a drug-drug interaction with oseltamivir is very low. In the ongoing Phase 2a challenge study (GV28985), study subjects received MHAA4549A followed by oseltamivir with no AEs attributable to the combination therapy noted to date. In addition, in this study the PK profile of oseltamivir in concomitantly treated subjects will be assessed.

1.3.2.2 Drug Mechanism and Preclinical Studies

The available pre-clinical data suggest that there is low risk for drug target-related safety events in healthy humans since MHAA4549A specifically targets an epitope on a viral protein (i.e., the human influenza A virus hemagglutinin glycoprotein), which is not

endogenously expressed in human tissues. Furthermore, there were no adverse MHAA4549A-related findings demonstrated in nonclinical studies at doses up to 150 mg/kg administered weekly for 5 weeks and no evidence of target present in host tissues.

1.3.2.3 Rationale for Selection of Phase 2b Study Population

The target patient population of hospitalized patients with severe influenza A requiring oxygen (O_2) or positive pressure ventilation (PPV) is considered an appropriate population to test MHAA4549A for the following reasons:

- Nonclinical safety data does not show any expected or unexpected toxicity.
- Clinical safety data for MHAA4549A demonstrate a well-tolerated safety profile:
  - AEs in the Phase 1 study (GV28916) were mild and did not show a dose relationship; there were no ATAs detected in patients treated with MHAA4549A.
  - In the ongoing Phase 2a study (GV28985), MHAA4549A was generally well tolerated. A few subjects in all treatment groups were observed to have transient elevations in alanine transaminase (ALT), aspartate transaminase (AST), and amylase levels. There was no dose-dependent relationship of the ALT/AST/amylase elevations with MHAA4549A and the overall event rate was in line with published rates associated with the influenza challenge model regardless of treatment arm: 27/100 [27%] in GV28985 vs. approximately 26% in previous challenge studies (Polakos 2006). There were no SAEs related to study drug. There were a total of 3 SAEs unrelated to MHAA4549A in two subjects. One subject reported depressive psychosis associated with influenza. The second subject reported a broken knee with a subsequent infection following a surgical procedure.
- Interim efficacy data in the Phase 2a challenge study (GV28985) demonstrated a significant decrease in viral shedding in the upper respiratory tract at the 3600 mg dose. There was a 97.5% ($p = 0.0051$) decrease in the area under viral load–time curve (AUEC) and a 77% ($p = 0.0024$) decrease in peak viral load by qPCR measurement in comparison to the placebo group, thus confirming proof of antiviral activity at the 3600 mg dose level. Symptom data in the Phase 2a study showed a decrease in the AUC of symptoms scores for the 3600-mg dose that is consistent with the virological results as illustrated in Table 1.

1.3.2.4 Patient Monitoring and Supervision

MHAA4549A will be administered to enrolled patients in a hospital environment under close medical supervision by physician investigators. Medical staff will be available for prompt evaluation and treatment of any adverse events. Emergency resuscitation equipment and emergency facilities will be readily available. Patients will undergo screening assessments to confirm eligibility, will be closely monitored during the administration of MHAA4549A, and will be resident for at least 24 hours following the administration of MHAA4549A. Furthermore, safety laboratory tests relating to the blood chemistries, including liver function tests, will be conducted.

An internal monitoring committee (IMC) in combination with a scientific oversight committee (SOC) will provide safety monitoring for the study in addition to the ongoing review of safety by the Medical Monitor and Safety Scientist. See Section 3.1.2 for more information.

The 120-day follow-up period in the Phase 1 and 2a studies allowed for monitoring of subjects for approximately 5 half-lives of MHAA4549A. No ATAs were detected in the Phase 1 study, while one subject in the Phase 2a study tested positive for ATAs at baseline and post-baseline timepoints as described in Section 1.2.2. The Phase 2b study will also include a safety follow-up period of 60 days and an unlimited collection of all SAEs believed related to MHAA4549A.

Based on the above data and design of this study, the Sponsor concludes that the benefit−risk profile of MHAA4549A in the population with severe influenza is favorable.

2. OBJECTIVES

2.1 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety of MHAA4549A in combination with oseltamivir compared with placebo and oseltamivir in patients with severe influenza A, focusing on the nature, frequency, and severity of serious and non-serious adverse events as well as effects on laboratory values, vital signs, electrocardiogram (ECG) parameters, ATAs, or other safety biomarkers

2.2 PRIMARY EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To determine the time to normalization of respiratory function of patients dosed with MHAA4549A in combination with oseltamivir compared to patients dosed with placebo and oseltamivir.

2.3 SECONDARY EFFICACY OBJECTIVES

The secondary efficacy objectives for this study are as follows:

- To measure clinical failure, as defined in Section 3.3.3, after 24 hours post-infusion of study drug
- To determine the time to clinical resolution of vital signs
- To measure mortality in patients
- To determine changes in the extent and duration of viral shedding in upper respiratory samples
- To measure the duration of hospital and/or ICU stay
- To measure antibiotic usage for respiratory indications

- To measure the frequency and severity of the following secondary complications of influenza:
  - Pneumonia (hospital acquired pneumonia [HAP]/ ventilator acquired pneumonia [VAP])
  - Exacerbations of chronic lung disease
  - Myocarditis
  - Acute respiratory distress syndrome (ARDS)
  - Otitis media
  - Other related complications
  - Readmission rates at 30 and 60 days after study treatment
- To measure duration of PPV
- To measure readmission rates

2.4 PHARMACOKINETIC OBJECTIVES

The major PK objective for this study is as follows:

- To characterize the PK profile of MHAA4549A in serum

The exploratory PK objectives for this study are as follows:

[redacted]

2.5 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are as follows:

[redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase 2b, randomized, double-blind, placebo-controlled study designed to assess the safety and clinical activity of a single intravenous (IV) dose of MHAA4549A in hospitalized patients with severe influenza A in combination with oseltamivir versus a comparator arm of placebo with oseltamivir. This study is planned to take place in approximately 170 study centers globally.

Patients will be randomized 1:1 into two treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir or a single IV dose of placebo with oseltamivir. All patients will receive oseltamivir, a NAI, as standard therapy for a minimum of 5 days after study drug administration. Oseltamivir at doses of 75 mg BID or 150 mg BID is permitted in order to be consistent with local standard of care practice. Treatment for longer than 5 days is permitted based on local investigator discretion. The patient must start Sponsor-supplied oseltamivir within 8 hours of study drug administration. The study has a planned enrollment of approximately 334 patients globally.

Hospitalized patients with an O_2 or PPV requirement will be evaluated for influenza A infection. Enrollment in this study requires ongoing treatment within 24 hours of hospital admission with one of the following:

- any PPV or
- any supplemental O_2 to maintain oxygen saturation (SpO_2) >92% (see Section 3.3.2)

Patients on PPV should not exceed 45% of the total patients enrolled.

A Sponsor-supplied rapid influenza test and/or a local polymerase chain reaction (PCR) test must be used as an aid in the diagnosis of influenza A infection.

[redacted]

At the time of randomization, patients who are eligible for enrollment, as described above, will be randomized to receive MHAA4549A at a dose of 3600 mg or placebo. Patients will be stratified by site, PPV versus supplemental O_2 at randomization, and suspected or confirmed bacterial pneumonia versus no bacterial pneumonia based on the status at randomization.

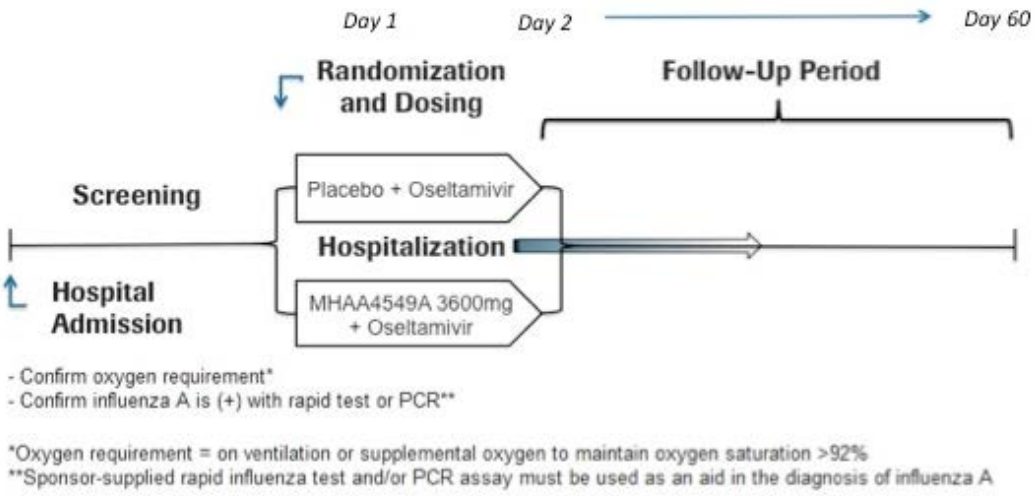
Eligible patients who are enrolled into the study will receive either a single IV infusion of MHAA4549A or a single IV infusion of placebo on Day 1. All patients must have the study drug infused within 48 hours of hospital admission or sooner if possible. All patients will receive oseltamivir for a minimum of 5 days (10 doses), starting on Day 1, beginning no later than 8 hours after study drug administration.

All patients will be followed and evaluated at minimum on a daily basis for the duration of their hospital stay consistent with the planned schedule of assessments. Any suspicion of bacterial superinfection should be thoroughly evaluated including microbiological confirmation, if possible. A follow-up study visit should occur on Day 14 ± 1 (if discharged before Day 14); Day 30 ± 4 days (if discharged before Day 30); and Day 60 ± 4 days (if discharged before Day 60).

Safety evaluations will be provided by an IMC and SOC, as defined in the IMC and SOC agreement (see Section 3.1.2).

A schedule of assessments is provided in Appendix 1a and Appendix 1b. A diagram of the study design is presented in Figure 1.

Figure 1 Phase 2b Study Design (GV29216)



3.1.2 Independent Monitoring Committee and Scientific Oversight Committee

A combined approach with both an IMC and a SOC is proposed to enhance patient safety. The IMC consists of Sponsor representatives from the following functions: Clinical Science, Drug Safety, Biostatistics, and Statistical Programming and Analysis. The IMC members will be unblinded to patient treatment and assignment. The Clinical Science representative on the IMC (IMC Chair) will be a person other than the Study Medical Monitor and will not be involved in the conduct of the study or have any contact

with study investigators or site staff. The Study Medical Monitor will remain blinded to individual treatment assignments, unless, in exceptional cases, specific circumstances require Study Medical Monitor unblinding after IMC Chair approval. The Drug Safety Scientist on the IMC will also not be involved in the conduct of the study or have any contact with the study investigators. The Biostatistician and Statistical Programmer are the only IMC members involved in the conduct of the study; however, they do not have any contact with study investigators, and all discussion within the IMC are kept confidential. All other Sponsor and Contract Research Organization personnel involved in the conduct of the study will remain blinded to individual treatment assignments.

The two SOC members are external experts in the field and will be unblinded to treatment allocation. The SOC may be further expanded by the IMC during the course of the study to include additional external experts if the need arises.

A detailed description of the procedures, data flow, and meeting schedule of the IMC and SOC will be provided in a separate IMC and SOC agreement.

3.1.3 End of Study

The end of study is defined as the first day when all patients have had a study completion visit or early termination visit or have otherwise been discontinued from the study.

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Study Design

Hospitalized influenza A infection represents a high unmet need, which, when left untreated, may progress to a more serious disease that may result in significant morbidity and mortality in otherwise healthy adults as well as in vulnerable populations.

This study is designed to estimate the improvement in outcome of a combination regimen of MHAA4549A with oseltamivir compared to a standard of care arm of placebo with oseltamivir. The study population will include hospitalized patients with influenza A requiring O_2 support and/or PPV support within 24 hours of hospital admission.

Study GV29216 will be a Phase 2b study involving approximately 334 patients. The sample size was determined based on an expected clinically meaningful difference of 1 – 2 days improvement in time to normalization of respiratory function between the control and treatment arms, assuming a 5-day median time to the time to normalization of respiratory function in the standard of care arm (Blackwood 2011; PREMIER® database).

This design ensures that all patients in the trial will receive the current NAI treatment, oseltamivir, as standard of care at a minimum, and will evaluate the clinical benefit of combining MHAA4549A with this standard of care regimen. Therefore, this study aims

to identify a regimen that could deliver maximum benefit in this high unmet need disease, while still treating all enrolled patients with the currently accepted standard of care.

3.2.2 Rationale for Patient Population and Primary Endpoint

Severe influenza, for the purpose of this study, is defined as requiring one of the following treatments: any supplemental O_2 to maintain an $SpO_2 > 92\%$ or PPV. PPV is defined as any mechanical positive pressure device to maintain oxygenation; this can include positive pressure mask and intubation. A Sponsor-supplied rapid influenza test and/or a local PCR must be used as an aid in the diagnosis of influenza A infection.

This patient population was chosen based on the rationale that respiratory failure is a hallmark of influenza and a major driver of morbidity and mortality, as well as hospitalization. The recovery from ventilator support has been shown to be directly proportional to time spent in the ICU (Blackwood 2011; PREMIER® database). Based upon an analysis of morbidity and mortality, the patient population that requires supplemental O_2 or ventilation on their first day of admission was determined to have a high unmet medical need as they have an estimated mortality of 9%–32%, and 27% require admission to the ICU, according to analysis of a database of over 70,000 hospitalized patients in the US from 2005–2012 (PREMIER® database).

Support for use of the respiratory endpoint in this population comes from recently published data demonstrating that a composite endpoint that captured respiratory rate, fever, heart rate, and blood pressure resolution was primarily driven by the respiratory component of the endpoint (Marty et al. 2014).

3.2.3 Rationale for Control Group and Treatment Window

In this study, the standard of care regimen for the control or comparator group is oseltamivir, an NAI. In the treatment groups, MHAA4549A will be dosed in addition to an oseltamivir standard of care regimen. The oseltamivir dose will be consistent with the local investigator practice at each site where the study will be conducted. Either 75 mg or 150 mg orally BID oseltamivir for a minimum of 5 days is permitted following treatment with MHAA4549A. Treatment for longer than 5 days is permitted based on local investigator discretion. The oseltamivir dosing regimen, including the renal dosing adjustment, is listed in Table 2. This control treatment was based on consideration of safety, ethics, and efficacy for treatment of severe influenza and is consistent with guidelines for antiviral treatment of hospitalized patients with influenza (Harper et al. 2009, Fiore 2011).

Table 2 Oseltamivir Dosing Regimen

Neuraminidase Inhibitor	Dosing Regimen	Duration of Therapy
Oseltamivir	75 mg or 150 mg orally BID [a] 75 mg oral once daily for adult patients with creatinine clearance (CrCL) between 10 and 30 mL/min [b]	5 days [c]

[a] 75 mg or 150 mg dose at the discretion of the investigator, and dose must be documented. Capsules can be opened and the granules administered via nasogastric tube, if required.

[b] No recommended dosing regimens are available for patients with end-stage renal disease undergoing routine hemodialysis or continuous peritoneal dialysis treatment.

[c] Longer treatment times are at the discretion of the investigator.

From a safety standpoint there are no expected drug interactions between MHAA4549A, a monoclonal antibody, and any NAI, which are small molecule drugs that bind to a different viral protein than MHAA4549A. In the Phase 2a challenge study, all subjects that were dosed with MHAA4549A also received a 5-day course of oseltamivir starting on Day 7. There were no safety effects attributable to the combination when the drugs were present concurrently. The pharmacokinetics of oseltamivir and its potential interaction with MHAA4549A are being assessed from this Phase 2a.

For this Phase 2b study, a combination of MHAA4549A and oseltamivir was determined to be the most clinically feasible treatment regimen, both from an ethical as well as a practical perspective. The treatment of all patients with oseltamivir ensures that all patients will receive standard of care given the high morbidity and mortality of hospitalized patients with influenza A along with guidelines from Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) stating NAIs are the standard of care for hospitalized patients with influenza A (Harper et al. 2009 and CDC Website). Further, pre-clinical efficacy data from a study using MHAA4549A and oseltamivir in combination, showed a potential synergistic effect of both compounds which may be due to the different and potentially complementary mechanisms of action, i.e. targeting viral hemagglutinin and neuraminidase.

Dosing of MHAA4549A is confined to a treatment window designed for best expected treatment success and to ensure that any observed effects can be attributed to the study drug with high confidence. MHAA4549A shall only be dosed within 5 days of symptom onset, within 3 days of initial treatment with a NAI, and no later than 48 hours after admission to the hospital. This proposed window is supported by data demonstrating that hospitalized influenza patients benefit from NAI treatment even at 5 days from symptom onset (Louie et al. 2012).

3.2.4 Rationale for MHAA4549A Dosage

A single IV dose of 3600 mg of MHAA4549A was selected to assess the efficacy of MHAA4549A and to provide data for further clinical development. The selection of dose

in this study for severely ill patients was based on the observed human pharmacokinetics in Phase 1 and the relationship between the pharmacokinetics, pharmacodynamics, and efficacy observed in a Phase 2a human challenge model of influenza. MHAA4549A was shown to be safe and well-tolerated at all dose levels (ranging from 1.5 mg/kg to 45 mg/kg for Phase 1 and 400-3600 mg for Phase 2a) through a follow-up period of 120 days post-dose in the Phase 1 and Phase 2a study. The dose level used in this study was determined following analysis of data from the Phase 2a study, GV28985, which demonstrated the following:

- The 3600-mg dose demonstrated a significant decrease in viral shedding in upper respiratory samples. Based on current interim analysis data, there was a 97.5% ($p = 0.0051$) decrease in AUEC and a 77.3% decrease in peak viral load by qPCR measurement compared to the placebo group.
- Symptom data in the Phase 2a study showed a decrease in the AUC of symptoms scores for the 3600-mg dose, as illustrated in Table 1, which is consistent with the virological results.
- The 1200-mg dose level was not efficacious
- There are no safety concerns at the 3600-mg dose level to date.
- Hospitalized patients generally have a longer duration of viral shedding and significantly more viral burden in the lower lung compartments; therefore, high concentrations of mAb are likely needed to achieve sufficient occupancy of the virus binding sites in the upper and lower respiratory compartments. Furthermore, higher concentrations of mAb are necessary to mitigate the risk of resistance for MHAA4549A .

The Phase 1 study was conducted using body-weight based dosing followed by a fixed dosing strategy that was used in the Phase 2a study. Thus, the fixed dosing regimen that was used in the Phase 2a study will be used for this study, given the practical advantages and positive safety profile of MHAA4549A to date. Further, fixed dosing is generally recommended with monoclonal antibodies, due to their minimal PK variability (Bai et al. 2012). The PK variability introduced by different dosing regimens (i.e., body-weight based dosing versus fixed dosing) is moderate relative to the variability generally observed in pharmacodynamics, efficacy, and safety and would not be expected to be clinically meaningful.

3.2.5 Rationale for Biomarker Assessments

[redacted]

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Adverse events and clinical laboratory abnormalities
- Vital signs, physical findings, ATAs, and clinical laboratory results during and following administration of MHAA4549A

3.3.2 Primary Efficacy Outcome Measure

The primary outcome measure for this study is as follows:

- Time to normalization of respiratory function defined as:
  - The time to cessation of O_2 support resulting in a stable $SpO_2 > 95\%$ for at least 24 hours (see Appendix 2 for details)

3.3.3 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- Clinical failure after 24 hours post-infusion of study drug; defined as:
  - Progression to increased O_2 requirement defined by an increase in oxygen supplementation from low flow oxygen (2 – 6 L/min) to high flow oxygen ($>$6 L/min) or from oxygen supplementation alone to any PPV
  - Progression to ICU
  - Prolonged ventilation or O_2 support defined by $>$2 weeks, or
  - Death
- Time to clinical normalization of vital signs (3/5 criteria must be met):
  - $SpO_2 > 95\%$ without supplemental O_2 for at least 24 hours
  - Core temperature $< 37.2°C$ immediately prior to receipt of any antipyretic drug, and at least 6-8 hours from the last dose of antipyretic or core temperature $>36°C$ in patients who are initially hypothermic
  - Heart rate (HR) $<$100/minute
  - Systolic blood pressure (SBP) $>$90 mmHg
- All-cause mortality at Day 14, Day 30, and Day 60
- Influenza A viral load in nasopharyngeal samples
  - AUEC
  - Peak viral load

  - Time to resolution of infection
- Duration of hospitalization
- Duration of ICU stay
- Antibiotic usage for respiratory infections
- Complications of influenza:
  - Pneumonia (HAP/VAP)
  - Exacerbations of chronic lung disease
  - Myocarditis
  - ARDS
  - Otitis media
  - Other related complications
- All-cause readmission at Day 30 and Day 60
- Duration of ventilation

3.3.4 Pharmacokinetic Outcome Measures

The primary PK outcome measures for this study are as follows:

- PK parameters for MHAA4549A in serum including total exposure (i.e., AUC), maximum observed concentration (C_{max}), clearance, half-life, and volume of distribution, when appropriate, as data allow

The exploratory PK outcome measures for this study are as follows:

[redacted]

3.3.5 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

[redacted]

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

This study aims to enroll approximately 334 men and women and is designed to assess the safety and clinical activity of a single IV administration of MHAA4549A in adult patients hospitalized with severe influenza A.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Hospitalized men or women ≥ 18 years of age on the day of signing the informed consent or obtaining surrogate consent from an authorized representative
- Diagnosis of influenza A where one or both of the following are used as aid(s) in diagnosis:
  - A Sponsor-supplied rapid influenza test
  - A local molecular (PCR) test
- One of the following markers of severity within 24 hours of hospital admission:
  - Requirement for PPV –or–
  - Requirement for O_2 supplementation to maintain $SpO_2 > 92\%$
- A negative urine or serum pregnancy test for women of child-bearing potential
- Patients of reproductive potential must agree to use reliable means of contraception as described below as a minimum (adherence to more stringent local requirements may be required):
  - For female patients: Use of two acceptable methods of contraception throughout the trial, including the active treatment phase AND for $120\ day$ after the last dose of MHAA4549A. Acceptable methods of contraception include: intrauterine device, systemic hormonal contraception (oral or depot), vaginal ring, tubal ligation of the female partner, vasectomy of the male partner, use of latex condoms plus spermicide by the male partner, or cervical cap plus spermicide (where the spermicide could be foam, vaginal suppository, gel, cream, etc.).

Male partners who have had a vasectomy should have the appropriate post-vasectomy documentation available of the absence of sperm in the ejaculate. The vasectomized male partner should be the sole partner for that subject.

- For male patients: Use of condoms *and refrain from sperm donation until* 30 days after dosing.
- Non-reproductive potential is defined below (but could be superseded by local definitions, if they are more stringent):

  Women who are postmenopausal (i.e., spontaneous amenorrhea for the past year confirmed by an FSH level greater than 40 mIU/mL unless the patient is receiving a hormonal therapy for their menopause)

  Women who are surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)

  Men who are surgically sterile (castration)

4.1.2 Exclusion Criteria

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

- Pregnant or lactating or intending to become pregnant during the study
  - Women who are not postmenopausal ($\geq$12 months of non-therapy-induced amenorrhea) or who are not surgically sterile must have a negative urine or serum pregnancy test result within 2 days prior to study treatment.
- *Hypersensitivity to monoclonal antibodies or to the active substance or any excipients of MHAA4549A study drug*
- *Hypersensitivity to the active substance or to any excipients of oseltamivir*
- Investigational therapy within the 30 days prior to study treatment
- Received prior therapy with any anti-influenza monoclonal antibody therapy including MHAA4549A 8 months prior to study treatment
- Current treatment (within 7 days of dosing) with amantadine or rimantidine
- Patients who have taken more than a total of 3 days (6 doses) of approved anti-influenza therapy (e.g., oral oseltamivir, inhaled zanamivir, or oral ribavirin) in the period from onset of symptoms and prior to enrollment
- Admission $>$ 48 hours prior to study treatment
- Onset of influenza symptoms $>$ 5 days prior to study treatment
- Positive influenza B or influenza A + B infection within 2 weeks prior to study treatment
- High probability of mortality in the next 48 hours as determined by the investigator
- Patient requiring home or baseline oxygenation therapy
- Patient with history of chronic lung disease resulting in baseline $SpO_2 < 95\%$

- Patient on a chronic dose of corticosteroids exceeding 10 mg/day of prednisone or equivalent steroid dose for a duration of greater than 14 days within 30 days of entry into study
- Patients with the following significant immune suppression:
  - Bone marrow or solid organ transplant in the previous 12 months
  - Cancer chemotherapy in the previous 12 month
  - HIV infection with most recent CD4 $<$ 200 cells/mL
  - Other significant immune suppression as determined by the investigator in discussion with the Sponsor Medical Monitor or representative
- Patient on extracorporeal membrane oxygenation (ECMO) at time of randomization
- Any disease or condition that would, in the opinion of the site investigator or Sponsor, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The randomization of patients will be managed by a central Interactive Voice and Web Response System (IxRS) through use of a dynamic hierarchical algorithm. The treatment assignments will be unblinded to selected Sponsor personnel to facilitate ongoing monitoring of safety and tolerability, including members of the IMC and SOC.

All patients will be randomly assigned to receive either MHAA4549A 3600 mg or placebo at a 1:1 ratio stratified by site, whether patient is on PPV vs supplemental O_2 at randomization, and whether the patient has suspected or confirmed bacterial pneumonia vs no bacterial pneumonia at randomization. All patients will receive oseltamivir (75 mg or 150 mg BID) for a minimum of 5 days. Treatment for longer than 5 days is permitted based on local investigator discretion.

Blinded personnel at each study site will make appropriate preparations and perform the IV infusions of study drug, as described in Section 4.3.3. The other parties who are involved in the conduct of the study (i.e., patients and blinded site personnel) will remain blinded to patient-specific treatment assignments until the final database lock after the completion of the study.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this trial. Bioanalytical laboratory personnel responsible for performing PK assays will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed. Samples from patients assigned to the comparator arm will not be analyzed except by request (e.g., to evaluate a possible error in study drug administration).

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code in IxRS. Treatment codes should not be broken except in emergency situations. *If the investigator wishes to know the identity of the study drug for any other reason, they should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event)*.

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all suspected unexpected serious adverse reactions (SUSAR)(see Section 5.6) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 MHAA4549A and Placebo

MHAA4549A, matching placebo, and up to 10-day supply of oseltamivir (Tamiflu®) will be supplied by the Sponsor. For information on the formulation, packaging, and handling of MHAA4549A and placebo; see the Pharmacy Manual and the MHAA4549A Investigator's Brochure.

The MHAA4549A vial delivers 10 mL (500 mg) of drug product solution, but may contain more (approximately 10.3 mL) than the stated volume to enable delivery of the entire 10 mL volume. MHAA4549A is formulated as 50 mg/mL in 10 mM sodium succinate, 240 mM sucrose, and 0.02% (w/v) polysorbate 20 at pH 5.5 and is contained in a 15 mL forma vitrum (USP/PH. Eur. Type 1) glass vial. The drug product is suitable for single use only and contains no preservatives.

Placebo for MHAA4549A has the same composition as the drug product (without MHAA4549A) and is supplied in an identical vial configuration. The placebo contains no preservatives and is suitable for single-use only. Placebo is formulated as 10 mM sodium succinate, 240 mM sucrose, and 0.02% polysorbate 20 at pH 5.5 in a total volume of 10 mL in a 15 mL forma vitrum (USP/PH. Eur. Type 1) glass vial.

MHAA4549A and placebo are supplied in identical blinded vials labeled with unique kit numbers. IxRS will assign kit numbers for each treatment arm; all treatment arms will be assigned the same total number of vials for each treatment, and the same preparation instructions. Placebo is identical to active MHAA4549A in formulation and appearance but does not contain active drug substance.

4.3.1.2 Oseltamivir (Tamiflu)

Oseltamivir (Tamiflu) is an influenza NAI indicated for treatment of acute, uncomplicated influenza. For information on the formulation, packaging, and handling of oseltamivir; see the local prescribing information for oseltamivir.

Storage: Capsules should be stored at 25°C (77.7°F); excursions permitted to 15° to 30°C (59° to 86°F).

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 MHAA4549A and Placebo

The randomization of patients will be managed by a central IxRS. All patients will be randomly assigned to receive either a single dose of MHAA4549A 3600 mg IV or placebo IV at a 1:1 ratio. Oseltamivir will be dispensed via IxRS. Oseltamivir dosing is described in Table 2.

Administration of MHAA4549A or placebo will be performed in a setting with emergency medical equipment and personnel who are trained to monitor for and respond to medical emergencies. A qualified physician will be on site during study drug administration for all patients.

A single dose of MHAA4549A or placebo will be delivered by IV infusion following dilution in 0.9% normal saline over approximately 60 minutes. Study drug should be delivered using a 0.22 μm in-line filter. Compatibility testing has shown that MHAA4549A is stable when diluted in 0.9% normal saline in a polyvinylchloride, polyolefin bag, or ethylene vinyl acetate bag (EVA), at or above a combined total concentration of 0.24 mg/mL up to 27.0 mg/mL. Study drug must be administered within the treatment window outlined in Section 3.1.1. Further detailed instructions for preparation of study drug can be found in the Pharmacy Manual.

There are no recommended dosage modifications for MHAA4549A since it is a single infusion. Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. General supportive measures will be taken to manage any AEs associated with overdose. Patients experiencing such AEs will be followed up clinically until the event has resolved.

Trained clinical site staff responsible for adequate and accurate study drug administration, accounting, and management will administer study drugs to patients. Study drug preparation and dosing instructions will be provided to each site. The exact times of study drug administration will be recorded in the relevant dispensing/administration logs and patient's source notes. Any noncompliance or problems with study drug administration will be recorded in the patient's source notes and reported to the Sponsor if appropriate.

4.3.2.2 Oseltamivir-Neuraminidase Inhibitor (NAI)

The Sponsor will be providing oseltamivir (Tamiflu®) for this study for up to a 10-day course. Dosage and administration should follow local prescribing information for oseltamivir. Either 75 mg or 150 mg of oseltamivir will be administered twice daily as described in Table 2. Capsules can be opened and the granules administered via nasogastric tube, if required.

Guidelines for dosage modification for renal dosing are presented in Table 2.

Any overdose or incorrect administration of oseltamivir should be noted on the oseltamivir Administration eCRF. Adverse events associated with an overdose or incorrect administration of oseltamivir should be recorded on the Adverse Event eCRF.

Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary, empty (used) oseltamivir packets and unused oseltamivir capsules to the study site at the next follow up visit. Patients will record the date and time when each oseltamivir capsule is administered.

4.3.3 Investigational Medicinal Product Accountability

Investigational medicinal products (IMPs) required for completion of this study (i.e., MHAA4549A and oseltamivir) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMP will be stored in a secure pharmacy or locked area with access limited to authorized personnel, in accordance with the details provided in the Investigator's Brochure and Pharmacy Manual. Upon receipt, MHAA4549A and placebo vials must be refrigerated at 2°C to 8°C until use. MHAA4549A does not contain antimicrobial preservatives; therefore, care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation. Dilute under appropriate aseptic conditions using 0.9% normal saline. The solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use should not exceed 24 hours at 2 to 8°C and/or 4 hours at ambient temperature (18°C – 24°C). If the dose solution is stored at 2°C – 8°C, it should be removed from refrigeration and allowed to reach room temperature prior to administration. If the infusion is interrupted and the combined ambient temperature storage and interruption time exceeds 4 hours, prepare a new dose solution to resume the infusion (see the Pharmacy Manual). Protect dose solutions from heat and intense light.

The total duration from the preparation of dose solutions to the end of infusion should not exceed 24 hours. Vials are intended for single use only; therefore, any remaining solution should be discarded (see the Pharmacy Manual).

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

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

4.4 POST-TRIAL ACCESS TO MHAA4549A

As this is single dose administration, Genentech does not intend to provide MHAA4549A to patients after the conclusion of the study or any earlier withdrawal. Patients may or may not be eligible for any potential subsequent trials of MHAA4549A under a separate protocol.

4.5 CONCOMITANT THERAPY AND FOOD

4.5.1 Permitted Therapy

Concomitant medication includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 30 days prior to screening to the study completion/discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. For any NAIs (e.g., oseltamivir, peramivir, zanamivir, laninimavir) that have been taken prior to study drug therapy, the number of doses and duration of therapy must be recorded.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

All therapies required for management of the patient's acute illness are permitted except for those listed below in Section 4.5.2.

4.5.2 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 7 days prior to study treatment, unless otherwise specified below: probenecid, amantadine, or rimantidine

Use of other NAIs, including but not limited to oral oseltamivir, inhaled zanamivir, oral ribavirin, laninimivir, and peramivir, are prohibited during the study, but allowed up to 3 days (6 doses) prior to study treatment as outlined in the exclusion criteria. If oseltamivir resistance is highly suspected or identified during treatment then, following discussion with the sponsor medical representative, an alternative NAI to oseltamivir may be used.

4.5.3 Prohibited Food

There are no prohibited foods for this study.

4.6 STUDY ASSESSMENTS

Please see Appendix 1a and Appendix 1b for the schedule of assessments performed during the study.

4.6.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed consent by authorized representatives may be obtained only if allowed by and in accordance with local regulations and Independent Review Board (IRB)/Independent Ethics Committee (IEC) policies and procedures. Informed Consent Forms (ICF) 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 randomization. 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.

4.6.2 Diagnostic Testing for Enrollment

All hospitalized patients with severe influenza A will be assessed for disease confirmation and enrollment into the study. A Sponsor-supplied rapid influenza test is required for the diagnosis of influenza A infection and uses a nasopharyngeal swab. When the Sponsor-supplied rapid influenza test is negative, the study inclusion criteria can be satisfied with a positive local molecular test (PCR) if the result is within the 48-hour screening window. Patients may be enrolled based on a positive local molecular test (PCR) result within the 48-hour screening window, but the rapid influenza test must still be conducted prior to randomization. Other tests may not be used for enrollment in the study unless the Sponsor has reviewed and approved the use of the diagnostic.

4.6.3 Medical History and Demographic Data

Medical history includes clinically significant diseases and procedures, including chronic respiratory disease, infections, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days prior to the screening visit. A careful assessment of the patient's baseline SpO_2 should be made especially if the patient has a history of severe chronic lung disease.

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

4.6.4 Priority of Assessments

When events warrant, or in the opinion of the investigator, safety issues become paramount, safety assessments will always have priority over all other measurements and procedures. Under routine circumstances, however, PK, nasal virological, and biomarker serum/plasma samples have priority over other measurements. The timing and number of safety measurements may be modified based on clinical evaluations.

4.6.5 Physical Examinations

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

At protocol designated visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed which includes, at a minimum, evaluation of general appearance, dermatological examination of the injection sites, evaluations directed by patient-reported symptoms, and any other evaluations that the investigator deems clinically relevant. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as AEs, if appropriate, on the AE eCRF.

4.6.6 Vital Signs

Vital signs will include measurements of resting SpO_2 (see Section 4.6.7 for measurement), respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressures after the patient has been in a seated or supine position for at least 10 minutes. Patients in intensive care may have vital signs assessed following local procedures, but those procedures should be captured in the eCRF in accordance with the eCRF instructions.

4.6.7 Oxygen Saturation Measurements

To ensure that the respiratory status is well recorded, the following daily measurements will be performed. Unless clinically contraindicated, all patients will have their SpO_2 and corresponding respiratory assessments recorded daily in the morning between 6 am – 12 pm local time. Patients on low-flow O_2 will have a daily trial of their SpO_2 while on and off the supplementation, as outlined in Appendix 2, and both values will be recorded.

If the patient is on oxygen supplementation, SpO_2 measured by pulse oximetry and the corresponding respiratory assessments (e.g. FiO_2, flow rate) will be recorded. If the patient is on PPV, partial pressure of O_2 (PaO_2) and the corresponding respiratory assessments (e.g. FiO_2, ventilator mode, ventilator respiratory rate, positive end-expiratory pressure) will be recorded.

4.6.8 Laboratory, Biomarker, and Other Biological Samples

Samples for the laboratory tests listed in Table 3 and Table 4 will be sent to the study site's local laboratory for analysis at screening and during the study, respectively.

Table 3 Laboratory Tests at Screening

Hematology:	**Clinical Chemistry:**
Hemoglobin	Thyroid stimulating hormone (optional)
Hematocrit	
Erythrocyte count (RBC)	**Serology:**
Leukocytes (WBC)	HIV Serology
Neutrophils, segmented & bands	
Lymphocytes	**Misc:**
Monocytes	Pregnancy Test (urine or serum; women of child-bearing potential)
Eosinophils	
Basophils	
Platelets	

Note: Investigators must document their review of each laboratory report by signing (or initialing) and dating each report.

Table 4 Laboratory Tests During the Study

Hematology:	**Clinical Chemistry (Blood):**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Bicarbonate
Leukocytes (WBC)	Chloride
Neutrophils, segmented & bands	Calcium
Lymphocytes	Phosphorus
Monocytes	Magnesium
Eosinophils	Glucose
Basophils	Urea nitrogen (BUN) or urea
Platelets	Creatinine
Erythrocyte Sedimentation Rate (ESR) (optional)	Total cholesterol
	Total protein
Coagulation:	Albumin
Activated partial thromboplastin time (APTT)	Total bilirubin
Prothrombin time (PT)	Alkaline phosphatase
International Normalized Ratio (INR)	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
Urinalysis:	Amylase
pH	Gamma-glutamyl transpeptidase (GGT) (if clinically indicated)
Specific gravity	
Glucose	C-reactive protein (CRP) (optional)
Protein	
Ketones	**Misc:**
Blood	Pregnancy Test (if clinically indicated)
Bilirubin	
Nitrite	
Leukocyte esterase	
Microscopic examination (if clinically indicated)	

Note: Investigators must document their review of each laboratory report by signing (or initialing) and dating each report.

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

- [redacted]
- [redacted]

- [redacted]

[redacted]

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

4.6.9 Electrocardiograms

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

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

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is $>$ 500 ms and/or $>$ 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QT interval corrected using Fridericia's formula (QTcF) has stabilized on two successive ECGs. The Medical Monitor should be notified. If QTcF is not available, QTcB may be recorded. Standard of care treatment may be instituted per the discretion of the investigator. If a PK sample

is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 4.9.2. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, medications known to prolong the QT interval, severe bradycardia).

4.6.10 [redacted]

[redacted]

4.7 APACHE AND SOFA SCORES

Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) scores are for patients that are admitted into the ICU. These assessments are not required for study conduct or entry but should be collected if available. The initial scores for APACHE and SOFA should be taken within 24 hours of entry into the ICU and at specified time points as seen in Appendix 1a.

For the calculation of the initial APACHE and SOFA scores, the worst values in the first 24 hours of ICU admission should be used. SOFA scores are only for patients admitted into the ICU that have available data for calculation (i.e., partial pressure of arterial oxygen/fraction of inspired oxygen [PaO_2/FiO_2] in mmHg). See Appendix 7 for SOFA score calculation.

4.8 OSELTAMIVIR MEDICATION DIARY

Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary, empty (used) oseltamivir packets, and unused oseltamivir capsules to the study site at the next follow up visit.

Patients will record the date and time when each oseltamivir capsule is administered.

4.9 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.9.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.9.2 Study Treatment Discontinuation

Patients must discontinue MHAA4549A infusion and therefore treatment if they experience any of the following:

- Infusion related reactions

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

- Pregnancy
- Serious skin/hypersensitivity reactions

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

The IMC and SOC may recommend to permanently discontinue dosing for all patients within one or both study arms in the event of a general safety concern.

4.9.3 Study Completion/Early Discontinuation Visit

Patients who complete all study visits through Day 60 are considered to have completed study. All patients who discontinue from the study early will be asked to complete all assessments for the current visit day and for the early discontinuation visit without duplication. Please see Schedule of Assessments provided in Appendix 1a for assessments performed at the Study Completion/Early Discontinuation visit.

4.9.4 Study and Site Discontinuation

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

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

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

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

MHAA4549A is not approved and is currently in clinical development. Thus, the entire safety profile is not known at this time. The safety plan for this study is based upon preclinical data and the previous Phase 1 and Phase 2a (interim) studies and is designed to ensure patient safety. It will include specific eligibility criteria and monitoring assessments as detailed below and above in Section 4.1.

The investigator, in consultation with the Sponsor, is responsible for assuring the safety of study participants who have entered this study and for taking appropriate action concerning any event that seems unusual, even if this event may be considered to be an unanticipated benefit to the study participant. The investigator will be responsible for a clinical assessment of the study participants before discharge from the study, and for the establishment of a discharge plan, if needed.

During the study, the incidence and nature of adverse events, serious adverse events, and laboratory abnormalities will be assessed. An ongoing blinded review of safety will be carried out by the Medical Monitor and a drug safety scientist. An unblinded review of safety will be performed on an ongoing regular basis by the IMC and SOC as described in the IMC and SOC agreement.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

Adverse events will be monitored throughout the entire study (enrollment through Day 60 or Early Discontinuation). If clinically significant signs or laboratory values are observed in a study participant, the investigator should repeat an assessment at the earliest opportunity. Only those events or laboratory values that exceed the level of clinical significance upon the repeat assessment will be considered an adverse event.

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Fatal (i.e., the adverse event actually causes or leads to death)

- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS); see Section 5.3.3, Appendix 8, and Appendix 9); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Non-serious adverse events of special interest (AESI) are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study 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 (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

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

- Adverse events associated with suspected cases of infusion-related reactions (IRR) which occur within 24 hours of study drug administration and may show the following signs and symptoms (for guidance on reporting AEs associated with IRR, see Section 5.3.5.1 below):
  - Fever and/or shaking chills
  - Flushing and/or itching
  - Alterations in heart rate and blood pressure
  - Dyspnea or chest discomfort
  - Back or abdominal pain
  - Nausea, vomiting, and/or diarrhea
  - Various types of skin rashes
  - Anaphylaxis
- Anaphylaxis due to IV drugs most often presents with the following signs and symptoms:
  - Cutaneous symptoms: flushing, itching, urticaria, and/or angioedema (usually of face, eyelids, or lips)
  - Respiratory symptoms: repetitive cough, sudden nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and or change in voice quality due to laryngeal edema
  - Cardiovascular symptoms: faintness, tachycardia (or less often bradycardia), tunnel vision, chest pain, hypotension, sense of impending doom, and/or loss of consciousness
  - Gastrointestinal symptoms: such as nausea, vomiting, abdominal cramping, and diarrhea

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until the Day 60 visit or Early Discontinuation visit. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any death or other serious adverse event that occurs after discharge, regardless of causality. The Sponsor should also be notified if the investigator becomes aware of a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

Investigators will seek information on adverse events and serious adverse events at each patient contact. All AEs, and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded.

The adverse event grading (severity) scale in the DAIDS v1.0 will be used for assessing AE severity (see Table 5).

Table 5 Adverse Event Grading (Severity) Scale

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical AE NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

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

Table 6 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Other Adverse Events

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF, unless the severity increases. If a persistent adverse event becomes more severe, it should be recorded as a separate event on the Adverse Event

eCRF. The initial (less severe) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became more severe. If a persistent adverse event becomes serious, it should be recorded as a separate event on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The initial (non-serious) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became serious.

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

5.3.5.4 Abnormal Laboratory Values

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

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment (laboratory abnormalities should be repeated at the first opportunity and only considered clinically significant if they persist on repeat assessment)

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

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

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment. Abnormal vital sign values should be repeated at the first opportunity and only considered clinically significant if they persist on repeat assessment)

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

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

the event) either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of severe influenza or any related co-morbidities should be recorded on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF, and immediately reported to the Sponsor as an SAE (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

5.3.5.8 Pre-existing Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of Influenza A Infection

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

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Adverse Events Associated with an Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No clinical safety data related to overdosing of MHAA4549A are available, however, overdoses with a monoclonal antibody theoretically could cause volume overload that can result in edema and/or heart failure.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

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

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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/IEC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

[redacted] Medical Monitor contact information:

Primary Medical Monitor: [redacted]

Telephone Nos.: US Office: [redacted]

US Mobile: [redacted]

Secondary Medical Monitor: [redacted]

Telephone Nos.: US Office: [redacted]

US Mobile: [redacted]

Genentech Medical Monitor contact information for all sites if above medical monitor cannot be reached:

Medical Monitor: [redacted]

Telephone Nos.: US Mobile [redacted]

US Office [redacted]

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. A paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to the Sponsor's Safety Risk Management department or its

designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided below per region:

Asia Pacific: [redacted]

Europe: [redacted]

Latin America: [redacted]

North America: [redacted]

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until the patient is at Day 60 or Early Discontinuation. Although the investigator is not required to actively monitor patients for adverse events after the patient has been discharged from the study, the Sponsor should be notified if the investigator becomes aware of any death or other serious adverse event that occurs after discharge from the study, if determined to be related to study drug by the investigator. The Sponsor should also be notified if the investigator becomes aware of a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug (see Section 5.4.3).

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

In the event that the EDC system is unavailable, a paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to investigators (see fax numbers provided in Section 5.4.2.1). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 120 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should

continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, a paper Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see fax numbers provided in Section 5.4.2.1). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant within 30 days after the dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

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

5.4.4 Investigator Follow-Up

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

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF and the Investigator document a discharge plan.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.4.5 Sponsor Follow-Up

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

5.5 POSTSTUDY ADVERSE EVENTS

At the time of study completion or study discontinuation, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient or their personal physician believes could be related to prior study drug treatment or study procedures.

The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 60 days after the dose of study drug). However, the Sponsor should be notified if the investigator becomes aware of any death, other serious adverse event, or non-serious adverse event of special interest occurring after the end of the adverse event reporting period, regardless of causality. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient or a female partner of a male patient exposed to study drug.

The investigator should report these events by completing and faxing a paper Serious Adverse Event Reporting Form and fax cover sheet to Safety Risk Management using the fax numbers provided to investigators (see Section 5.4.2.1).

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

The Sponsor will promptly evaluate all serious adverse events including suspected unexpected serious adverse reactions (SUSARs) and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, IECs, and applicable health authorities based on applicable legislation.

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

- MHAA4549A Investigator's Brochure
- Local prescribing information for oseltamivir

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

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

Certain adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting. These anticipated events include, but are not limited to, the following:

- Asymptomatic elevations of ALT, AST, and or amylase without corresponding elevations of bilirubin have been shown to be increased during influenza A infection (Polakos 2006)
- Influenza associated disease and or complications of influenza

An IMC and SOC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

All efficacy analyses will be conducted according to the intent-to-treat principle and will include all patients who meet the following condition with patients allocated to the treatment arm to which they were randomized:

- Randomized patients who have confirmed influenza A infection as confirmed by a central PCR test from Day 1 samples

Safety analyses will include all patients who were included in the randomization and who received at least one dose of study medication, with patients allocated to the treatment arm associated with the regimen actually received.

No formal hypothesis testing will be done in this study. As a result, no adjustment for a type 1 error will be made to account for the multiplicity of analyses.

Final efficacy and safety analyses of the total study population will be conducted at the end of the study after all patients have completed all study assessments and the database has been cleaned and closed. Further details of the analyses, including analysis of the exploratory endpoints, will be contained in the statistical analysis plan

(SAP) which will be prepared and finalized before the first optional interim analysis (see Section 6.7) or the final efficacy and safety analysis, if no interim analysis takes place.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is estimation of the effect size and hypothesis generation regarding the effect of MHAA4549A on the time to normalization of respiratory function relative to the standard of care rather than hypothesis testing. Point and interval estimates will be obtained. A total of 334 patients will be enrolled in this study in order to obtain approximately 300 evaluable patients (an estimated dropout rate of 10%). It is assumed that the median time to normalization of respiratory function in the control arm is 5 days. This sample size (approximately 150 patients per arm) provides 75% power to detect a treatment difference of 1 day for the primary endpoint assuming a 2-sided alpha of 0.2.

Operating characteristics (power) under other possible assumptions for 2-sided alpha of 0.05 and true differences of 1 to 2 days are provided in Table 7.

Table 7 Operating Characteristics for Proposed Study Design for Several Possible True Underlying Median Values

	True Underlying Median for MHAA4549A		
	3 days	3.5 days	4 days
Hazard Ratio	0.60	0.70	0.80
Power of log-rank test [a]	99%	86%	48%
95% confidence interval for true hazard ratio [b]	(0.48, 0.75)	(0.56, 0.88)	(0.64, 1.00)

Note: Operating characteristics are based on the following assumptions: 300 evaluable patients, event times are exponentially distributed, median time to normalization of respiratory function in the control arm is 5 days, and patients are followed for 60 days.

[a] Two-sided $\alpha = 0.05$.

[b] Confidence intervals are based on the assumption that the point estimate is equal to the true underlying value of the hazard ratio in each column.

It should be noted that the study is underpowered for detection of minimally clinically meaningful differences at a 2-sided alpha of 0.05 such as a true hazard ratio of 0.80 (see third column of Table 7.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue (early discontinuation of treatment or early termination from the study), and complete the study will be tabulated by treatment group using descriptive statistics. Reasons for early discontinuation of treatment or early termination from the study will be listed and summarized by treatment group. Any eligibility criteria exceptions and other protocol deviations will also be summarized by treatment group.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics of the patient will be summarized for all randomized patients by treatment group by use of descriptive statistics. Baseline is defined as the last available value prior to study drug administration.

During the study; patient disposition, concurrent treatment, and compliance with study treatment and visits will be summarized on the safety analysis population using descriptive statistics.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized patients who are confirmed to be influenza A infected, with patients grouped according to the treatment assigned at randomization.

Time to event data will be computed using Kaplan-Meier methodology and stratified Cox proportional hazards models and will be summarized using n, median when estimable, hazard ratios, and 95% confidence intervals. Patients who are lost to follow-up (while event free) will be censored at the time that they are last known to be event free.

Estimation of the treatment difference of proportions and its 95% confidence interval will be calculated using stratum-adjusted Mantel-Haenszel methodology (Koch et al. 1989). For continuous endpoints, Analysis of Covariance methods (after appropriate transformation of data) will be used to estimate treatment differences and 95% confidence intervals.

Other than censoring in the time to event analyses, no other imputation for missing data will be performed.

6.4.1 Primary Efficacy Endpoint

- Median time to normalization of respiratory function

6.4.2 Secondary Efficacy Endpoints

- Proportion of patients with clinical failure after 24 hours post-infusion of study drug
- Median time to clinical resolution of vital signs
- Hazard ratio for mortality at Day 14, Day 30, and Day 60
- Mean and median AUC of viral load
- Mean and median peak viral load
- Median duration of viral shedding in upper respiratory samples
- Median duration of hospitalization
- Median duration of ICU stay
- Proportion of patients requiring antibiotics for respiratory indications during study

- Proportion of patients with influenza secondary complications
- Median duration of ventilation
- Proportion of patients who are readmitted by Day 30 and Day 60

6.4.3 Subgroup Analyses

Subgroup analyses will be performed to examine the consistency of the treatment estimates with use of the primary and selected secondary endpoints. Subgroups will include the stratification factors as well as patients who are identified at baseline as influenza A positive by the upper, lower, or both airways and by patients with bacterial co-infections at admission. Additional subgroups may be added following assessment of baseline characteristics as exploratory analyses.

6.5 SAFETY ANALYSES

The safety analyses will include all randomized patients who received study drug, with patients grouped according to the treatment actually received. Safety parameters to be evaluated include adverse events (including deaths, serious adverse events, discontinuations due to adverse events, and the incidence and severity of adverse events), clinical laboratory tests, vital signs (including SpO_2 measurements), and ECGs.

All collected adverse event data will be listed by study site and patient number.
All adverse events that occur on or after treatment on Day 1 will be summarized for each treatment group by mapped term, appropriate thesaurus levels, body system, and event within each body system, and toxicity grade. In addition, all serious adverse events, including deaths, will be listed separately and summarized. SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) that occur between consent and first dose of study medication will be listed separately.

Laboratory data with values outside of the normal ranges will be identified. In addition, select laboratory data will be summarized by treatment group using descriptive summary statistics.

The absolute and percentage changes from baseline in vital sign parameters will be computed, and changes deemed clinically significant by the Investigator will be noted. Appropriate descriptive summary statistics will be provided for all vital sign parameters

6.6 PHARMACOKINETIC ANALYSES

Individual and mean serum MHAA4549A concentration versus time data will be tabulated and plotted. The serum pharmacokinetics of MHAA4549A will be summarized by estimating total serum drug exposure (i.e., AUC), C_{max}, C_{min}, total serum clearance, half-life, and volume of distribution, as data allow. Estimates for these parameters will be tabulated and summarized (e.g., mean, standard deviation, coefficient of variation).

Inter-patient variability will be evaluated. MHAA4549A serum concentration–time data may be compared with available data from other MHAA4549A clinical studies.

[redacted]

[redacted]

6.7 OPTIONAL INTERIM ANALYSIS

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

If conducted, an interim analysis would be for administrative purposes only (i.e., internal planning or decision making) and would not impact the conduct of the current study in any way. A nominal type I error penalty of 0.0001 will be taken.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

The Consent Forms must be signed and dated by the patient or the patient’s authorized representative as applicable and in accordance with local regulations, and IRB/IEC policies, before his or her participation in the study. The case history or clinical records

for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments (see Section 9.1).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/IEC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible

for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC, and archived in the site's study file.

8.4 CONFIDENTIALITY

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

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

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate, financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient, last visit [LPLV]).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and

data integrity to the Sponsor and to the IRB/IEC in accordance with established IRB/IEC policies and procedures.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

Genentech, Inc., a member of the Roche group, is the Sponsor of this study. A clinical research organization (CRO) may provide clinical operations oversight, including but not limited to project management, clinical monitoring and site management, data quality support, medical monitoring, and some safety reporting and regulatory activities as specified in study management plans. Genentech will provide CRO oversight, develop the database and randomization scheme, and conduct statistical programming and analysis. An IMC and SOC will provide safety monitoring for the study in addition to the ongoing review of safety by the Medical Monitor and Safety Scientist.

EDC will be utilized for this study. An IxRS will be used to assign patient numbers, randomize patients into study through use of a dynamic hierarchical algorithm, and manage site drug supply. A central laboratory will be used for sample management and storage until shipment to specialty laboratories or Genentech for analysis.

9.5 PROTOCOL AMENDMENTS

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

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

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APPENDIX 1a
Schedule of Assessments: Hospitalization Days

Notes: Unless otherwise indicated, all assessments on Day 1 should be performed prior to study drug administration; x's within parentheses, i.e., (x), indicate optional assessments. Please refer to Follow-up Period table for visits to be completed after patient is discharged from hospital prior to Day 60.

	Screening	Hospitalized Days (only to be completed while patients are hospitalized)															D60
Day (D)	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D14	D20	D25	Hospital Discharge [a]	D30	Study Completion or Early Discontinuation while Hospitalized
Confirm study drug administration can occur within 48 hours of hospital admission																	
Informed consent [b]	x																
Rapid influenza A test [c]	x																
Local influenza A PCR test [d]	x																
Inclusion/exclusion criteria	x																
Medical history and demographic data	x																
Confirm onset of flu symptoms (≤ 5 days prior to study drug administration on Day 1)	x																
Confirm history of baseline $SpO_2 > 92\%$	x																
Pregnancy screening [e]	x																
Confirm O_2 requirement [f]	x																
Respiratory Assessment [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
APACHE score [j]		(x^z)										(x)			(x)	(x)	(x)
SOFA score [k]		(x^z)						(x)				(x)			(x)	(x)	(x)
Electrocardiogram (12-lead) [l]		x				x						x			x	x	x
Randomization		x															

APPENDIX 1a (cont'd)
Schedule of Assessments: Hospitalization Days

	Screening	Hospitalized Days (only to be completed while patients are hospitalized)															
Day (D)	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D14	D20	D25	Hospital Discharge [a]	D30	D60 Study Completion or Early Discontinuation while Hospitalized
MHAA4549A administration		x[m]															
Oseltamivir administration [n]		x	x	x	x	x	(x)	(x)	(x)	(x)	(x)						
Complete physical examination [o]	x	(x)															
Limited, symptom-directed physical examination [p]			x	x	x	x						x			x	x	x
Weight & height, BMI [q]	x[q]	x				x						x			x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [r]	x		x			x						x			x	x	x
Chemistry panel [r]	(x)[aa]	x	x			x						x			x	x	x
Coagulation panel [r]		x				x						x			x	x	x
Erythrocyte sedimentation rate		(x)	(x)			(x)						(x)			(x)	(x)	(x)
C-reactive protein		(x)	(x)			(x)						(x)			(x)	(x)	(x)
Urinalysis [r, s]		x	x			x						x			x	x	x
Serology (HIV) [bb, r]	x																
Upper respiratory tract sample (NP sample) [t]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
[redacted]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Flu antibodies (HAI)		x										x			x	x	x
[redacted]		x														x	x
Serum for MHAA4549A PK measurements [v]		x	x	x		x		x				x			x	x	x

APPENDIX 1a (cont'd)
Schedule of Assessments: Hospitalization Days

Day (D)	Screening	Hospitalized Days (only to be completed while patients are hospitalized)													Hospital Discharge [a]	D30	D60 Study Completion or Early Discontinuation while Hospitalized
	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D14	D20	D25			
[redacted]		x				x									(x)[x]		
[redacted]		x	x	x		x		x			x	x	x	x	x	x	x
[redacted]		x	x	x		x		x			x	x	x	x	x	x	x
[redacted]		x													x	x	x
[redacted]		x														x	x
[redacted]		x													x	x	x
[redacted]		x													x	x	x
[redacted]															x		
Oseltamivir medication diary [cc]															x		

[redacted]; APACHE = Acute Physiology and Chronic Health Evaluation; ATA = Anti-therapeutic antibodies; BMI = body mass index; D = day; Dx = diagnostics; eCFR = electronic Case Report Form; ECG = electrocardiogram; HAI = hemagglutinin inhibition; [redacted] ICU = Intensive Care Unit; IRB/IEC = Independent Review Board/Independent Ethics Committee; NAI = neuraminidase inhibitor; NP = nasopharyngeal; O_2 = oxygen; PaO_2/FiO_2 = partial pressure of oxygen/fraction of inspired oxygen; PCR = polymerase chain reaction; PD = pharmacodynamics; PK = pharmacokinetic; PPV = positive pressure ventilation; qPCR = quantitative Polymerase Chain Reaction; RBCs = red blood cells; SOFA = Sequential Organ Failure Assessment; SpO_2 = oxygen saturation measured by pulse oximetry; WBCs = white blood cells.

APPENDIX 1a (cont'd)
Schedule of Assessments: Hospitalization Days

[a] Assessments to be performed irrespective of day of discharge. Assessments on discharge day will supersede assessments for matching day except for the study completion/early discontinuation visit (e.g., If a patient is discharged from the hospital on Day X, use assessments under "hospital discharge" column instead of the Day X column and record under the hospital discharge folder in the eCRF. If a patient discontinues from the study early on Day X, complete all assessments under the Day X column and "early discontinuation" column without duplication, and record under the early discontinuation folder in the eCRF).

[b] Informed consent must be obtained from all patients. For patients who are unable to consent, an authorized representative may be used if allowed by local regulations and IRB/IEC policy.

[c] Sponsor-supplied rapid influenza test using nasopharyngeal swabs.

[d] If the Sponsor-supplied rapid influenza test is negative, local influenza PCR testing can be used to confirm influenza A and satisfy entry criteria if results are received within screening/hospitalization window (48 hours). Patients can be enrolled based on a positive local influenza PCR test result within the 48 hour screening window, but the rapid influenza test must still be conducted prior to randomization.

[e] A urine pregnancy test should be sent only for women considered by the investigator to be of childbearing potential, see exclusion criteria. This result must be available prior to randomization. If urine testing is not available at the site, blood already collected from an existing sample may be tested for pregnancy.

[f] Confirm patient requires supplemental O_2 or PPV within 24 hours of hospital admission.

[g] All patients will have their on-study SpO_2 and corresponding respiratory assessments recorded daily in the morning between 6 am – 12 pm local time; screening SpO_2 may be taken outside this window. Patients on low flow O_2 should have a daily trial of their SpO_2 while on and off the supplementation and both values will be recorded. If the patient is on oxygen supplementation, SpO_2 measured by pulse oximetry and the corresponding respiratory assessments (e.g. FiO_2, flow rate) will be recorded. If the patient is on PPV, PaO_2 and the corresponding respiratory assessments (e.g. FiO_2, ventilator mode, ventilator respiratory rate, positive end-expiratory pressure) will be recorded.

[h] Concomitant medications should be recorded for 30 days prior to screening, through the study completion/early discontinuation visit. See exclusion criteria in Section 4.5.2 for prohibited therapies.

[i] Vital signs will be collected within 1 hour before MHAA4549A infusion and within 1 hour after completion of MHAA4549A infusion include temperature, respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure. Temperature should be measured using the same methodology throughout the study and should be measured prior to administration of any antipyretic drugs. In patients who have multiple vital signs taken during any day, the most abnormal value should be recorded from that 24-hour period. Temperature, blood pressure, respiratory rate, and heart rate will be completed after the patient has been supine for > 5 minutes. The worst/most abnormal value from the last 24-hour period should be recorded for patients who are in the ICU.

[j] APACHE scores are optional and only for patients that are in the ICU. For calculation of the screening APACHE score, the worst values in the preceding 24 hours should be used. APACHE scores are not required for study conduct or entry but should be collected if available.

[k] SOFA scores are only for patients in the ICU that have available data such as PaO_2/FiO_2 (mmHg). See Appendix 7 for SOFA score calculation.

[l] Patient should rest in a supine position for 10 minutes prior.

[m] Patient will be a resident for at least 24 hours following administration of MHAA4549A.

[n] Oseltamivir must be given for a minimum of 5 days. Treatment longer than 5 days is permitted based on the discretion of the investigator [indicated by (x)].

[o] Complete physical examination includes evaluations of general appearance of head, eye, ear, nose, and throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as adverse events, if appropriate.

[p] Limited, symptom-directed physical examination includes, at a minimum, evaluation of general appearance, dermatological examination of the injection sites, evaluations directed by patient-reported symptoms, and any other evaluations that the investigator deems clinically relevant. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as adverse events, if appropriate.

[q] Height will be obtained at screening only. Weight will be obtained at all indicated visits. Height and weight will be recorded in centimeters and kilograms, respectively.

[r] Local laboratory measurements should be utilized.

[s] Urinalysis includes pH, specific gravity, glucose, protein, ketones, blood, bilirubin, nitrite, and leukocyte esterase. Microscopic examination (e.g., sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) will be performed if clinically indicated.

[redacted]

[v] Day 1 serum PK samples are to be drawn 30 (± 5) minutes pre-dose of MHAA4549A, 60 (± 15) minutes after the end of infusion. PK samples will be drawn from the contralateral arm from that used for drug infusion and must be labeled with the exact time of draw.

[redacted]

[x] If patient is discharged on or before Day 5, the oseltamivir PK sample should be taken on the discharge day.

[redacted]

[z] Assessment to be conducted based on entry into ICU; may vary from patient to patient.

[aa] For optional thyroid stimulating hormone test.

[bb] HIV serology result not needed for randomization.

[cc] Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary, empty (used) oseltamivir packets and unused oseltamivir capsules to the study site at the next follow up visit. Patients will record the date and time when each oseltamivir capsule is administered.

APPENDIX 1b
Schedule of Assessments: Follow-Up Period

- If a patient is discharged prior to Day 14, he/she will need to complete the following assessments for Day 14 ,Day 30, and Day 60 below.
- If a patient is discharged prior to Day 30 and after Day 14, he/she will need to complete the following assessments for Day 30 and Day 60 below.
- If a patient is discharged prior to Day 60 but after Day 30, he/she will need to complete the following assessments for Day 60 below.
- If patient is hospitalized for Day 14, Day 30, and/or Day 60, please refer to Appendix 1a.

Day (D)	D14 ± 1 (If discharged BEFORE D14)	D30 ± 4 (If discharged BEFORE D30)	Day 60 ± 4 (Study Completion) or Early Discontinuation
Concomitant medications [a]	x	x	x
Vital signs [b]	x	x	x
Electrocardiogram (12-lead) [c]	x	x	x
Weight & height, BMI [d]	x	x	x
Adverse events	x	x	x
Hematology [e]	x	x	x
Chemistry panel [e]	x	x	x
Coagulation panel [e]	x	x	x
Urinalysis [e]	x	x	x
Flu antibodies (HAI)	x	x	x
[redacted]		x	x
Serum for MHAA4549A PK measurements [f]	x	x	x
[redacted]	x	x	x
[redacted]	x	x	x
[redacted]		x	x
[redacted]		x	x
[redacted]		x	x
[redacted]		x	x

[redacted]; ATA = Anti-therapeutic antibodies; BMI = body mass index; D = day; Dx = diagnostics; eCFR = electronic Case Report Form; ECG = electrocardiogram; HAI = hemagglutinin inhibition; [redacted]; PD = pharmacodynamics; PK = pharmacokinetic.

[a] Concomitant medications should be recorded for 30 days prior to screening, through the study completion/early discontinuation visit. See exclusion criteria in Section 4.5.2 for prohibited therapies.

APPENDIX 1b (cont'd)
Schedule of Assessments: Follow-up Period

[b] Vital signs include temperature, respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure. Temperature should be measured using the same methodology throughout the study and should be measured prior to study drug administration of any antipyretic drugs. In patients who have multiple vital signs taken during any day, the most abnormal value should be recorded from that 24-hour period. Temperature, blood pressure, respiratory rate, and heart rate will be completed after the patient has been supine for > 5 minutes.

[c] ECG should be recorded after the patient has rested in a supine position for 10 minutes.

[d] Height will be obtained at screening only. Weight will be obtained at all indicated visits. Height and weight will be recorded in meters and kg, respectively.

[e] Local laboratory measurements should be used.

[f] PK samples should be drawn from the opposite arm from the one used for drug infusion and must be labeled with the exact time of draw.

[redacted]

APPENDIX 2
Time to Normalization of Respiratory Function

For the purposes of this study, the time to normalization of respiratory function will be defined as the time to removal of the patient from O_2 supplementation in order to maintain an $SpO_2 > 95\%$.

Patients who are on low flow O_2 (2-6L/min) should receive a daily trial off O_2 in the morning between 6 am – 12 pm as described below.

1. Patient should be resting or sitting.

2. Patient should be fitted with pulse oximeter, and their SpO_2 should be checked once while on O_2 and then again 3 – 5 minutes after turning off O_2 supplementation.

3. If the $SpO_2 > 95\%$, then the time and reading should be recorded. Notify the study doctor so that he/she can make a clinical judgment to determine whether the O_2 can be removed.

4. If the patient is off O_2 for 24 hours and his/her reading the subsequent day is >95%, then the endpoint is considered satisfied. The recorded time for the endpoint corresponds with the initial discontinuation of O_2 and reading.

APPENDIX 3

[redacted]

APPENDIX 4

[redacted]

[redacted]

[redacted]

APPENDIX 5

[redacted]

APPENDIX 6

[redacted]

APPENDIX 7
SOFA Score Calculation

Administration of MHAA4549A will be performed in a setting with emergency medical equipment and personnel who are trained to monitor for and respond to medical emergencies. A qualified physician will be on site during study drug administration for all patients.

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Airway management equipment
- O_2
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

Stop the study drug infusion.

Maintain an adequate airway.

Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.

Continue to observe the patient and document observations.

APPENDIX 8
DAIDS Toxicity Grading Tables for Clinical Abnormalities

From the FDA Guidance document 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials' (September 2007)

Vital Signs [a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) [b] (°F)*	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40.0 102.1 – 104.0	>40 >104
Tachycardia – beats per minute	101- 115	116 – 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia – beats per minute [c]	50 – 54	45 – 49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) – mmHg	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mmHg	91 – 95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mmHg	85 – 89	80 – 84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	>25	Intubation

[a] Subject should be at rest for all vital sign measurements.

[b] Oral/tympanic temperature; no recent hot or cold beverages or smoking.

[c] When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

APPENDIX 8 (cont'd)
DAIDS Toxicity Grading Tables for Clinical Abnormalities

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/ vomiting	No interference with activity or 1 – 2 episodes/ 24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 g/ 24 hours	4 – 5 stools or 400 – 800 g/ 24 hours	5 or more watery stools or > 800 g/ 24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity no requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

APPENDIX 9
DAIDS Toxicity Grading Tables for Laboratory Abnormalities

Adapted from Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007 DRAFT and FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials

Abbreviations used in the table:
[redacted]; CPK = creatine phosphokinase; Dec = Decreased; IV = Intravenous; LLN = Lower limit of normal; Mod = Moderate; Req = Required; Rx = Therapy; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = Upper limit of normal.

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 – 10.5 g/dL	8.0 – 9.4 g/dL	6.5 – 7.9 g/dL	<6.5 gm/dL
Absolute Neutrophil Count	1,000 – 1,500/mm^3	750 – 999/mm^3	500 – 749/mm^3	<500/mm^3
*Platelets	125,000 – 140,000/mm^3	100,000 – 124,999/mm^3	25,000 – 99,999/mm^3	<25,000/mm^3
WBCs	11,000 – 13,000/mm^3	13,000 – 15,000/mm^3	15,000 – 30,000/mm^3	>30,000 or <1,000/mm^3
*Lymphocytes Decrease – cell/mm^3	750 – 1,000	500 – 749	250 – 499	<250
*Eosinophils – cell/mm^3	650 – 1500	1501 – 5000	>5000	Hypereosinophilic
Abnormal Fibrinogen	Low: 100 – 200 mg/dL High: 400 – 600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: <50 mg/dL	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20 – 40 mcg/mL	41 – 50 mcg/mL	51 – 60 mcg/mL	>60 mcg/mL
Prothrombin Time (PT)	1.01 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin Time (APTT)	1.01 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3 x ULN	>3 x ULN
Methemoglobin	5.0 – 9.9%	10.0 – 14.9%	15.0 – 19.9%	>20.0%

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

APPENDIX 9 (cont'd)
DAIDS Toxicity Grading Tables for Laboratory Abnormalities

CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130 – 135 mEq/L	123 – 129 mEq/L	116 – 122 mEq/L	<116 mEq/L or abnormal sodium with mental status changes or seizures
Hypernatremia	146 – 150 mEq/L	151 – 157 mEq/L	158 – 165 mEq/L	>165 mEq/L or abnormal sodium with mental status changes or seizures
Hypokalemia	3.0 – 3.4 mEq/L	2.5 – 2.9 mEq/L	2.0 – 2.4 mEq/L or intensive replacement therapy or hospitalization required	<2.0 mEq/L or abnormal potassium with paresis ileus or life-threatening arrhythmia
Hyperkalemia	5.6 – 6.0 mEq/L	6.1 – 6.5 mEq/L	6.6 – 7.0 mEq/L	>7.0 mEq/L or abnormal potassium with life-threatening arrhythmia
Hypoglycemia	55 – 64 mg/dL	40 – 54 mg/dL	30 – 39 mg/dL	<30 mg/dL or abnormal glucose with mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 – 160 mg/dL	161 – 250 mg/dL	251 – 500 mg/dL	>500 mg/dL or abnormal glucose with ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 – 7.8 mg/dL	7.7 – 7.0 mg/dL	6.9 – 6.1 mg/dL	<6.1 mg/dL or abnormal calcium with life threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6 – 11.5 mg/dL	11.6 – 12.5 mg/dL	12.6 – 13.5 mg/dL	>13.5 mg/dL or abnormal calcium with life-threatening arrhythmia
Hypomagnesemia	1.4 – 1.2 mEq/L	1.1 – 0.9 mEq/L	0.8 – 0.6 mEq/L	<0.6 mEq/L or abnormal magnesium with life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 – <1.25 x ULN	1.25 – <1.5 x ULN	1.5 – 1.75 x ULN	>1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 – <1.5 x ULN	1.5 – <2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 – 8.0 x ULN	>8.0 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 – 8.0 x ULN	>8.0 x ULN
GGT	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 – 8.0 x ULN	>8.0 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 – 8.0 x ULN	>8.0 x ULN
Amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	>5.1 x ULN
Lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	>5.1 x ULN
*CPK – mg/dL	1.25 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 10.0 x ULN	>10 x ULN

*From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg – 1 g loss/day	2-3+ or 1-2 g loss/day	4+ or 2-3.5 g loss/day	Nephrotic syndrome or >3.5 g loss/day
Hematuria	Microscopic only <10 rbc/hpf	Gross, no clots >10 rbc/hpf	Gross, with or without clots, OR red blood casts	Obstructive or required transfusion
*Glucose	Trace	1+	2+	Hospitalization for hyperglycemia

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

PROTOCOL

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY, IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION**
PROTOCOL NUMBER:	GV29216
VERSION NUMBER:	5 (Global)
EUDRACT NUMBER:	2014-000461-43
IND NUMBER:	117,318
TEST PRODUCT:	MHAA4549A
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	30 May 2014
DATE AMENDED:	Version 2: 14 August 2014 Version 3 (VHP Only): 25 September 2014 Version 4 (Russia Only): 30 January 2015 Version 5 (Global): See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	20-Mar-2015 16:25:55

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PROTOCOL AMENDMENT RATIONALE

This Version 5 amendment consolidates elements of two previous country-specific amendments and revises the study design to add a third treatment arm (i.e., 8400 mg treatment arm). The rationale for previous amendments (i.e., Version 3 and Version 4) is listed for the convenience of sites that did not receive these versions of the protocol.

RATIONALE FOR VERSION 3 (VHP ONLY)

Protocol GV29216 was amended in Version 3 was revised to incorporate VHP feedback and reflects the following changes:

- Male partners of female patients who have had a vasectomy should have appropriate post-vasectomy documentation available of the absence of sperm in the ejaculate (see Section 4.1.1).
- Female patients should use two acceptable methods of contraception throughout the trial, including the active treatment phase AND for 120 days after the last dose of MHAA4549A (see Section 4.1.1).
- Male patients should use condoms and refrain from donating sperm until 30 days after dosing (see Section 4.1.1).
- Exclusion criteria “hypersensitivity to monoclonal antibodies or to the active substance or any excipients of MHAA4549A study drug” and “hypersensitivity to the active substance or to any excipients of oseltamivir” (see Section 4.1.2)

RATIONALE FOR VERSION 4 (RUSSIA ONLY)

Protocol GV29216 was amended in Version 4 (Russia Only) to address comments from the Ministry of Healthcare of the Russian Federation, as follows:

- [redacted]
- Changed “mAb” to “monoclonal antibody” throughout the protocol
- Clarified rationale for biomarker assessments
- Updated exclusion criteria to exclude patients with hypersensitivity to monoclonal antibodies or to the active substance or any excipients of MHAA4549A study drug, hypersensitivity to the active substance or to any excipients of oseltamivir, and patients with a creatinine clearance $\leq$10 mL/min
- [redacted]
- Clarification of repeating any abnormal assessment or clinically significant laboratory findings

In addition, changes were made to clarify inclusion/exclusion criteria and study procedures, as follows:

- Contraception requirements in inclusion criteria

- Exclusion criteria to exclude patients on current treatment with probenecid to stay consistent with the prohibited treatments section
- Unblinded personnel at each study site will prepare the intravenous infusions of study drug and that the Sponsor will provide masking bags and blinded study personnel with administer the study drug
- Placebo is identical to active MHAA4549A in formulation, but not appearance
- The adverse event reporting period

Additionally, updates were made to the protocol, as follows:

- Contact information for reporting serious adverse events and non-serious adverse events of special interest
- Investigator follow-up instructions (Section 5.4.4)
- Poststudy adverse events reporting instructions (Section 5.5)
- Addition of publication of data and protection of trade secrets instructions (Section 9.5)
- Replacement of SOFA score calculations (Appendix 7)
- Addition of anaphylaxis precautions and management instructions (Appendix 10)

The Sponsor considers that changes in this amendment will increase the safety monitoring in this Phase 2b study without any significant impact on the scientific value of the trial, nor will they have any significant impact on the safety or mental or physical integrity of study patients.

RATIONALE FOR VERSION 5 (GLOBAL)

Protocol GV29216 was amended in Version 5 to add a high-dose arm (i.e., 8400 mg MHAA4545A) and to harmonize relevant regional feedback into a global amendment.

GV29216 will assess severely ill patients who may be infected with various influenza A strains and who have a higher viral burden and longer duration of viral shedding than the healthy volunteers in GV28985. This population may benefit from doses higher than 3600 mg. Therefore, the study design has been updated to include the addition of an 8400-mg treatment arm for further dose ranging. A Phase 1 study (GV29609) investigating the 8400-mg dose in healthy volunteers has completed dosing, and interim safety data is provided in the introduction.

The addition of the 8400-mg treatment necessitated an adjustment in the infusion rate to 120 minutes for MHAA4549A and placebo. In addition, to mitigate any concerns with safety monitoring, the study design was expanded to include an initial safety assessment by the Internal Monitoring Committee and the Scientific Oversight Committee of a sentinel safety cohort consisting of the first 30 patients enrolled or those patients enrolled during the first influenza season, whichever occurs first.

Version 5 also contains revisions to support the changes discussed above as well as updates to the background sections, as follows:

- The time to normalization end point was adjusted operationally based on investigator feedback to allow greater flexibility to be in line with local standard course of clinical care
- The sample size was adjusted to approximately 330 patients.
- The MHAA4549A dosing rationale was updated to support the 8400-mg dose.
- The background clinical safety and efficacy summaries were updated with the most current data concerning MHAA4549A. Preliminary safety data from the Phase 1 study (GV29609) was included in the clinical safety section to support the use of the 8400-mg treatment arm in this study (GV29216).
- Sections that previously required a protocol clarification letter were updated: use of unblinded personnel to prepare the IV infusions of study drug and the use of masking bags, SOFA score calculation, and anaphylaxis management instructions.
- The contraception language in the inclusion criteria was updated.
- PaO_2 conversion table included as an appendix to allow greater flexibility with standard clinical practice.

SUMMARY OF CHANGES:
VERSION 5 AMENDMENT

This Version 5 amendment consolidates elements of two previous country-specific amendments and revises the study design to add a third treatment arm (i.e., 8400-mg treatment arm). The Summaries of Changes for previous amendments (i.e., Version 3 and Version 4) relevant to Version 5 are listed in this section for the convenience of sites that did not receive these versions of the protocol. However, only Version 5 revisions are presented as italicized text in the body of the protocol.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol.

SUMMARY OF CHANGES: Version 3 (VHP Only)

SECTION 4.1.1: Inclusion Criteria

- Patients of reproductive potential must agree to use reliable means of contraception as described below as a minimum (adherence to more stringent local requirements may be required):
  - For female patients: Use of two acceptable methods of contraception throughout the trial, including the active treatment phase AND for *120 days* ~~24 weeks~~ after the last dose of MHAA4549A. Acceptable methods of contraception include: intrauterine device, systemic hormonal contraception (oral or depot), vaginal ring, tubal ligation of the female partner, vasectomy of the male partner, use of latex condoms plus spermicide by the male partner, or cervical cap plus spermicide (where the spermicide could be foam, vaginal suppository, gel, cream, etc.). *Male partners who have had a vasectomy should have the appropriate post-vasectomy documentation available of the absence of sperm in the ejaculate. The vasectomized male partner should be the sole partner for that patient.*
  - For male patients: Use ~~of~~ condoms *and refrain from sperm donation until* ~~for~~ 30 days after dosing ~~when circulating drug levels remain high~~.

SECTION 4.1.2: Exclusion Criteria

- *Hypersensitivity to monoclonal antibodies or to the active substance or any excipients of MHAA4549A study drug*
- *Hypersensitivity to the active substance or to any excipients of oseltamivir*
- ~~Hypersensitivity to mABs or any constituents of study drug~~

SUMMARY OF CHANGES: Version 4 (Russia Only)

GENERAL REVISIONS

The abbreviation "mAb" was removed and "monoclonal antibody" spelled out throughout. The list of abbreviations was updated.

SECTION 1.2.2: Clinical Safety Background

In GV28985, *the immunogenicity incidence rate among the 60 subjects who received MHAA4549A was 0%. One subject* tested positive for anti-therapeutic antibodies (ATAs) ~~This subject tested positive for ATA~~ at baseline and post-baseline. This *subject* was in the placebo group, which included 32 other subjects, resulting in an immunogenicity prevalence rate (ATA-positive rate at baseline) of 3.1% and an immunogenicity incidence rate (ATA titers post-baseline) of 3.1%, as well, within the placebo group. Overall, study GV28985 had an immunogenicity prevalence rate of 1%. ~~The immunogenicity incidence rate amongst the 60 subjects who received MHAA4549A was 0%.~~

SECTION 2.3: SECONDARY EFFICACY OBJECTIVES

- To determine changes in the extent and duration of viral shedding in ~~upper respiratory samples~~ *nasopharyngeal samples as a measure of the pharmacodynamic response*

SECTION 2.4: PHARMACOKINETIC OBJECTIVES

- To characterize the PK profile of MHAA4549A in [redacted] and/or [redacted]

SECTION 2.5: EXPLORATORY OBJECTIVES

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

SECTION 3.1.1: Overview of Study Design

[redacted]

SECTION 3.2.5: Rationale for Biomarker Assessments

[redacted]

SECTION 3.3.3: Secondary Efficacy Outcome Measures

- Time to clinical ~~normalization~~ *resolution* of vital signs (3/5 criteria must be met):

SECTION 3.3.4: Pharmacokinetic Outcome Measures

- [redacted]

SECTION 3.3.5: Exploratory Outcome Measures

[redacted]

SECTION 4.1.1: Inclusion Criteria

- For female patients: Use of two acceptable methods of contraception throughout the trial, including the active treatment phase AND for *120 days* after the last dose of MHAA4549A. Acceptable methods of contraception include: intrauterine device, systemic hormonal contraception (oral or depot), vaginal ring, tubal ligation of the female partner, vasectomy of the male partner, use of latex condoms plus spermicide by the male partner, or cervical cap plus spermicide (where the spermicide could be foam, vaginal suppository, gel, cream, etc.). *Male partners who have had a vasectomy should provide the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate. The vasectomized male partner should be the sole partner for that subject.*
- For male patients: Use of condoms *and refrain from sperm donation until* 30 days after dosing ~~when circulating drug levels remain high~~.

SECTION 4.1.2: Exclusion Criteria

- Hypersensitivity to monoclonal antibodies~~mABs~~ or to the active substance or any ~~constituents~~ excipients of MHAA4549A study drug
- Hypersensitivity to the active substance or to any excipients of oseltamivir
- Creatinine clearance ≤ 10 mL/min

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Unblinded personnel (i.e., unblinded site pharmacist or other designated, qualified, unblinded study personnel) at each study site will *prepare the IV infusions of study drug*, as described in Section 4.3.3. *The Sponsor will provide masking bags, and blinded study personnel will administer the study drug.* The other parties who are involved in the conduct of the study (i.e., patients and blinded site personnel) will remain blinded to patient-specific treatment assignments until the final database lock after the completion of the study.

SECTION 4.3.1.1: MHAA4549A and Placebo

Placebo is identical to active MHAA4549A in formulation ~~and appearance~~ but does not contain active drug substance.

SECTION 4.3.2.1: MHAA4549A and Placebo

The randomization of patients will be managed by a central IxRS. All patients will be randomly assigned to receive either a single dose of MHAA4549A 3600 mg IV or placebo IV at a 1:1 ratio. ~~Oseltamivir will be dispensed via~~ *Oseltamivir 75 mg and 150 mg will be supplied via IxRS.*

A single dose of MHAA4549A or placebo will be delivered by IV infusion following dilution in 0.9% normal saline over approximately ~~60~~*120* minutes. Compatibility testing has shown that MHAA4549A is stable when diluted in 0.9% normal saline in a polyvinylchloride *bag*, polyolefin bag, or ethylene vinyl acetate bag (EVA), at ~~or above a combined total concentration~~*concentrations* of 0.24 mg/mL up to 27.0 mg/mL.

SECTION 4.3.2.2: Oseltamivir-Neuraminidase Inhibitor (NAI)

Oseltamivir 75 mg and 150 mg will be supplied via IxRS. For renally impaired patients requiring the 30-mg dose strength, the Sponsor will supply oseltamivir or reimburse sites for oseltamivir per local regulations.

SECTION 4.6.5:

[redacted]

SECTION 4.6.6:

[redacted]

SECTION 4.6.10: <u>Laboratory, Biomarker, and Other Biological Samples</u>

[redacted]

[redacted]

SECTION 5.2.1: Adverse Events

Adverse events will be monitored throughout the entire study (enrollment through Day 60 or Early Discontinuation). ~~If clinically significant signs or laboratory values are observed in a study participant, the investigator should repeat an assessment at the earliest opportunity. Only those events or laboratory values that exceed the level of clinical significance upon the repeat assessment will be considered an adverse event.~~

SECTION 5.3.1: Adverse Event Reporting Period

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until the Day 60 visit or Early Discontinuation visit. After this period, the investigator *should report any serious adverse events that are believed to be related to prior study drug treatment* ~~is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any death or other serious adverse event that occurs after discharge, regardless of causality. The Sponsor should also be notified if the investigator becomes aware of a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug~~ (see Section 5.5).

SECTION 5.3.5.4: Abnormal Laboratory Values

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event. *Investigators should promptly repeat any abnormal assessment or clinically significant laboratory result. Only those findings that remain clinically significant upon a repeat assessment will be considered adverse events.*

SECTION 5.4.1: Emergency Medical Contacts

Medical Monitor: [redacted]

Telephone Nos.: US ~~Mobile~~ *Office* [redacted]

US ~~Office~~ *Mobile* [redacted]

SECTION 5.4.2.1: Events That Occur Prior to Study Drug Initiation

A paper Serious Adverse Event */ Adverse Event of Special Interest* Reporting Form ~~and fax cover sheet~~ should be completed and faxed *or scanned and emailed* to the Sponsor's Safety Risk Management department or its designee immediately (i.e., no more than 24

hours after learning of the event), using the ~~fax numbers~~*contact information* provided below per region:

Region	*Fax Number*	*Email Address*
Asia Pacific	[redacted]	[redacted]
Europe	[redacted]	
Latin America	[redacted]	
North America	[redacted]	

~~Asia Pacific:~~ [redacted]

~~Europe:~~ [redacted]

~~Latin America:~~ [redacted]

~~North America:~~ [redacted]

SECTION 5.4.2.2: Events that Occur after Study Drug Initiation

In the event that the EDC system is unavailable, a paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed *or scanned and emailed* to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the ~~fax numbers~~*contact information* provided to investigators (see ~~fax numbers provided in~~ Section 5.4.2.1). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

SECTION 5.4.3.1: Pregnancies in Female Patients

In the event that the EDC system is unavailable, a paper Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed*,* ~~and~~ faxed, *or scanned and emailed* to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the ~~fax numbers~~*contact information* provided to investigators (see ~~fax numbers provided in~~ Section 5.4.2.1). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

SECTION 5.4.4: Investigator Follow Up

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. ~~If, after follow up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF and the Investigator document a discharge plan.~~

SECTION 5.5: POSTSTUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period, defined as 60 days after the last dose of study drug (see Section 5.3.1), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to Roche or its designee, either by faxing or by scanning and emailing the Serious Adverse Event / Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators (refer to site binder).~~At the time of study completion or study discontinuation, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient or their personal physician believes could be related to prior study drug treatment or study procedures.~~

~~The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 60 days after the dose of study drug). However, the Sponsor should be notified if the investigator becomes aware of any death, other serious adverse event, or non serious adverse event of special interest occurring after the end of the adverse event reporting period, regardless of causality. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient or a female partner of a male patient exposed to study drug.~~

SECTION 6.4.2: Secondary Efficacy Endpoints

- Median duration of viral shedding in ~~upper respiratory samples~~*nasopharyngeal samples*

SECTION 9.5: *PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS*

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information from the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website: http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been

filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

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

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

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

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

APPENDIX 1a: Schedule of Assessments: Hospitalization Days

In the list of procedures, "Upper respiratory tract sample (NP sample)" was changed to "Nasopharyngeal sample," and [redacted] as changed to "[redacted]

A footnote for "Oseltamivir administration" was changed as follows:

[n] Oseltamivir must be given for a minimum of 5 days. Treatment longer than 5 days is permitted based on the discretion of the investigator [indicated by (x)]. *See Table 2 for oseltamivir dosing guidelines and recommended renal dose adjustments.*

APPENDIX 7: SOFA Score Calculation

Variables	*SOFA Score*				
	0	***1***	***2***	***3***	***4***
Respiratory (PaO_2/FiO_2, mmHg)	*>400*	*≤400*	*≤300*	*≤200[a]*	*≤100[a]*
Coagulation (Platelets x $10^3/\mu L$) [b]	*>150*	*≤150*	*≤100*	*≤50*	*≤20*
Liver (Bilirubin, mg/dL) [b]	*<1.2*	*1.2 –1.9*	*2.0 –5.9*	*6.0 –11.9*	*>12.0*
Cardiovascular (Hypotension)	*No hypotension*	*MAP <70 mmHg*	*Dop ≤5 or dob (any dose) [c]*	*Dop >5, epi ≤0.1, or norepi ≤0.1[c]*	*Dop >15, epi >0.1, or norepi >0.1[c]*
Central Nervous System (Glasgow Coma Score Scale)	*15*	*13 –14*	*10 –12*	*6 –9*	*<6*
Renal (Creatinine, mg/dL or urine output, mL/day) [d]	*<1.2*	*1.2 –1.9*	*2.0 –3.4*	*3.5 –4.9 or <500*	*>5.0 or <200*

Norepi =norepinephrine; Dob =dobutamine; Dop =dopamine; Epi =epinephrine; FiO_2 =fraction of inspired oxygen; MAP =mean arterial pressure; PaO_2 =partial pressure of arterial oxygen.

[a] *Values are with respiratory support.*

[b] *To convert bilirubin from mg/dL to μmol/L, multiply by 17.1.*

[c] *Adrenergic agents administered for at least 1 hour (doses given are in μg/kg per minute).*

[d] *To convert creatinine from mg/dL to μmol/L, multiply by 88.4.*

References for Appendix 7:

Ferreira FL, Bota DP, Bross A et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001; 286(14):1754–1758

Vincent JL, de Mendonca A, Cantraine F et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;26(11): 1793–1800.

~~Administration of MHAA4549A will be performed in a setting with emergency medical equipment and personnel who are trained to monitor for and respond to medical emergencies. A qualified physician will be on site during study drug administration for all patients.~~

~~The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:~~

- ~~Airway management equipment~~
- ~~O_2~~
- ~~Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice~~

- ~~Antihistamines~~
- ~~Corticosteroids~~
- ~~IV infusion solutions, tubing, catheters, and tape~~

~~The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:~~

- ~~Stop the study drug infusion.~~
- ~~Maintain an adequate airway.~~
- ~~Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.~~
- ~~Continue to observe the patient and document observations.~~

APPENDIX 10: Anaphylaxis Precautions and Management

This appendix was added.

SUMMARY OF CHANGES: Version 5 (Global)

SECTION 1.2.1: Nonclinical Background

This antibody binds to a highly conserved epitope on the influenza A hemagglutinin *(HA)* stalk region, which allows broad neutralization of the influenza A virus by blocking the ~~hemagglutinin~~*HA*-mediated, membrane-fusion event in the late endosome.

SECTION 1.2.2: Clinical Safety Background

SECTION 1.2.2.1: *Phase 1 Entry-into-Human Study GV28916*

~~In addition, the MHAA4549A pharmacokinetics were generally dose proportional, and appeared to have a pharmacokinetic (PK) profile consistent with that of a human IgG1 antibody that lacks known endogenous host targets.~~

SECTION 1.2.2.2: *Phase 2a Influenza Nasal Challenge Study GV28985*

The second study was a Phase 2a challenge study (GV28985) in 101 healthy volunteers infected with a H3N2 (A/Wisconsin/67/2005) strain of influenza virus. ~~Fixed dosing was selected for this study and is further described in Section.~~ Sixty subjects received doses of 400 mg, 1200 mg, or 3600 mg MHAA4549A*,* and ~~41~~*32* subjects received placebo following nasal inoculation of influenza A virus one day earlier. ~~The interim efficacy analysis in~~ *includes the Intent to Treat (ITT) infected population who* ~~received placebo (N=21), 400 mg MHAA4549A (N=11), 1200 mg MHAA4549A (N=13), 3600 mg MHAA4549A (N=14), and~~ oseltamivir ~~(N=2).~~ *starting on Day 1. One subject was randomized and inoculated, but not dosed.* ~~All subjects have completed dosing, and interim PK and efficacy data are available in the Investigator's Brochure and upon request.~~

Most AEs appeared to reflect symptoms of an active influenza infection and occurred primarily within the first 21 days after patients received their virus inoculation and dose of MHAA4549A or placebo (123 of 213: 58%). Following the resolution of the influenza symptoms, even though levels of MHAA4549A remained relatively high, the number of AEs dropped and remained low throughout the remainder of the study: 59 of 213 (28%) of all AEs occurred between Study Days 22 and 60, and 31 of 213 (15%) of all AEs occurred between Study Days 61 and 120. Differences between treatment groups in the number and severity of AEs during the first 22 days appeared to reflect variability in the extent and severity of the influenza infection. Throughout the entire study, the pattern of AEs did not differ substantially between subjects who received placebo and subjects who received any dose of MHAA4549A.

The percentage of AEs that investigators judged to be related to study drug treatment was 12/33 (36%) for the 400-mg group, 10/40 (25%) for the 1200-mg group, 11/52 (21%) for the 3600-mg group, and 25/88 (28%) for subjects receiving placebo. Of those AEs considered related, however, 15 of 25 (60%) in the placebo cohort and 26 of 33

(79%) in all MHAA4549A cohorts consisted of elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or amylase. These laboratory abnormalities have been shown to be associated with the influenza infection (Polakos et al 2006; Yingying 2011) and were not observed in either the previous or subsequent Phase 1 studies (GV28916, GV29609) where MHAA4549A was administered to subjects without influenza infection.

There were 3 SAEs in Study GV28985, none of which were assessed as related to MHAA4549A. One was in a subject hospitalized with a depressive psychosis. Due to his previous history of depression and the known association of psychosis with influenza infections, the Investigator considered this event unrelated to study drug. The other 2 SAEs were in one subject who fell and required a surgical repair of a fractured tibial plateau. This same subject was subsequently hospitalized for her second SAE, which was a post-surgical wound infection. Neither of these events was considered related to study treatment.

~~During this study, elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and amylase levels were observed within the first 2 weeks after inoculation with A/Wisconsin/67/2005 and dosing with MHAA4549A. Previous experience with this challenge model has shown ALT/AST/amylase elevations to be associated with the influenza infection itself (Polakos 2006). Consistent with previous trials, In GV28985, there was no relationship of elevations in AST, ALT, or amylase with either dose or exposure (e.g., placebo: 22.0%, 400 mg: 35.0%, 1200 mg: 25.0%, 3600 mg: 20.0%).~~

~~In GV28985, most AEs were Grade 1 or Grade 2 (mild or moderate) and appeared to reflect the symptoms of the influenza infection.~~

- ~~In the 400 mg group, 15 (75.0%), 1 (5.0%), and 2 (10.0%) subjects reported Grade 1, 2, and 3 AEs respectively.~~
- ~~In the 1200 mg group, 9 (45.0%), 6 (30.0%), and 1 (5.0%) subjects reported Grade 1, 2, and 3 AEs, respectively.~~
- ~~In the 3600 mg group, 10 (50.0%), 5 (25.0%), 1 (5.0%) subjects reported Grade 1, 2, and 3 AEs, respectively.~~

~~One (5.0%) subject reported a Grade 4 AE in the 3600 mg group, which was a lower limb fracture, not related to MHAA4549A.subjects in the placebo group reported 18 (56.3%) Grade 1 AEs, 8 (25.0%) Grade 2 AEs, and 2 (6.3%) Grade 3 AEs. In addition, there were no drug related SAEs, deaths, or discontinuations due to AEs. There were a total of 3 SAEs unrelated to MHAA4549A in two subjects. One subject reported depressive psychosis associated with influenza. There were a total of 3 SAEs unrelated to MHAA4549A in two subjects. One subject reported depressive psychosis associated with influenza. The second subject reported a broken knee with a subsequent SAE of infection following a surgical procedure. The immunogenicity incidence rate amongst the 60 subjects who received MHAA4549A was 0%.~~

SECTION 1.2.2.3: Phase 1 High-Dose Safety Study *GV29609*

A Phase 1 (GV29609) study was initiated to evaluate the safety and tolerability of a single intravenous (IV) doses of 8400 mg and 10800 mg MHAA4549A as compared to placebo when administered to 14 healthy volunteers. The starting dose of 8400 mg was based on simulations from a semi-quantitative pharmacokinetic model (Figure 2) developed from the Phase 2a challenge study (GV28985), which suggests that the 8400 mg may be the minimum dose that is expected to show a separation of nasal exposure from a dose of 3600 mg. The simulation assumes that pharmacokinetics can be extrapolated at doses above 3600 mg and that the PK profile in severely ill patients is similar to the PK profile of healthy volunteers in the Phase 2a challenge study. The highest proposed dose of 10800 mg was chosen in GV29609 to provide safety coverage for those exposures that might be reached in a 40-kg individual dosed with a flat dose of 8400 mg.

GV29609 is currently on-going, but preliminary analysis of unblinded safety data up to day 57 shows that the 8400 mg and 10800 mg treatment groups are safe and well tolerated.

- *In subjects who revcieved the 8400 mg MHAA4549A (N=4):*
  - *3 of 4 subjects reported 12 AEs.*
  - *6 AEs were reported as related to 8400 mg MHAA4549A: 3 headaches, 1 pruritus, 1 peripheral swelling, and 1 nasal congestion*
- *In subjects who received 10800 mg MHAA4549A (N=4):*
  - *4 of 4 subjects reported 7 AEs.*
  - *3 AEs reported as related to 10800 mg MHAA4549A treatment group: 1 nausea, 1 headache, and 1 asthenia*
- *In subjects who received placebo (N=6):*
  - *2 of 6 subjects reported 5 AEs*
  - *1 AE was reported as related to study drug: 1 headache*

All AEs were reported as mild except for an unrelated moderate AE of an increase in creatinine kinase in one subject who received 10800 mg MHAA4549A. There were no SAEs and no subjects have discontinued the study for any reason.

As in both previous studies, headache was the most common AE. Headache was reported by 3 subjects (37.5%) who received 8400 mg group MHAA4549A: 1 subject (12.5%) who received 10800 mg MHAA4549A and 2 subjects (33.0%) who received placebo.

Based on this data, MHAA4549A is considered generally safe and well tolerated ~~to date at all doses tested, including the 3600 mg dose~~.

SECTION 1.2.3: Clinical Efficacy Background

The Phase 1 study (GV28916) demonstrated that MHAA4549A pharmacokinetics were generally dose proportional. The PK profile appeared consistent with that of a human IgG1 antibody that lacks known endogenous host targets.

In the Phase 2a challenge study (GV28985), 101 healthy volunteers were inoculated with influenza virus 24-36 hours prior to dosing with MHAA4549A. Following inoculation, 60 subjects received doses of 400 mg, 1200 mg, or 3600 mg MHAA4549A, 32 subjects received placebo, 8 subjects received a 5-day course of oseltamivir, and 1 subject was not dosed. The interim efficacy analysis presented in Table 1 included the Intent-to-Treat (ITT) infected population followed until at least Day 29 who received 400 mg MHAA4549A (N =11), 1200 mg MHAA4549A (N =13), 3600 mg MHAA4549A (N =14), placebo (N =21), and oseltamivir (N =2). Analysis of efficacy from the 3600-mg dose level demonstrated a statistically significant decrease in viral shedding from *the* upper respiratory tract as measured by the area under the curve (97*.5*% reduction by quantitative polymerase chain reaction [qPCR]) and peak viral load (77% reduction by qPCR*). All subjects have completed dosing, and interim PK and efficacy data are available in the Investigator's Brochure and upon request.* ~~) as shown in .~~

In ~~this~~*the GV28985* study, *all subjects received* oseltamivir ~~was~~ started on Day 7 for a 5-day course, and there were no observed AEs or imbalances in safety events that were considered attributable to interactions between oseltamivir and MHAA4549A. The PK profile of MHAA4549A and oseltamivir in GV28985 are being analyzed to exclude potential drug-drug interactions*,* and *this analysis* will be available before the start of this study *(*GV29216~~.~~*).*

Composite clinical symptom scores from Study GV28985 for the ~~Intent to Treat (ITT) infected population who received placebo (N=21), 400 mg MHAA4549A (N=11), 1200 mg MHAA4549A (N=13), 3600 mg MHAA4549A (N=14), and oseltamivir (N=2)~~*ITT infected (ITTI) population* are shown in Table 1.

The responses observed in the Phase 2a study (GV28985) suggest that a higher dose may provide better efficacy in a population with established infection. An 8400-mg dose will be included in this Phase 2b study for further dose ranging. The rationale for selected dosages is further explained in Section 3.2.4.

SECTION 1.3.1: Study Rationale

~~The~~ *Two* Phase 1 *(GV28916, GV29609)* studies ~~and Phase 2a studies~~ have demonstrated that MHAA4549A is safe and well tolerated to date in healthy volunteers

at doses up to 8400 mg. ~~including those who were inoculated with influenza A virus.~~ Data from *a* Phase 2a study *(GV28985) demonstrates safety in healthy subjects inoculated with influenza virus and* ~~also~~ provides evidence that the 3600 mg dose of MHAA4549A is effective in reducing viral titers in healthy volunteers inoculated with influenza A virus. ~~These findings,~~ *W*~~w~~hen combined with previous nonclinical studies *that showed* MHAA4549A to have in vitro and in vivo efficacy, a well-tolerated safety profile, and anti-viral activity, *these findings* support further clinical development of MHAA4549A.

Initially, this GV29216 Phase 2b study enrolled patients in a two-arm treatment study comparing 3600 mg MHAA4549A with oseltamivir versus placebo with oseltamivir.

This *current* Phase 2b study has *added an additional arm to evaluate* ~~been designed to estimate~~ the improvement in outcome of a combination therapy of *3600 mg* MHAA4549A ~~3600 mg~~ *with oseltamivir or of 8400 mg MHAA4549A* with oseltamivir versus placebo with oseltamivir. All patients will *receive* oseltamivir, which is part of the recommended standard of care.

This study (GV29216) will assess severely ill patients who may be infected with various influenza A strains, have a higher viral burden and longer duration of viral shedding than the healthy volunteers in GV28985, and who may, therefore, require doses higher than 3600 mg. A Phase 1 (GV29609) study is currently on-going to assess the safety, tolerability, and pharmacokinetics of 8400-mg and 10800-mg doses of MHAA4549A. The starting dose of 8400 mg was selected based on simulations from a semi-quantitative PK model developed from the Phase 2a challenge study (GV28985), suggesting that 8400 mg MHAA4549A may be the minimum dose that is expected to show a separation of nasal exposure from a dose of 3600 mg. This simulation assumes that pharmacokinetics can be extrapolated at doses above 3600 mg and that the PK profile in severely ill patients is similar to the PK profile of healthy volunteers in Phase 2a challenged with influenza A virus. The 10800-mg dose was chosen to provide assurance of safety for the increased MHAA4549A levels that may be reached in smaller individuals who received 8400 mg.

A preliminary, unblended analysis of the safety data from GV29609 up to Day 57 has shown that the 8400-mg and 10800-mg treatment groups are safe and well tolerated. In subjects who received 8400 mg MHAA4549A, 3 of 4 subjects reported 12 AEs. In subjects who received 10800 mg MHAA4549A, 4 of 4 subjects reported 7 AEs. In subjects who received placebo, 2 of 6 subjects reported 5 AEs. All AEs were reported as mild, except for one unrelated moderate AE of an increase in creatinine kinase in one subject who received 10800 mg MHAA4549A. There were no SAEs and no subjects have discontinued the study for any reason. As in previous studies, headache was the most common AE, and was reported by 3 subjects (37.5%) who received 8400 mg MHAA4549A, 1 subject (12.5%) who received 10800 mg MHAA4549A, and

2 subjects (33.0%) who received placebo. As a result, the Sponsor feels that the 8400-mg dose is safe to include in Study GV29216.

The 8400-mg dose is also expected to be safe based upon previous nonclinical and clinical safety assessments. Nonclinical safety data do not show any expected or unexpected toxicity.

SECTION 1.3.2.1: Treatment in Combination with Oseltamivir

In the Phase 2a challenge study (GV28985), study subjects received MHAA4549A followed by oseltamivir with no AEs attributable to the combination therapy noted to date. In addition, in this *Phase 2b* study the PK profile of oseltamivir in concomitantly treated subjects will be assessed.

SECTION 1.3.2.3: Rationale for Selection of Phase 2b Study Population

- Clinical safety data for MHAA4549A demonstrate a well-tolerated safety profile:
  - *AEs in the Phase 1 study (GV28916) were mild and did not show a dose relationship; there were no ATAs detected in patients treated with MHAA4549A after 120 day follow-up visit.*
  - *All AEs in GV29609 from a preliminary analysis of unblinded safety data up to day 57 were reported as mild except for an unrelated moderate AE of an increase in creatinine kinase in one subject who received 10800 mg MHAA4549A. There were no SAEs and no subjects have discontinued the study for any reason.*

~~Interim efficacy data in the Phase 2a challenge study (GV28985) demonstrated a significant decrease in viral shedding in the upper respiratory tract at the 3600 mg dose. There was a 97.5% (p = 0.0051) decrease in the area under viral load time curve (AUEC) and a 77% (p = 0.0024) decrease in peak viral load by qPCR measurement in comparison to the placebo group, thus confirming proof of antiviral activity at the 3600 mg dose level. Symptom data in the Phase 2a study showed a decrease in the AUC of symptoms scores for the 3600 mg dose that is consistent with the virological results as illustrated in Table 1.~~

SECTION 1.3.2.4: Patient Monitoring and Supervision

In addition to the regularly scheduled safety reviews of the patient data by the IMC and SOC, an additional sentinel safety cohort of the first 30 patients or patients after the first influenza season, whichever occurs first, will be assessed by the IMC and SOC.

No ATAs were detected in the Phase 1 study, while one subject *who received placebo* in the Phase 2a study tested positive for ATAs at baseline and post-baseline timepoints as described in Section 1.2.2

SECTION 2.3: SECONDARY EFFICACY OBJECTIVES

The secondary efficacy objectives for this study are as follows:

- [redacted]
- To measure antibiotic usage for respiratory ~~indications~~*infections*

SECTION 2.5: EXPLORATORY OBJECTIVES

[redacted]

SECTION 3.1.1: Overview of Study Design

This is a Phase 2b~~,~~ *(GV29216),* randomized, double-blind, placebo-controlled study designed to assess the safety and clinical activity of a single ~~intravenous (~~IV~~)~~ dose of *3600 mg MHAA4549A or a single IV dose of 8400 mg* MHAA4549A in hospitalized patients with severe influenza A in combination with oseltamivir versus a comparator arm of placebo with oseltamivir. This study is planned to take place in approximately 170 study centers globally.

Initially, GV29216 ~~randomized 1:1~~ *targeted enrollment* into two treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir or a single IV dose of placebo with oseltamivir.

In this version of the protocol, patients will be randomized 1:1*:1 into three treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir, a single IV dose of 8400 mg of MHAA4549A with oseltamivir, or a single IV dose of placebo with oseltamivir.* All patients will receive oseltamivir, a NAI, as standard therapy for a minimum of 5 days after study drug administration. Oseltamivir at doses of 75 mg *twice daily (*BID*)* or 150 mg BID is permitted in order to be consistent with local standard of care practice. Treatment for longer than 5 days is permitted based on local investigator discretion. The patient must start ~~Sponsor-supplied~~ oseltamivir ~~within~~*no later than* 8 hours *after completion* of study drug administration. The study has a planned enrollment of approximately ~~334~~*330* patients globally.

A Sponsor-~~supplied rapid~~*approved* influenza test ~~and~~ *that includes influenza antigen test* or ~~a local~~*influenza* polymerase chain reaction (PCR) test must be used as an aid in the diagnosis of influenza A infection.

[redacted]

At the time of randomization, patients who are eligible for enrollment, as described above, will be randomized to receive *3600 mg* MHAA4549A ~~at a dose of 3600~~ *or 8400* mg *MHAA4549A* or placebo. Patients will be stratified by ~~site~~*country*, PPV versus supplemental O_2 at randomization, and suspected or confirmed bacterial pneumonia versus no bacterial pneumonia based on the status at randomization.

Eligible patients who are enrolled into the study will receive ~~either~~ a single IV infusion of *3600 mg MHAA4549A or a single IV infusion of 8400 mg* MHAA4549A or a single IV infusion of placebo on Day 1. All patients must ~~have the~~*begin* study drug ~~infused~~*infusion* within 48 hours of hospital admission or sooner if possible. All patients will receive oseltamivir for a minimum of 5 days (10 doses), starting on Day 1, beginning no later than 8 hours after *completion of* study drug administration.

Safety evaluations will *also* be provided by an IMC and SOC, as defined in the IMC and SOC agreement (see Section 3.1.2). *If after review of available study data, the IMC and SOC conclude that there is a significant toxicity or worsening disease associated with MHAA4549A, they may recommend stopping further enrollment in the study.*

An additional safety cohort of the first 30 patients, or patients from the first influenza season, whichever occurs first, will be assessed by the IMC and SOC. A review of chemistry laboratory test results, AEs, SAEs, vital signs, and deaths will be assessed.

SECTION 3.1.2: ~~Independent~~ *Internal* Monitoring Committee and Scientific Oversight Committee

Section title was changed, but no changes were made within the section text.

SECTION 3.2.1: Rationale for Study Design

Study GV29216 will be a Phase 2b study involving approximately ~~334~~*330* patients.

SECTION 3.2.2: Rationale for Patient Population and Primary Endpoint

A Sponsor-~~supplied rapid~~*approved* influenza test ~~and/~~*, which includes influenza antigen test* or ~~a local~~ PCR *test,* must be used as an aid in the diagnosis of influenza A infection.

The proposed primary efficacy outcome measure in this study is "Time to normalization of respiratory function," defined as oxygen saturation ~~>~~≥ *95% without oxygen supplementation*. Support for use of *a* respiratory endpoint in this population comes from recently published data demonstrating that a composite endpoint that captured respiratory rate, fever, heart rate, and blood pressure resolution was primarily driven by the respiratory component of the endpoint (Marty et al. 2014). *Given that influenza infections generally do not cause systemic infections and influenza disease is restricted to the respiratory tract, the Sponsor believes that the primary endpoint represents a clinically meaningful outcome*

in this patient population (as shown by analysis of PREMIER database) and measures an important physiologically relevant pharmacodynamic response parameter of MHAA4549A. This endpoint is a measure of patient function, measures a symptom that represents a serious consequence of influenza, and is consistent with clinically relevant endpoints discussed in the US Food and Drug Administration (FDA) Guidance, "Influenza: Developing Drugs for Treatment and/or Prophylaxis" (FDA 2011).

SECTION 3.2.3: Rationale for Control Group and Treatment Window

In the treatment groups, MHAA4549A will be dosed in addition to ~~an~~ oseltamivir. ~~standard of care regimen. The oseltamivir dose will be consistent with the local investigator practice at each site where the study will be conducted.~~

If oseltamivir resistance is highly suspected or identified during treatment ~~*then,*~~ *or oseltamivir route of administration challenges are encountered, then* following discussion with the Sponsor medical representative, an alternative NAI to oseltamivir may be used.

The treatment of all patients with oseltamivir ensures that all patients will receive *the* standard of care. *G*~~g~~iven the high morbidity and mortality of hospitalized patients with influenza A along with guidelines from Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA)*, it is recommended that* ~~stating~~ NAIs are the standard of care for hospitalized patients with influenza A (Harper et al. 2009 and CDC Website).

MHAA4549A shall only be dosed within 5 days of ~~symptom~~ onset~~, within 3 days~~ of ~~initial treatment with a NAI, and~~ *symptoms (including fever, chills, malaise, dry cough, loss of appetite, myalgias, coryza, or nausea),* no later than 48 hours after admission to the hospital~~.~~*, and if a subject has taken less than a total of 6 doses (3 doses for peramivir) of approved anti-influenza therapy from onset of symptoms.* This proposed window is supported by data demonstrating that hospitalized influenza patients benefit from NAI treatment even at 5 days from ~~symptom~~ onset *of symptoms* (Louie et al. 2012). *The patient must start the standard-of-care oseltamivir no later than 8 hours after completion of MHAA4549A administration.*

SECTION 3.2.4: Rationale for MHAA4549A Dosage

A single IV dose of 3600 mg *MHAA4549A or a single IV dose* of *8400 mg* MHAA4549A was selected to assess the efficacy of MHAA4549A and to provide data for further clinical development.

The dose ~~level used in~~*levels selected for* this study ~~was~~*were* determined following analysis of data from the Phase 2a study~~,~~ *(*GV28985~~,~~*)*, which demonstrated the following:

- *When compared to placebo, a decrease in viral shedding was observed at the 400 mg dose but not at the 1200 mg dose, which may be due to variability in the challenge model and differences in infection rate, infection peak, virus level in the nasopharynx, nasal pharmacokinetics, immune status, and other inter-subject differences.*
- There ~~are~~*were* no safety concerns at ~~the 3600 mg~~*any* dose level ~~to date.~~*associated with MHAA4549A.*
- Hospitalized patients generally have a longer duration of viral shedding and significantly more viral burden in the lower lung compartments; therefore, high concentrations of monoclonal antibody are likely needed to achieve sufficient occupancy of the virus binding sites in the upper and lower respiratory compartments. Furthermore, higher concentrations of monoclonal antibody may mitigate the risk of resistance for MHAA4549A*, supporting addition of the 8400 mg MHAA4549A treatment arm.*

- *Exploratory exposure-response analysis of GV28985 indicated that higher exposure appears to be associated with improved efficacy. Volunteers with nasal maximum concentration greater than the median value had shorter time to resolution of viral shedding compared with volunteers in the placebo group (median: 75.8 hours vs. 113.7 hours). However, volunteers with a nasal maximum concentration less than the median value had similar time to resolution of viral shedding compared with volunteers in the placebo group (median 113.7 hours vs 112.1 hours).*

The Phase 2a challenge study (GV28985) confirmed proof of activity in decreasing area under viral load-time curve, consistent with symptom data at the 3600-mg dose level. GV29216 will assess severely ill patients who may be infected with various influenza strains, have a higher viral burden and longer duration of viral shedding than the healthy volunteers in Study GV28985, and who may, therefore, require doses higher than 3600-mg. As a result, an ongoing Phase 1 (GV29609) study was initiated to evaluate the safety and tolerability of two single IV doses of 8400 mg and 10800 mg MHAA4549A as compared to placebo when administered to 14 healthy volunteers. The starting dose of 8400 mg was selected based on simulations from a semi-quantitative PK model (Figure 2) developed from the Phase 2a challenge study, which suggests that 8400 mg may be the minimum dose that is expected to show a separation of nasal exposure from a dose of 3600 mg. This simulation assumes that pharmacokinetics can be extrapolated at doses above 3600 mg and that the PK profile in severely ill patients is similar to the PK profile of healthy volunteers in the Phase 2a challenge study. The highest proposed dose of 10800 mg was chosen in GV29609 to provide safety coverage for those exposures that might be reached in a 40-kg individual dosed with a flat dose of 8400 mg. Preliminary analysis of unblinded safety data up to day 57 shows that the 8400 mg and 10800 mg treatment groups are safe and well tolerated. In subjects who

received 8400 mg MHAA4549A, 3 of 4 subjects reported 12 AEs. In subjects who received 10800 mg MHAA4549A, 4 of 4 subjects reported 7 AEs. In subjects who received placebo, 2 of 6 subjects reported 5 AEs. All AEs were reported as mild except for an unrelated moderate AE of an increase in creatinine kinase in one subject who received 10800 mg MHAA4549A. There were no SAEs and no subjects have discontinued the study for any reason. Headache was the most common adverse event. Headache was reported by 3 subjects (37.5%) who received 8400 mg MHAA4549A, 1 subject (12.5%) who received 10800 mg MHAA4549A, and 2 subjects (33.0%) who received placebo.

Nonclinical safety data do not show any expected or unexpected toxicity. Weekly administration of MHAA4549A (total of 5 doses) in Sprague-Dawley rats was well tolerated up to 150 mg/kg (the highest dose tested). Ex vivo tissue cross-reactivity study data showed no specific binding of MHAA4549A to any of the human or rat tissues examined.

Therefore, the 8400-mg dose is expected to be safe based upon previous nonclinical and clinical safety assessments and will be included in this Phase 2b study for further dose ranging.

Although ~~T~~*t*he *Phase 1 study (GV28916)* was conducted using body-weight based dosing*, the subsequent Phase 2a study GV28985 and high-dose Phase 1 study GV29609 used* ~~followed by~~ a fixed dosing strategy ~~that was used in the Phase 2a study.~~ Thus, the fixed dosing regimen ~~that was used in the Phase 2a study~~ will be used for this study, given the *comparable MHAA4549A PK profiles, the* practical advantages*,* and *the* positive safety profile of MHAA4549A to date.

Figure 2, Predictions from a Semi-Quantitative Pharmacokinetic Model of Nasal Exposure, was added.

SECTION 3.3.2: Primary Efficacy Outcome Measures

- The time to cessation of O_2 support resulting in a stable SpO_2 ~~>~~≥ 95% ~~for at least 24 hours~~ (see Appendix 2 for details)

SECTION 3.3.3: Secondary Efficacy Outcome Measures

- Clinical failure after 24 hours post-infusion of study drug; defined as:
  - Progression to increased O_2 requirement defined by an increase in oxygen supplementation from low flow oxygen (2 – 6 L/min) to high flow oxygen (> 6 L/min) or from oxygen supplementation alone to any PPV *or extracorporeal membrane oxygenation (ECMO)*
- Time to clinical resolution of vital signs (3/5 criteria must be met):
  - SpO_2 ~~>~~≥ 95% without supplemental O_2 ~~for at least 24 hours~~

- *Respiratory rate <24 breaths per minute without supplemental O_2*
- Heart rate (HR) < 100 *beats*/minute

Influenza A viral load in nasopharyngeal samples

- AUEC *(qPCR)*
- Peak viral load *(qPCR)*
- Time to resolution of infection *(qPCR)*
- [redacted]

SECTION 3.3.5: Exploratory Outcome Measures

[redacted]

SECTION 4.1: PATIENTS

This study aims to enroll approximately ~~334~~*330* men and women and is designed to assess the safety and clinical activity of a single IV administration of *3600 mg MHAA4549A or a single IV administration of 8400 mg* MHAA4549A in adult patients hospitalized with severe influenza A.

SECTION 4.1.1: Inclusion Criteria

Patients must meet the following criteria for study entry:

- Diagnosis of influenza A where ~~one or both of the following are~~*a Sponsor-approved influenza test is* used as *an* aid~~(s)~~ in diagnosis. *A Sponsor-approved influenza test includes*:
  - ~~A Sponsor supplied rapid influenza test~~
  - ~~*A local*~~ *Influenza antigen test –OR–*
  - Influenza PCR test
- *For women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use two adequate methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment period and for at least 120 days after the last dose of study drug*

Abstinence is only acceptable if it is in line with 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.*

Barrier *methods must always be supplemented with the use of a spermicide.*

Examples of contraceptive methods with a failure rate of *< 1% per year include tubal ligation, male sterilization, hormonal implants, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.*

Male partners who have had a vasectomy should have the appropriate post-vasectomy documentation available of the absence of sperm in the ejaculate. The vasectomized male partner should be the sole partner for that patient.

- *For men: agreement to remain abstinent or use a condom during the treatment period and for at least 30 days after the last dose of study drug and agreement to refrain from donating sperm during this same period*

  Men with a pregnant partner must agree to remain abstinent or use a condom for the duration of the pregnancy.

  Abstinence is only acceptable if it is in line with 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.

SECTION 4.1.2: Exclusion Criteria

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

- Pregnant or lactating or intending to become pregnant during the study
  - Women who are not postmenopausal (*postmenopausal defined as* ≥ 12 months of non-therapy-induced amenorrhea) or who are not surgically sterile must have a negative urine or serum pregnancy test result within 2 days prior to study treatment.
- Current treatment (within 7 days of dosing) with *probenecid,* amantadine*,* or rimantidine
- Patients who have taken more than a total of ~~3 days (~~6 doses~~)~~ *(3 doses of peramivir)* of ~~approved~~ anti-influenza therapy (e.g., ~~oral~~ oseltamivir, ~~inhaled~~ zanamivir, *, peramivir* ~~or oral ribavirin~~) in the period from onset of symptoms and prior to ~~enrollment~~*study treatment*
- Onset of influenza symptoms *(including fever, chills, malaise, dry cough, loss of appetite, myalgias, coryza, or nausea) >* 5 days prior to study treatment
- *Creatinine clearance ≤10 mL/min*
- *Patients who received nasally administered influenza A vaccine within the last 7 days*

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The randomization of patients will be managed by a central Interactive Voice and Web Response System (IxRS) through use of a dynamic hierarchical algorithm~~.~~ *which includes a random component.*

All patients will be randomly assigned to receive *3600 mg* MHAA4549A ~~3600~~*, 8400* mg *MHAA4549A,* or placebo at a 1:1*:1* ratio stratified by ~~site~~*country*, whether patient is on PPV vs supplemental O_2 at randomization, and whether the patient has suspected or confirmed bacterial pneumonia vs no bacterial pneumonia at randomization. *Initially GV29216 randomly assigned patients to receive either 3600 mg MHAA4549A, or placebo at a 1:1 ratio. The updated randomization scheme takes into account the numbers already allocated to these two arms and strata prior to allocating to the three arm design so that by the end of the study there will be an approximate 1:1:1 allocation between the three arms.*

All patients will receive oseltamivir (~~75 mg or 150 mg BID~~*as described in Table 2*) for a minimum of 5 days.

SECTION 4.3.1.1: MHAA4549A and Placebo

The Sponsor will supply MHAA4549A~~,~~ *and* matching placebo~~, and up to 10-day supply of oseltamivir (Tamiflu®) will be supplied by the Sponsor.~~. For information on the formulation, packaging, and handling of MHAA4549A and placebo~~;~~*,* see the Pharmacy Manual and the MHAA4549A Investigator's Brochure.

SECTION 4.3.1.2: Oseltamivir (Tamiflu®)

Oseltamivir (Tamiflu®*)* is an influenza NAI indicated for treatment of acute, uncomplicated influenza. *The Sponsor will provide oseltamivir capsules for up to a 10-day treatment course.*

SECTION 4.3.2.1: MHAA4549A and Placebo

The randomization of patients will be managed by a central IxRS. All patients will be randomly assigned to receive either a single dose of MHAA4549A 3600 mg IV or *MHAA4549A 8400 mg IV or* placebo IV at a 1:1*:1* ratio.

A single dose of MHAA4549A or placebo will be delivered by IV infusion following dilution in 0.9% normal saline over approximately ~~60~~*120* minutes. Compatibility testing has shown that MHAA4549A is stable when diluted in 0.9% normal saline in a polyvinylchloride *bag*, polyolefin bag, or ethylene vinyl acetate bag (EVA), at ~~or above a combined total concentration~~*concentrations* of 0.24 mg/mL up to 27.0 mg/mL.

SECTION 4.3.2.2: Oseltamivir-Neuraminidase Inhibitor (NAI)

The Sponsor will *supply* oseltamivir (Tamiflu®) for this study for up to a 10-day course. ~~Dosage and administration should follow local prescribing information for oseltamivir.~~ Either 75 mg or 150 mg of oseltamivir will be administered twice daily as described in Table 2. Capsules can be opened and the granules administered via nasogastric tube, if required. *Doses should be captured in the eCRF.*

SECTION 4.4: POST-TRIAL ACCESS TO MHAA4549A

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:
http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

SECTION 4.5.2: Prohibited Therapy

Use of other NAIs, including but not limited to ~~oral~~ oseltamivir, ~~inhaled~~ zanamivir, ~~oral ribavirin, laninimivir,~~ and peramivir, are prohibited during the study, but allowed up to ~~3 days (~~*a total of* 6 doses~~)~~ *(3 doses for peramivir) in the period from onset of symptoms and* prior to study treatment as outlined in the exclusion criteria. *Patients must start standard-of-care oseltamivir no later than 8 hours after completion of MHAA4549A administration.* If oseltamivir resistance is highly suspected or identified during treatment *or if oseltamivir route of administration challenges are encountered,* then, following discussion with the *Sponsor's* medical representative, an alternative NAI to oseltamivir may be used.

SECTION 4.6.2: Diagnostic Testing for Enrollment

All hospitalized patients with severe influenza A ~~will~~ *must* be assessed for disease confirmation *prior to* and enrollment into the study. A Sponsor~~-supplied rapid~~ *approved* influenza test is required ~~for~~*as an aid in* the diagnosis of influenza A infection~~ and uses~~. *This requires* a nasopharyngeal swab~~. When~~ *be introduced into one nostril. Note that* the ~~Sponsor supplied rapid~~ influenza *antigen* test ~~is negative, the study inclusion criteria can be satisfied with a positive local molecular~~*or influenza PCR* test ~~(PCR) if the~~ result ~~is~~*must be available* within the 48-hour screening window. ~~Patients may be enrolled based on a positive local molecular test (PCR) result within the 48-hour screening window, but the rapid influenza test must still be conducted prior to randomization. Other tests may not be used for enrollment in the study unless the Sponsor has reviewed and approved the use of the diagnostic.~~

SECTION 4.6.3: Medical History and Demographic Data

A careful assessment of the patient's baseline SpO_2 *will* ~~should~~ be made especially if the patient has a history of severe chronic lung disease.

SECTION 4.6.4: Priority of Assessments

Assessments on Day 1 must be concluded prior to dosing as specified in Appendix 1a. Any screening assessments completed prior to consent as standard of care do not need to be repeated if done within the screening period.

SECTION 4.6.7: Physical Examinations

At protocol designated visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed which *include* ~~includes~~, at a minimum, evaluation of general appearance, dermatological examination of the injection sites, evaluations directed by patient-reported symptoms, and any other evaluations that the investigator deems clinically relevant.

SECTION 4.6.8: Vital Signs

Vital signs will include measurements of~~ resting SpO_2 (see Section 4.6.7 for measurement),~~ respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressures after the patient has been in a seated or supine position for at least 10 minutes.

SECTION 4.6.9: Oxygen Saturation Measurements

If the patient is on oxygen supplementation, SpO_2 measured by pulse oximetry and the corresponding respiratory assessments (e.g., FiO_2, flow rate) will be recorded. If the patient is on PPV, partial pressure of *arterial* O_2 (PaO_2) and the corresponding respiratory assessments (e.g., FiO_2, ventilator mode, ventilator respiratory rate, positive end expiratory pressure) will be recorded. *If clinically appropriate (i.e., the patient is on non-invasive PPV), the conversion table in Appendix 11 may be used for PaO_2.*

SECTION 4.6.10: Laboratory, Biomarker, and Other Biological Samples

[redacted]

SECTION 4.6.12: [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

SECTION 4.7: APACHE AND SOFA SCORES

The initial scores for APACHE and SOFA should be taken within 24 hours of entry into the ICU and at *the* time points *specified* in Appendix 1a.

SECTION 4.9.2: Study Treatment Discontinuation

Patients must discontinue MHAA4549A infusion and therefore treatment if they experience any of the following:

- ~~Infusion~~ *Life threatening infusion*-related reactions

SECTION 4.9.3: Study Completion/Early Discontinuation Visit

All patients who discontinue from the study early will be asked to complete all assessments for the ~~current visit day and for the~~ early discontinuation visit ~~without duplication.~~.

Section 5.4.2.2: Events That Occur after Study Drug Initiation

In the event that the EDC system is unavailable, a paper Serious Adverse Event / *Adverse Event of Special Interest* Reporting Form should be completed and faxed or scanned and emailed to Safety Risk Management or its designee immediately (i.e., no

more than 24 hours after learning of the event), using the contact information provided to investigators (see Section 5.4.2.1).

SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Results will be presented both for the MHAA4549A 3600 mg and 8400 mg treatment groups separately and combined for the purpose of comparison to standard of care.

SECTION 6.1: DETERMINATION OF SAMPLE SIZE

Approximately 330 patients will be enrolled ~~in this study in order to obtain approximately 300 evaluable patients (an estimated dropout rate of 10%).~~ . It is assumed that the median time to normalization of respiratory function in the control arm is 5 days. This sample size (approximately ~~150~~*110* patients per arm) provides ~~75~~*71*% power to detect a treatment difference of 1 day for the primary endpoint *in both MHAA4549A arms* assuming a 2-sided alpha of 0.2~~.~~ *and no difference in efficacy between the two active arms. If the 3600-mg dose shows a treatment difference of 1 day and the 8400-mg dose shows a treatment difference of 1.5 days or more then this sample size provides > 86% power assuming a 2-sided alpha of 0.2.*

Operating characteristics (power) under other possible assumptions for 2-sided alpha of 0.~~05~~*2* and true differences of ~~1~~*0.5* to 2 days are provided in Table 7.

Table 7, Operating Characteristics for Proposed Study Design for Several Possible True Underlying Median Values, was modified as follows: hazard ratios were added, power of log-rank test values were added, and footnotes were revised. In addition, the row containing 95% CIs was removed.

It should be noted that the study is underpowered for detection of minimally clinically meaningful differences at a 2-sided alpha of 0.05 such as a true hazard ratio of 0.80 ~~(see third column of .~~*in both MHAA4549A arms.*

SECTION 6.4.3: Subgroup Analyses

Subgroups will include the stratification factors as well as patients who are identified at baseline as influenza A positive by the upper, lower, or both airways and by patients with bacterial co-infections at admission~~.~~ *as well as by the influenza season during which the patient was randomized.*

SECTION 10: References

Centers for Disease Control and Prevention (CDC). ~~*2011*~~*2014-~~2012~~ 2015* Influenza antiviral medications [resource on the Internet]. ~~*2012b*~~ *2015* [Updated ~~*2014*~~*2015, ~~Mar 21~~ Jan 9*; cited 201*5*~~4~~ *Jan*]. Available from: http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.

Writing Committee of the World Health Organization (WHO) consultation on human influenza A/H5. Avian influenza A (H5N1) infection in humans. N Engl J Med 2005; 353: 1374-85.

Yingying C. Abnormal liver chemistry in patients with influenza A H1N1. Liver Int 2011; 31(6): 902.

APPENDIX 1a: Schedule of Assessments: Hospitalization Days

Before the assessment table, the following text was added: *Any screening assessments completed prior to consent as standard of care do not need to be repeated if done within the screening period. If a patient is unable to be present at the site for a follow-up visit, a telephone visit is permitted.*

In the list of procedures, "Rapid A influenza test" was changed to "Sponsor-approved influenza test." Table footnotes were updated to match changes in protocol body. Footnote designations and order were updated to place them in order.

APPENDIX 1b: Schedule of Assessments: Follow-up Period

- If a patient is discharged *after Day 14 but* prior to Day 30, he/she will need to complete the following assessments for Day 30 and Day 60 below.
- If a patient is discharged *after Day 30, but* prior to Day 60, he/she will need to complete the following assessments for Day 60 below.

Table footnotes were updated to match changes in protocol body.

APPENDIX 2: Time to Normalization of Respiratory Function

For the purposes of this study, the time to normalization of respiratory function will be defined as the time to removal of the patient from O_2 supplementation in order to maintain an SpO_2 ~~>~~≥ 95%.

- If the SpO_2 ~~>~~≥ 95%, then the time and reading should be recorded. Notify the study doctor so that he/she can make a clinical judgment to determine whether the O_2 can be removed.
- ~~If the patient is off O_2 for 24 hours and his/her reading the subsequent day is >95%, then the endpoint is considered satisfied.~~ The recorded time for the endpoint corresponds with the initial discontinuation of O_2 and reading.

APPENDIX 3: [redacted]

[redacted]

APPENDIX 4: [redacted]

[redacted]

[redacted]

APPENDIX 5: [redacted]

[redacted]

[redacted]

[redacted]

APPENDIX 6: [redacted]

[redacted]

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

Abbreviations were updated throughout the document, and additional minor changes have been made to improve clarity and consistency. The amendment number was updated throughout the protocol. Substantive new information appears in italics. Citations were added in the text representing the new reference material. This amendment represents cumulative changes to the original protocol.

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY, IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION**
PROTOCOL NUMBER:	GV29216
VERSION NUMBER:	5 (Global)
EUDRACT NUMBER:	2014-000461-43
IND NUMBER:	117,318
TEST PRODUCT:	MHAA4549A
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION**
PROTOCOL NUMBER:	GV29216
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IND NUMBER:	117,318
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INDICATION:	INFLUENZA A
SPONSOR:	Genentech, Inc.

Objectives

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety of MHAA4549A in combination with oseltamivir compared with placebo and oseltamivir in patients with severe influenza A, focusing on the nature, frequency, and severity of serious and non-serious adverse events (AEs), as well as effects on laboratory values, vital signs, electrocardiogram (ECG) parameters, anti-therapeutic antibodies (ATA), *and* other safety biomarkers

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To determine the time to normalization of respiratory function of patients dosed with MHAA4549A in combination with oseltamivir compared to patients dosed with placebo and oseltamivir

The secondary efficacy objectives for this study are as follows:

- The secondary efficacy objectives for this study are as follows:
- To measure clinical failure after 24 hours post-infusion of study drug
- To determine the time to clinical resolution of vital signs
- To measure mortality in patients
- To determine changes in the extent and duration of viral shedding in nasopharyngeal samples as a measure of pharmacodynamic response
- [redacted]
- To measure the duration of hospital and/or intensive care unit (ICU) stay
- To measure antibiotic usage for respiratory *infections*
- To measure the frequency and severity of the following secondary complications of influenza:
  - Pneumonia (hospital acquired pneumonia [HAP]/ ventilator acquired pneumonia [VAP])

- Exacerbations of chronic lung disease
- Myocarditis
- Acute respiratory distress syndrome (ARDS)
- Otitis media
- Other related complications
- Readmission rates at 30 and 60 days after study treatment

- To measure duration of positive pressure ventilation (PPV)
- To measure readmission rates

Pharmacokinetic Objectives

The major pharmacokinetic (PK) objective for this study is as follows:

- To characterize the PK profile of MHAA4549A in serum

The exploratory PK objectives for this study are as follows:

[redacted]

Exploratory Objectives

The exploratory objectives for this study are as follows:

[redacted]

Study Design

Description of Study

This is a Phase 2b *(GV29216),* randomized, double-blind, placebo-controlled study designed to assess the safety and clinical activity of a single intravenous (IV) dose of *3600 mg MHAA4549A or a single IV dose of 8400 mg* MHAA4549A in hospitalized patients with severe influenza A in combination with oseltamivir versus a comparator arm of oseltamivir with placebo.

Initially, GV29216 enrolled and randomized *patients* into two treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir or a single IV dose of placebo with oseltamivir.

Patients will be randomized 1:1:1 into three treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir, a single IV dose of 8400 mg of MHAA4549A with oseltamivir, or a single IV dose of placebo with oseltamivir. All patients will receive oseltamivir, a NAI, as standard

therapy for a minimum of 5 days, starting after study drug administration. Oseltamivir at doses of 75 mg twice daily (BID) or 150 mg BID is permitted in order to be consistent with local standard of care practice. Treatment for longer than 5 days is permitted based on local investigator discretion. The patient must start Sponsor-supplied oseltamivir *no later than* 8 hours *after completion* of study drug administration.

Patients hospitalized with an oxygen (O_2) or PPV requirement will be evaluated for influenza A infection. Enrollment in this study requires ongoing treatment within 24 hours of hospital admission with one of the following: any PPV or any supplemental O_2 to maintain oxygen saturation (SpO_2) > 92%.

A Sponsor-*approved* influenza test*, which includes influenza antigen test* and/or *influenza* polymerase chain reaction (PCR) test must be used as an aid in the diagnosis of influenza A infection.

At the time of randomization, patients who are eligible for enrollment will be randomized to receive a single IV infusion of *3600 mg* MHAA4549A *or 8400 mg MHAA4549A* or placebo, *which* will be administered on Day 1. All patients must *begin* study drug *infusion* within 48 hours of hospital admission or sooner if possible; therefore, screening must be completed within this window. All patients will receive oseltamivir for a minimum of 5 days (10 doses), starting on Day 1 beginning no later than 8 hours after *completion of* study drug administration. All patients will be followed for 60 days from the time of study drug administration.

Number of Patients

The study has a planned enrollment of approximately 33*0* patients (adult men and women) globally. Patients will receive *3600 mg* MHAA4549A*, 8400 mg,* or placebo in 1:1*:1* ratio. The number of patients on PPV should not exceed 45% of the total enrolled patients.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Men or women ≥ 18 years of age on day of signing informed consent or obtaining surrogate consent from an authorized representative
- Diagnosis of influenza A *where a Sponsor-approved influenza test is used as an aid in diagnosis. A Sponsor-approved influenza test includes*:
  - *Influenza antigen test –OR–*
  - Influenza polymerase chain reaction (PCR) test
- One of the following markers of severity within 24 hours of hospital admission:
  - Requirement for PPV, OR
  - Requirement for O_2 supplementation to maintain $SpO_2 > 92\%$
- A negative urine or serum pregnancy test for women of childbearing potential
- Patients of reproductive potential must agree to use reliable means of contraception as described below as a minimum (adherence to more stringent local requirements may be required):
  - *For women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use two adequate methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment period and for at least 120 days after the last dose of study drug*

    Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

    Barrier methods must always be supplemented with the use of a spermicide.

Examples of contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, hormonal implants, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.

– *For men: agreement to remain abstinent or use a condom during the treatment period and for at least 30 days after the last dose of study drug and agreement to refrain from donating sperm during this same period*

Men with a pregnant partner must agree to remain abstinent or use a condom for the duration of the pregnancy.

Abstinence is only acceptable if it is in line with 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.

Non-reproductive potential is defined below (but could be superseded by local definitions, if they are more stringent):

– Women who are postmenopausal (i.e., spontaneous amenorrhea for the past year confirmed by an follicle stimulating hormone [FSH] level greater than 40 mIU/mL unless the patient is receiving a hormonal therapy for their menopause)

– Women who are surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)

– Men who are surgically sterile (castration)

Exclusion Criteria

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

- Pregnant or lactating, or intending to become pregnant during the study
  - Women who are not postmenopausal (*postmenopausal defined as* ≥ 12 months of non-therapy-induced amenorrhea) or who are not surgically sterile must have a negative urine or serum pregnancy test result within 2 days prior to study treatment
- Hypersensitivity to monoclonal antibodies or to the active substance or any excipients of MHAA4549A study drug
- Hypersensitivity to the active substance or to any excipients of oseltamivir
- Investigational therapy within the 30 days prior to study treatment
- Received prior therapy with any anti-influenza monoclonal antibody therapy (including MHAA4549A) 8 months prior to study treatment
- Current treatment (within 7 days of dosing) with probenecid, amantadine, or rimantidine
- Patients who have taken more than a total of 6 doses (*3 doses for peramivir*) of anti-influenza therapy (e.g., oseltamivir, zanamivir, *peramivir*) in the period from onset of symptoms and prior to *study treatment*
- Admission > 48 hours prior to study treatment
- Onset of influenza symptoms *(including fever, chills, malaise, dry cough, loss of appetite, myalgias, coryza, or nausea)* > 5 days prior to study treatment
- Positive influenza B or influenza A + B infection within 2 weeks prior to study treatment
- High probability of mortality in the next 48 hours as determined by the investigator
- Patient requiring home or baseline oxygenation therapy
- Patient with history of chronic lung disease resulting in baseline SpO_2 < 95%
- Patient on chronic dose of corticosteroids exceeding 10 mg/day of prednisone or equivalent steroid dose for a duration of greater than 14 days within 30 days of entry into study
- *Creatinine clearance ≤10 mL/min*
- *Patients who received nasally administered influenza A vaccine within the last 7 days*
- Patients with the following significant immune suppression:

  - Bone marrow or solid organ transplant in the previous 12 months
  - Cancer chemotherapy in the previous 12 month
  - Human immunodeficiency virus (HIV) infection with most recent CD4 $<$ 200 cells/mL
  - Other significant immune suppression as determined by the investigator in discussion with the Sponsor Medical Monitor or representative
- Patient on extracorporeal membrane oxygenation (ECMO) at time of randomization
- Any disease or condition that would, in the opinion of the site investigator or Sponsor, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol

Length of Study

This study will consist of the following study periods:

- A screening period of 48 hours, beginning at time of hospital $admission$
- A treatment period of 1 day, during which patients will receive a single dose of MHAA4549A or placebo and a minimum of 5 days of oseltamivir.
- A follow-up period beginning at hospital discharge through 60 days post study drug (MHAA4549A/placebo) administration

End of Study

The end of the study is defined as the first day when all patients have had a study completion visit or early termination visit or have otherwise been discontinued from the study.

Outcome Measures

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- AEs and clinical laboratory abnormalities
- Vital signs, physical findings, ATAs, and clinical laboratory results during and following administration of MHAA4549A

Efficacy Outcome Measures

The primary outcome measure for this study is as follows:

- Time to normalization of respiratory function defined as:
  - The time to cessation of O_2 support resulting in a stable $SpO_2 \geq 95\%$

The secondary efficacy outcome measures for this study are as follows:

- Clinical failure after 24 hours post-infusion of study drug defined as:
  - Progression to increased O_2 requirement defined by an increase in oxygen supplementation from low flow oxygen (2 – 6 L/min) to high flow oxygen ($>$ 6 L/min) or from oxygen supplementation alone to any PPV $or\ ECMO$
  - Progression to ICU
  - Prolonged ventilation or O_2 support defined by $>$ 2 weeks, or
  - Death
- Time to clinical resolution of vital signs (3/5 criteria must be met):
  - $SpO_2 \geq 95\%$ without supplemental O_2
  - Respiratory rate $<$ 24 breaths per minute without supplemental O_2
  - Core temperature $<$ 37.2°C immediately prior to receipt of any antipyretic drug, and at least 6-8 hours from the last dose of antipyretic or core temperature $>$ 36°C in patients who are initially hypothermic
  - Heart rate (HR) $<$ 100 $beats$/minute
  - Systolic blood pressure (SBP) $>$ 90 mmHg

- All-cause mortality at Day 14, Day 30, and Day 60
- Influenza A viral load in nasopharyngeal samples
  - *Area under viral load-time curve* (AUEC; *qPCR)*
  - Peak viral load *(qPCR)*
  - Time to resolution of infection *(qPCR)*
  - [redacted]
- Duration of hospitalization
- Duration of ICU stay
- Antibiotic usage for respiratory infections
- Complications of influenza:
  - Pneumonia (HAP/VAP)
  - Exacerbations of chronic lung disease
  - Myocarditis
  - ARDS
  - Otitis media
  - Other related complications
- All-cause readmission at Day 30 and Day 60
- Duration of ventilation

Pharmacokinetic Outcome

The primary PK outcome measures for this study are as follows:

- PK parameters for MHAA4549A in serum including total exposure (i.e., area under the curve [AUC]), maximum observed concentration (C_{max}), clearance, half-life, and volume of distribution, when appropriate, as data allow

The exploratory PK outcome measures for this study are as follows:

- [redacted]

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

[redacted]

[redacted]

Investigational Medicinal Products

An investigational medicinal product (IMP) is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, excluding marketed products unless the product is 1) used or assembled (formulated or packaged) differently than the authorized form, 2) used for an unauthorized indication, or 3) used to gain further information about the authorized form (Directive 2001/20/EC Article 2[d]). A non-investigational medicinal product (NIMP) is a medicinal product that is intended for use in a clinical trial per the protocol but does not fall under the definition of IMP. Further details can be found in the following *European Union* (EU) guidance: Guidance on Investigational Medicinal Products and Non-Investigational Medicinal Products (effective March 2011).

MHAA4549A and Placebo

A single 3600-mg dose of MHAA4549A *or a single 8400-mg dose of MHAA4549A* or dose of placebo will be delivered by IV infusion following dilution in 0.9% normal saline over approximately *120* minutes. Study drug should be delivered using a 0.22 μm in-line filter. Placebo will be identical to active MHAA4549A in formulation, but will not contain active drug substance.

Oseltamivir (Tamiflu®)

*O*seltamivir (Tamiflu®) 75 mg or 150 mg will be administered BID for a minimum of 5 days. Capsules can be opened and the granules administered via nasogastric tube, if required.

Statistical Methods

Primary Analysis

All efficacy analyses will be conducted according to the intent-to-treat principle and will include all patients who meet the following condition with patients allocated to the treatment arm to which they were randomized:

- Randomized patients who have confirmed influenza A infection by a central PCR test from Day 1 samples.

The primary and secondary efficacy analyses will include all randomized patients who are confirmed to be influenza A infected, with patients grouped according to the treatment assigned at randomization.

Time to event data will be computed using Kaplan-Meier methodology and stratified Cox proportional hazards models and will be summarized using n, median when estimable, hazard ratios, and 95% confidence intervals. Patients who are lost to follow-up (while event free) will be censored at the time that they are last known to be event free.

Estimation of the treatment difference of proportions and its 95% confidence interval will be calculated using stratum-adjusted Mantel-Haenszel methodology. For continuous endpoints, Analysis of Covariance methods (after appropriate transformation of data) will be used to estimate treatment differences at 95% confidence intervals.

Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of

the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

If conducted, an interim analysis would be for administrative purposes only (i.e., internal planning or decision making) and would not impact the conduct of the current study in any way. A nominal type I error penalty of 0.0001 will be taken. In addition, as discussed below, the Sponsor will conduct interim safety analyses separate from and in conjunction with the above.

Determination of Sample Size

A total of *330* patients will be enrolled in this study. It is assumed that the median time to normalization of respiratory function in the control arm is 5 days

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
[redacted]	[redacted]
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Acture respiratory distress syndrome
AST	Aspartate aminotransferase
ATA	anti-therapeutic antibody
AUC	Area under serum concentration-time curve
AUEC	Area under viral load-time curve
BID	Twice a day
°C	Celsius
CDC	Centers for Disease Control and Prevention
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CPK	Creatine phosphokinase
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ECMO	Extracorporeal membrane oxygenation
EDC	electronic data capture
EU	European Union
EVA	Ethylene vinyl acetate
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HA	Hemagglutinin
HAI	Hemagglutinin inhibition
HAP	Hospital Acquired Pneumonia
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus

hMPV	*Human metapneumovirus*
HPLC	High-performance liquid chromatography
HR	Heart rate
HRP	Horseradish peroxidase
HRV	*Human rhinovirus*
[redacted]	[redacted]
IC_{50}	Concentration required for 50% inhibition
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IDSA	*Infectious Diseases Society of America*
IEC	Independent Ethics Committee
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IQR	*Interquartile range*
IRB	Institutional Review Board
IRR	Infusion-related reactions
ITT	Intent-to-treat
IV	Intravenous
IxRS	Interactive voice and web response system
LFTs	Liver function tests
LPLV	last patient, last visit
NA	Neuraminidase
NAI	Neuraminidase inhibitor
NIMP	*Non-investigational medicinal product*
NP	Nasopharyngeal
O_2	Oxygen
PaO_2	Partial pressure of arterial oxygen
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PE	Paired end
PK	Pharmacokinetic
PIV	*Parainfluenza virus*
PPV	Positive pressure ventilation
qPCR	Quantitative Polymerase Chain Reaction
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula

RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SOC	Scientific Oversight Committee
SOFA	Sequential Organ Failure Assessment
SpO_2	Oxygen saturation by pulse oximetry
SUSAR	Suspected unexpected serious adverse reactions
$TCID_{50}$	50% tissue culture infectious dose
ULN	Upper limit of normal
US	United States
UVTM	Universal viral transport medium
VAP	Ventilation Acquired Pneumonia
WBC	White blood cell

1. BACKGROUND

1.1 BACKGROUND ON INFLUENZA

Influenza A is a membrane-enveloped RNA virus that causes significant morbidity and mortality. Currently, there is a great need in hospitalized influenza patients for a parenteral therapeutic option that is well tolerated, can rapidly resolve influenza-related signs and symptoms, decrease mortality, reduce hospital and intensive care unit (ICU) stays, as well as have a prolonged window for initiation of treatment beyond the current standard of care (i.e., within 48 hours of the onset of flu symptoms).

Approximately 200,000 to 278,000 patients are hospitalized with severe influenza infections annually in the United States (US) (Thompson et al. 2004; Zhou et al. 2012), and assuming the same rate reported in the US, an estimated 319,000 to 445,000 patients are hospitalized in the European Union (EU). Hospitalization due to severe influenza is associated with high mortality (4%–8%), ICU admission (5%–17%; Lee and Ison 2012), mechanical ventilation support in an ICU setting (7%–11%; Doshi et al. 2011), and prolonged hospital stays (5−9 days; Lee and Ison 2012). 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).

Influenza infection is an upper and lower respiratory disease with a broad spectrum of presentations that can result in fever, shortness-of-breath, pneumonia, respiratory failure, secondary respiratory infections, and even death. The standard of care therapy for patients hospitalized with influenza consists of supportive measures and administration of available antiviral agents, primarily neuraminidase inhibitors (NAI) that include but are not limited to oseltamivir, zanamivir, and peramivir. However, a significant unmet medical need still exists in the severely ill patient population, as evidenced by the considerable degree of morbidity and mortality in this setting. To address this need, the Sponsor is developing a highly-specific anti-influenza A (MHAA4549A) antibody therapy for treatment of hospitalized patients with severe influenza.

1.2 BACKGROUND ON MHAA4549A

1.2.1 Nonclinical Background

MHAA4549A is a human monoclonal IgG1 antibody that binds to the influenza A virus and is cloned from a single-human plasmablast cell isolated from an influenza vaccinated donor (Nakamura et al. 2013). This antibody binds to a highly conserved epitope on the influenza A hemagglutinin (HA) stalk region, which allows broad neutralization of the influenza A virus by blocking the HA-mediated, membrane-fusion event in the late endosome.

In vitro, MHAA4549A is capable of neutralizing all current clinically relevant influenza A strains. In vivo, efficacy of MHAA4549A has been demonstrated in mouse models of influenza A infection, both as a single agent and in combination with oseltamivir.

MHAA4549A specifically targets an epitope on the human influenza A *HA* glycoprotein, which does not appear to be endogenously expressed on human or rat tissues and, therefore, is unlikely to be present in the absence of viral infection. Weekly administration of MHAA4549A (total of 5 doses) in Sprague-Dawley rats was well tolerated up to the maximum feasible dose of 150 mg/kg. Ex vivo tissue cross-reactivity study data showed no specific binding of MHAA4549A to any of the human or rat tissues examined.

1.2.2 Clinical Safety Background

To date, MHAA4549A has been shown to be safe and well tolerated in two clinical studies, which altogether enrolled 122 healthy volunteers.

1.2.2.1 *Phase 1 Entry-into-Human Study GV28916*

The first study was a Phase 1 study (GV28916) in 21 healthy volunteers where single doses of 1.5 mg/kg, 5 mg/kg, 15 mg/kg, and 45 mg/kg were tested with an extended follow-up period of 120 days. MHAA4549A was safe and well tolerated with no serious adverse events (SAEs). All adverse events (AEs) were mild or mild to moderate and resolved fully before the end of the study's follow-up period. No anti-therapeutic antibodies (ATAs) were detected in this study.

1.2.2.2 *Phase 2a Influenza Nasal Challenge Study GV28985*

The second study was a Phase 2a challenge study (GV28985) in 101 healthy volunteers infected with a H3N2 (A/Wisconsin/67/2005) strain of influenza virus. Sixty subjects received doses of 400 mg, 1200 mg, or 3600 mg MHAA4549A, and *32* subjects received placebo following nasal inoculation of influenza A virus one day earlier. *Eight subjects* received oseltamivir *starting on Day 1. One subject was randomized and inoculated, but not dosed.*

Most AEs appeared to reflect symptoms of an active influenza infection and occurred primarily within the first 21 days after patients received their virus inoculation and dose of MHAA4549A or placebo (123 of 213: 58%). Following the resolution of the influenza symptoms, even though levels of MHAA4549A remained relatively high, the number of AEs dropped and remained low throughout the remainder of the study: 59 of 213 (28%) of all AEs occurred between Study Days 22 and 60, and 31 of 213 (15%) of all AEs occurred between Study Days 61 and 120. Differences between treatment groups in the number and severity of AEs during the first 22 days appeared to reflect variability in the extent and severity of the influenza infection. Throughout the entire study, the pattern of AEs did not differ substantially between subjects who received placebo and subjects who received any dose of MHAA4549A.

The percentage of AEs that investigators judged to be related to study drug treatment was 12/33 (36%) for the 400-mg group, 10/40 (25%) for the 1200-mg group, 11/52 (21%) for the 3600-mg group, and 25/88 (28%) for subjects receiving placebo. Of those AEs considered related, however, 15 of 25 (60%) in the placebo cohort and 26 of 33 (79%) in all MHAA4549A cohorts consisted of

elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or amylase. These laboratory abnormalities have been shown to be associated with the influenza infection (Polakos et al 2006; Yingying 2011) and were not observed in either the previous or subsequent Phase 1 studies (i.e., GV28916, GV29609) where MHAA4549A was administered to subjects without influenza infection.

There were 3 SAEs in Study GV28985, none of which were assessed as related to MHAA4549A. One was in a subject hospitalized with a depressive psychosis. Due to his previous history of depression and the known association of psychosis with influenza infections, the Investigator considered this event unrelated to study drug. The other 2 SAEs were in one subject who fell and required a surgical repair of a fractured tibial plateau. This same subject was subsequently hospitalized for her second SAE, which was a post-surgical wound infection. Neither of these events was considered related to study treatment.

In GV28985, the immunogenicity incidence rate amongst the 60 subjects who received MHAA4549A was 0%. One subject tested positive for ATAs. This subject tested positive for ATA at baseline and post baseline. This subject was in the placebo group, which included 32 other subjects, resulting in an immunogenicity prevalence rate (ATA-positive rate at baseline) of 3.1% and an immunogenicity incidence rate (ATA titers post-baseline) of 3.1%, as well, within the placebo group. Overall, study GV28985 had an immunogenicity prevalence rate of 1%.

1.2.2.3 Phase 1 High Dose Safety Study *GV29609*

A Phase 1 (GV29609) study was initiated to evaluate the safety and tolerability of a single intravenous (IV) doses at 8400 mg or 10800 mg MHAA4549A as compared to placebo when administered to 14 healthy volunteers. The starting dose of 8400 mg was based on simulations from a semi-quantitative pharmacokinetic model (Figure 2) developed from the Phase 2a challenge study (GV28985), which suggests that the 8400 mg may be the minimum dose that is expected to show a separation of nasal exposure from a dose of 3600 mg. The simulation assumes that pharmacokinetics can be extrapolated at doses above 3600 mg and that the PK profile in severely ill patients is similar to the PK profile of healthy volunteers in the Phase 2a challenge study. The highest proposed dose of 10800 mg was chosen in GV29609 to provide safety coverage for those exposures that might be reached in a 40-kg individual dosed with a flat dose of 8400 mg.

GV29609 is currently on-going, but preliminary analysis of unblinded safety data up to day 57 shows that the 8400 mg and 10800 mg treatment groups are safe and well tolerated.

- *In subjects who received 8400 mg MHAA4549A (N=4):*
  - *3 of 4 subjects reported 12 AEs*

- *6 AEs were reported as related to 8400 mg MHAA4549A: 3 headaches, 1 pruritus, 1 peripheral swelling, and 1 nasal congestion*

- *In subjects who received 10800 mg MHAA4549A (N=4):*
  - *4 of 4 subjects reported 7 AEs*
  - *3 AEs reported as related to the 10800 mg MHAA4549A treatment group: 1 nausea, 1 headache, and 1 asthenia*
- *In subjects who received placebo (N=6):*
  - *2 of 6 subjects reported 5 AEs*
  - *1 AE was reported as related to study drug: 1 headache*

All AEs were reported as mild except for an unrelated moderate AE of an increase in creatinine kinase in one subject who received 10800 mg MHAA4549A. There were no SAEs and no subjects have discontinued the study for any reason.

As in both previous studies, headache was the most common AE. Headache was reported by 3 subjects (37.5%) who received 8400 mg MHAA4549A: 1 subject (12.5%) who received 10800 mg MHAA4549A and 2 subjects (33.0%) who received placebo.

Based on this data, MHAA4549A is considered generally safe and well tolerated.

1.2.3 Clinical Efficacy Background

The Phase 1 study (GV28916) demonstrated that MHAA4549A pharmacokinetics were generally dose proportional. The PK profile appeared consistent with that of a human IgG1 antibody that lacks known endogenous host targets.

In the Phase 2a challenge study (GV28985), 101 healthy volunteers were inoculated with influenza virus 24-36 hours prior to dosing with MHAA4549A. Following inoculation, 60 subjects received doses of 400 mg, 1200 mg, or 3600 mg MHAA4549A, 32 subjects received placebo, 8 subjects received a 5-day course of oseltamivir, and 1 subject was not dosed. The interim efficacy analysis presented in Table 1 included the Intent-to-Treat (ITT) infected population followed until at least Day 29 who received 400 mg MHAA4549A (N =11), 1200 mg MHAA4549A (N =13), 3600 mg MHAA4549A (N =14), placebo (N =21), and oseltamivir (N =2). Analysis of efficacy from the 3600-mg dose level demonstrated a statistically significant decrease in viral shedding from *the* upper respiratory tract as measured by the area under the curve (97.5% reduction by quantitative polymerase chain reaction [qPCR]) and peak viral load (77% reduction by qPCR*). All subjects have completed dosing, and interim PK and efficacy data are available in the Investigator's Brochure and upon request.*

In *the GV28985* study, *all subjects received* oseltamivir started on Day 7 for a 5-day course, and there were no observed AEs or imbalances in safety events that were considered attributable to interactions between oseltamivir and MHAA4549A. The PK profile of MHAA4549A and oseltamivir in GV28985 are being analyzed to exclude potential drug-drug interactions, and *this analysis* will be available before the start of this study (GV29216).

Table 1 Interim Efficacy Results from Phase 2a Challenge Study (GV28985)

		MHAA4549A			Oseltamivir
Endpoint	Placebo (N=21)	400 mg (N=11) % reduction (p-value)[a]	1200 mg (N=13) % reduction (p-value)[a]	3600 mg (N=14) % reduction (p-value)[a]	75 mg BID (N=2) % reduction (p-value)[a]
Median qPCR Viral AUEC (log_{10} vc/mL x hour)	458.1	247.2 46.0% (0.0455)	444.4 3.0% (0.9020)	11.3 97.5% (0.0051)	57.4 87.5% (0.0558)
Median qPCR Peak Viral Load (log_{10} vc/mL)	6.38	5.08 20.4% (0.0187)	6.36 0.3% (1.0000)	1.45 77.3% (0.0024)	2.30 63.9% (0.0947)
Median Total Clinical Symptom AUEC	207.7	87.5 57.9% (0.2000)	192.1 7.5% (0.8743)	37.7 81.8% (0.2887)	8.1 96.1% (0.0855)

AUEC = area under viral load–time curve; qPCR = quantitative polymerase chain reaction.

[a] Comparison of active and placebo using nonparametric Wilcoxon rank-sum test. All p-values are unadjusted for multiple testing.

The A/Wisconsin/67/2005 virus induced mild symptoms that were predominantly captured in the upper respiratory tract symptoms that included runny nose, stuffy nose, and sneezing.

The Symptom Diary Cards used a scale of 0-3, where Grade 0 is absence, Grade 1 is just noticeable, Grade 2 is bothersome but does not prevent participation in activities, and Grade 3 is bothersome and interferes with activities. Composite clinical symptom scores from Study GV28985 for the *ITT infected (ITTI) population* are shown in Table 1.

Given the variability of the symptom scores the results were not statistically significant. However, there was a decrease in the AUEC of symptoms scores for the 3600-mg dose, which is consistent with the virological results described in Table 1. Data from the oseltamivir treated group is also shown, but it should be noted that only 2 subjects were in the ITT infected population.

The responses observed in the Phase 2a study (GV28985) suggest that a higher dose may provide better efficacy in a population with established infection. An 8400-mg

dose will be included in this Phase 2b study for further dose ranging. The rationale for selected dosages is further explained in Section 3.2.4.

See the MHAA4549A Investigator's Brochure for additional details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

Two Phase 1 *(GV28916, GV29609)* studies have demonstrated that MHAA4549A is safe and well tolerated to date in healthy volunteers *at doses up to 8400 mg*. Data from *a* Phase 2a study *(GV28985) demonstrates safety in healthy subjects inoculated with influenza virus and* provides evidence that the 3600 mg dose of MHAA4549A is effective in reducing viral titers in healthy volunteers inoculated with influenza A virus. *W*hen combined with previous nonclinical studies *that showed* MHAA4549A to have in vitro and in vivo efficacy, a well-tolerated safety profile, and anti-viral activity, *these findings* support further clinical development of MHAA4549A.

In this Phase 2b study (GV29216), MHAA4549A is being evaluated in combination with the current standard of care (oseltamivir), to decrease the severity and duration of viral infection with influenza A virus with the ultimate goal of reducing the clinical symptoms of infection as compared to oseltamivir with placebo. There are three primary goals for this Phase 2b study:

- Demonstrate the safety and efficacy of MHAA4549A in combination with oseltamivir in hospitalized influenza A patients
- Demonstrate a reduction in the extent and duration of viral burden in upper and lower lung compartments in order to gain an understanding of the PK/pharmacodynamic (PD) and PD/efficacy relationships
- Demonstrate and evaluate the optimal endpoints for study in hospitalized patients with influenza A, given the lack of precedence for approval in patients hospitalized with influenza infection, an area of high unmet medical need

Initially, this GV29216 Phase 2b study enrolled patients in a two-arm treatment study comparing 3600 mg MHAA4549A with oseltamivir versus placebo with oseltamivir.

This *current* Phase 2b study has *added an additional arm to evaluate* the improvement in outcome of a combination therapy of *3600 mg* MHAA4549A *with oseltamivir or of 8400 mg MHAA4549A* with oseltamivir versus placebo with oseltamivir. All patients will *receive* oseltamivir, which is part of the recommended standard of care. In addition, and as discussed above, MHAA4549A is a human monoclonal antibody that has, to date, shown an acceptable safety profile, a PK profile consistent with that of a IgG1 human antibody that lacks known endogenous host targets, and demonstrated antiviral activity at the planned dose level of 3600 mg.

This study (GV29216) will assess severely ill patients who may be infected with various influenza A strains, have a higher viral burden and longer duration of viral shedding than the healthy volunteers in GV28985, and who may, therefore, require doses higher than 3600 mg. A Phase 1 (GV29609) study is currently on-going to assess the safety, tolerability, and pharmacokinetics of 8400-mg and 10800-mg doses of MHAA4549A. The starting dose of 8400 mg was selected based on simulations from a semi-quantitative PK model developed from the Phase 2a challenge study (GV28985), suggesting that 8400 mg MHAA4549A may be the minimum dose that is expected to show a separation of nasal exposure from a dose of 3600 mg. This simulation assumes that pharmacokinetics can be extrapolated at doses above 3600 mg and that the PK profile in severely ill patients is similar to the PK profile of healthy volunteers in Phase 2a challenged with influenza A virus. The 10800-mg dose was chosen to provide assurance of safety for the increased MHAA4549A levels that may be reached in smaller individuals who received 8400 mg.

A preliminary, unblinded analysis of the safety data from GV29609 up to Day 57 has shown that the 8400-mg and 10800-mg treatment groups are safe and well tolerated. In subjects who received 8400 mg MHAA4549A, 3 of 4 subjects reported 12 AEs. In subjects who received 10800 mg MHAA4549A, 4 of 4 subjects reported 7 AEs. In subjects who received placebo, 2 of 6 subjects reported 5 AEs. All AEs were reported as mild, except for one unrelated moderate AE of an increase in creatinine kinase in one subject who received 10800 mg MHAA4549A. There were no SAEs and no subjects have discontinued the study for any reason. As in previous studies, headache was the most common AE, and was reported by 3 subjects (37.5%) who received 8400 mg MHAA4549A, 1 subject (12.5%) who received 10800 mg MHAA4549A, and 2 subjects (33.0%) who received placebo. As a result, the Sponsor feels that the 8400-mg dose is safe to include in Study GV29216.

The 8400-mg dose is also expected to be safe based upon previous nonclinical and clinical safety assessments. Nonclinical safety data do not show any expected or unexpected toxicity.

1.3.2 Benefit-Risk Assessment

1.3.2.1 Treatment in Combination with Oseltamivir

All patients in the study will receive oseltamivir as the current standard of care treatment, either with or without MHAA4549A. Therefore, at a minimum, all patients will be treated with *the* standard of care for influenza. Given that MHAA4549A is an antibody, the potential for a drug-drug interaction with oseltamivir is very low. In the Phase 2a challenge study (GV28985), study subjects received MHAA4549A followed by oseltamivir with no AEs attributable to the combination therapy noted to date. In addition, in this *Phase 2b* study the PK profile of oseltamivir in concomitantly treated subjects will be assessed.

1.3.2.2 Drug Mechanism and Preclinical Studies

The available pre-clinical data suggest that there is low risk for drug target-related safety events in healthy humans since MHAA4549A specifically targets an epitope on a viral protein (i.e., the human influenza A virus *HA* glycoprotein), which is not endogenously expressed in human tissues. Furthermore, there were no adverse MHAA4549A-related findings demonstrated in nonclinical studies at doses up to 150 mg/kg administered weekly for 5 weeks and no evidence of target present in host tissues.

1.3.2.3 Rationale for Selection of Phase 2b Study Population

The target patient population of hospitalized patients with severe influenza A requiring oxygen (O_2) or positive pressure ventilation (PPV) is considered an appropriate population to test MHAA4549A for the following reasons:

- Nonclinical safety data does not show any expected or unexpected toxicity.
- Clinical safety data for MHAA4549A demonstrate a well-tolerated safety profile:
  - *AEs in the Phase 1 study (GV28916) were mild and did not show a dose relationship; there were no ATAs detected in patients treated with MHAA4549A after 120 day follow-up visit.*
  - *All AEs in GV29609 from a preliminary analysis of unblinded safety data up to day 57 were reported as mild except for an unrelated moderate AE of an increase in creatinine kinase in one subject who received 10800 mg MHAA4549A. There were no SAEs and no subjects have discontinued the study for any reason.*

In the Phase 2a study (GV28985), MHAA4549A was generally well tolerated. A few subjects in all treatment groups were observed to have transient elevations in ALT, AST, and amylase levels. There was no dose-dependent relationship of the ALT/AST/amylase elevations with MHAA4549A and the overall event rate was in line with published rates associated with the influenza challenge model regardless of treatment arm: 27/100 [27%] in GV28985 vs. approximately 26% in previous challenge studies (Polakos 2006, *Yingying 2011*). There were no SAEs related to study drug. There were a total of 3 SAEs unrelated to MHAA4549A in two subjects. One subject reported depressive psychosis associated with influenza. The second subject reported a broken knee with a subsequent infection following a surgical procedure.

1.3.2.4 Patient Monitoring and Supervision

MHAA4549A will be administered to enrolled patients in a hospital environment under close medical supervision by physician investigators. Medical staff will be available for prompt evaluation and treatment of any AEs. Emergency resuscitation equipment and emergency facilities will be readily available. Patients will undergo screening assessments to confirm eligibility, will be closely monitored during the administration of MHAA4549A, and will be resident for at least 24 hours following the administration of

MHAA4549A. Furthermore, safety laboratory tests relating to the blood chemistries, including liver function tests will be conducted.

An internal monitoring committee (IMC) in combination with a scientific oversight committee (SOC) will provide safety monitoring for the study in addition to the ongoing review of safety by the Medical Monitor and Safety Scientist. See Section 3.1.2 for more information.

In addition to the regularly scheduled safety reviews of the patient data by the IMC and SOC, an additional sentinel safety cohort of the first 30 patients or patients after the first influenza season, whichever occurs first, will be assessed by the IMC and SOC.

The 120-day follow-up period in the Phase 1 and 2a studies allowed for monitoring of subjects for approximately 5 half-lives of MHAA4549A. No ATAs were detected in the Phase 1 study, while one subject *who received placebo* in the Phase 2a study tested positive for ATAs at baseline and post-baseline timepoints as described in Section 1.2.2. The Phase 2b study will also include a safety follow-up period of 60 days and an unlimited collection of all SAEs believed related to MHAA4549A.

Based on the above data and design of this study, the Sponsor concludes that the benefit−risk profile of MHAA4549A in the population with severe influenza is favorable.

2. OBJECTIVES

2.1 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety of MHAA4549A in combination with oseltamivir compared with placebo and oseltamivir in patients with severe influenza A, focusing on the nature, frequency, and severity of serious and non-serious AEs as well as effects on laboratory values, vital signs, electrocardiogram (ECG) parameters, ATAs, *and* other safety biomarkers

2.2 PRIMARY EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To determine the time to normalization of respiratory function of patients dosed with MHAA4549A in combination with oseltamivir compared to patients dosed with placebo and oseltamivir.

2.3 SECONDARY EFFICACY OBJECTIVES

The secondary efficacy objectives for this study are as follows:

- To measure clinical failure, as defined in Section 3.3.3, after 24 hours post infusion of study drug
- To determine the time to clinical resolution of vital signs

- To measure mortality in patients
- To determine changes in the extent and duration of viral shedding in nasopharyngeal samples as a measure of the pharmacodynamic response
- [redacted]
- To measure the duration of hospital and/or ICU stay
- To measure antibiotic usage for respiratory *infections*
- To measure the frequency and severity of the following secondary complications of influenza:
  - Pneumonia (hospital acquired pneumonia [HAP]/ ventilator acquired pneumonia [VAP])
  - Exacerbations of chronic lung disease
  - Myocarditis
  - Acute respiratory distress syndrome (ARDS)
  - Otitis media
  - Other related complications
  - Readmission rates at 30 and 60 days after study treatment
- To measure duration of PPV
- To measure readmission rates

2.4 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objectives for this study are as follows:

- To characterize the PK profile of MHAA4549A in serum

The exploratory PK objectives for this study are as follows:

- [redacted]
- [redacted]

2.5 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- [redacted]
- [redacted]

[redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a Phase 2b *(GV29216),* randomized, double-blind, placebo-controlled study designed to assess the safety and clinical activity of a single IV dose of *3600 mg MHAA4549A or a single IV dose of 8400 mg* MHAA4549A in hospitalized patients with severe influenza A in combination with oseltamivir versus a comparator arm of placebo with oseltamivir. This study is planned to take place in approximately 170 study centers globally.

Initially, GV29216 targeted enrollment into two treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir or a single IV dose of placebo with oseltamivir.

In this version of the protocol, patients will be randomized 1:1*:1 into three treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir, a single IV dose of 8400 mg of MHAA4549A with oseltamivir, or a single IV dose of placebo with oseltamivir.* All patients will receive oseltamivir, a NAI, as standard therapy for a minimum of 5 days after study drug administration. Oseltamivir at doses of 75 mg *twice a day (*BID*)* or 150 mg BID is permitted in order to be consistent with local standard of care practice. Treatment for longer than 5 days is permitted based on local investigator discretion. The patient must start oseltamivir *no later than* 8 hours *after completion* of study drug administration. The study has a planned enrollment of approximately *330* patients globally.

Hospitalized patients with an O_2 or PPV requirement will be evaluated for influenza A infection. Enrollment in this study requires ongoing treatment within 24 hours of hospital admission with one of the following:

- any PPV or

- any supplemental O_2 to maintain oxygen saturation (SpO_2) > 92% (Section 3.3.2)

Patients on PPV should not exceed 45% of the total patients enrolled.

A Sponsor-*approved* influenza test *that includes influenza antigen test* or *influenza* polymerase chain reaction (PCR) test must be used as an aid in the diagnosis of influenza A infection.

[redacted]

At the time of randomization, patients who are eligible for enrollment, as described above, will be randomized to receive *3600 mg* MHAA4549A *or 8400* mg *MHAA4549A* or placebo. Patients will be stratified by *country*, PPV versus supplemental O_2 at randomization, and suspected or confirmed bacterial pneumonia versus no bacterial pneumonia based on the status at randomization.

Eligible patients who are enrolled into the study will receive a single IV infusion of *3600 mg MHAA4549A or a single IV infusion of 8400 mg* MHAA4549A or a single IV infusion of placebo on Day 1. All patients must *begin* study drug *infusion* within 48 hours of hospital admission or sooner if possible. All patients will receive oseltamivir for a minimum of 5 days (10 doses), starting on Day 1, beginning no later than 8 hours after *completion of* study drug administration.

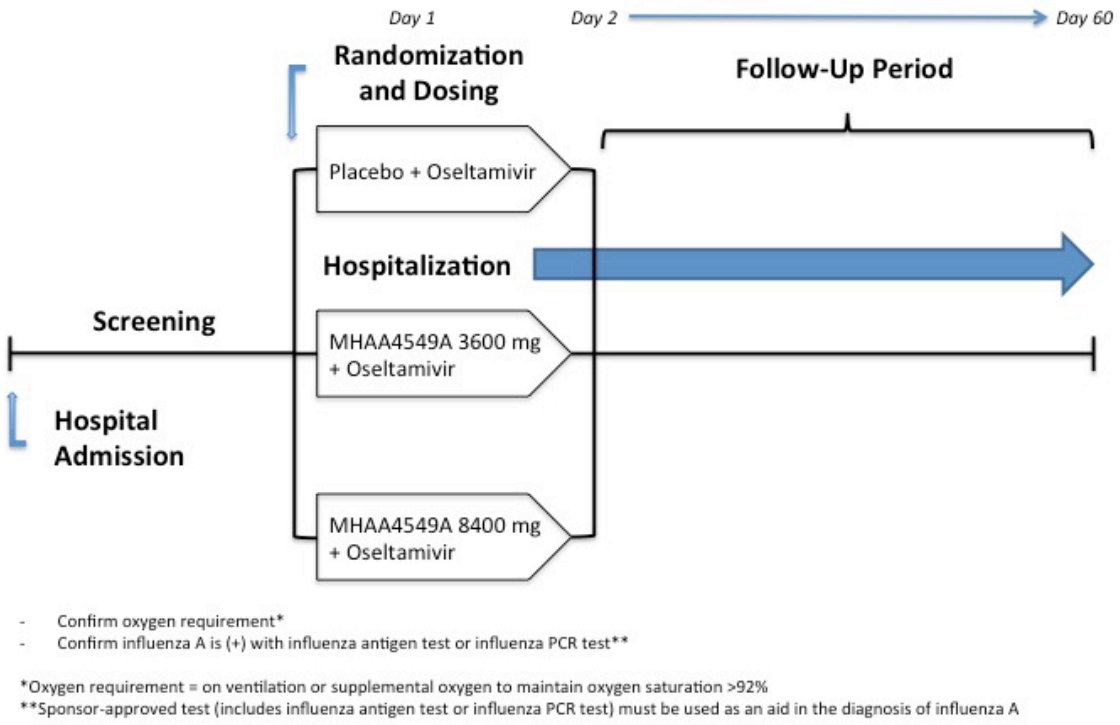
All patients will be followed and evaluated at minimum on a daily basis for the duration of their hospital stay consistent with the planned schedule of assessments. Any suspicion of bacterial superinfection should be thoroughly evaluated including microbiological confirmation, if possible. A follow-up study visit should occur on Day 14 ±1 (if discharged before Day 14); Day 30±4 days (if discharged before Day 30); and Day 60±4 days (if discharged before Day 60).

Safety evaluations will *also* be provided by an IMC and SOC, as defined in the IMC and SOC agreement (see Section 3.1.2). *If after review of available study data, the IMC and SOC conclude that there is a significant toxicity or worsening disease associated with MHAA4549A, they may recommend stopping further enrollment in the study.*

An additional safety cohort of the first 30 patients, or patients from the first influenza season (whichever occurs first), will be assessed by the IMC and SOC. A review of chemistry laboratory test results, AEs, SAEs, vital signs, and deaths will be assessed.

A schedule of assessments is provided in Appendix 1a and Appendix 1b. A diagram of the study design is presented in Figure 1.

Figure 1 Phase 2b Study Design (GV29216)



3.1.2 *Internal* Monitoring Committee and Scientific Oversight Committee

A combined approach with both an IMC and a SOC is proposed to enhance patient safety. The IMC consists of Sponsor representatives from the following functions: Clinical Science, Drug Safety, Biostatistics, and Statistical Programming and Analysis. The IMC members will be unblinded to patient treatment and assignment. The Clinical Science representative on the IMC (IMC Chair) will be a person other than the Study Medical Monitor and will not be involved in the conduct of the study or have any contact with study investigators or site staff. The Study Medical Monitor will remain blinded to individual treatment assignments, unless, in exceptional cases, specific circumstances require Study Medical Monitor unblinding after IMC Chair approval. The Drug Safety Scientist on the IMC will also not be involved in the conduct of the study or have any contact with the study investigators. The Biostatistician and Statistical Programmer are the only IMC members involved in the conduct of the study; however, they do not have any contact with study investigators, and all discussion within the IMC are kept confidential. All other Sponsor and Contract Research Organization personnel involved in the conduct of the study will remain blinded to individual treatment assignments.

The two SOC members are external experts in the field and will be unblinded to treatment allocation. The SOC may be further expanded by the IMC during the course of the study to include additional external experts if the need arises.

A detailed description of the procedures, data flow, and meeting schedule of the IMC and SOC will be provided in a separate IMC and SOC agreement.

3.1.3 End of Study

The end of study is defined as the first day when all patients have had a study completion visit or early termination visit or have otherwise been discontinued from the study.

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Study Design

Hospitalized influenza A infection represents a high unmet need, which, when left untreated, may progress to a more serious disease that may result in significant morbidity and mortality in otherwise healthy adults as well as in vulnerable populations.

This study is designed to estimate the improvement in outcome of a combination regimen of MHAA4549A with oseltamivir compared to a standard of care arm of placebo with oseltamivir. The study population will include hospitalized patients with influenza A requiring O_2 support and/or PPV support within 24 hours of hospital admission.

Study GV29216 will be a Phase 2b study involving approximately 330 patients. The sample size was determined based on an expected clinically meaningful difference of $1-2$ days improvement in time to normalization of respiratory function between the control and treatment arms, assuming a 5 day median time to the time to normalization of respiratory function in the standard of care arm (Blackwood 2011; Premier Inc, Charlotte, NC).

This design ensures that all patients in the trial will receive the current NAI treatment, oseltamivir, as standard of care at a minimum, and will evaluate the clinical benefit of combining MHAA4549A with this standard of care regimen. Therefore, this study aims to identify a regimen that could deliver maximum benefit in this high unmet need disease, while still treating all enrolled patients with the currently accepted standard of care.

3.2.2 Rationale for Patient Population and Primary Endpoint

Severe influenza, for the purpose of this study, is defined as requiring one of the following treatments: any supplemental O_2 to maintain an $SpO_2 > 92\%$ or PPV. PPV is defined as any mechanical positive pressure device to maintain oxygenation; this can include positive pressure mask and intubation. A Sponsor-*approved* influenza test*, which includes influenza antigen test* or *influenza* PCR *test,* must be used as an aid in the diagnosis of influenza A infection.

This patient population was chosen based on the rationale that respiratory failure is a hallmark of influenza and a major driver of morbidity and mortality, as well as hospitalization. The recovery from ventilator support has been shown to be directly proportional to time spent in the ICU (Blackwood 2011; Premier Inc, Charlotte, NC). Based upon an analysis of morbidity and mortality, the patient population that requires supplemental O_2 or ventilation on their first day of admission was determined to have a high unmet medical need as they have an estimated mortality of 9%-32%, and 27% require admission to the ICU, according to analysis of a database of over 70,000 hospitalized patients in the US from 2005-2012 (Premier Inc, Charlotte, NC).

The proposed primary efficacy outcome measure in this study is "Time to normalization of respiratory function," defined as oxygen saturation $\geq 95\%$ *without oxygen supplementation*. Support for use of *a* respiratory endpoint in this population comes from recently published data demonstrating that a composite endpoint that captured respiratory rate, fever, heart rate, and blood pressure resolution was primarily driven by the respiratory component of the endpoint (Marty et al. 2014). *Given that influenza infections generally do not cause systemic infections and influenza disease is restricted to the respiratory tract, the Sponsor believes that the primary endpoint represents a clinically meaningful outcome in this patient population (as shown by analysis of PREMIER database) and measures an important physiologically relevant pharmacodynamic response parameter of MHAA4549A. This endpoint is a measure of patient function, measures a symptom that represents a serious consequence of influenza, and is consistent with clinically relevant endpoints discussed in the US Food and Drug Administration (FDA) Guidance, "Influenza: Developing Drugs for Treatment and/or Prophylaxis" (FDA 2011).*

3.2.3 Rationale for Control Group and Treatment Window

In this study, the standard of care regimen for the control or comparator group is oseltamivir, an NAI. In the treatment groups, MHAA4549A will be dosed in addition to oseltamivir. Either 75 mg or 150 mg orally BID oseltamivir for a minimum of 5 days is permitted following treatment with MHAA4549A. Treatment for longer than 5 days is permitted based on local investigator discretion (WHO 2005, Fiore 2011, CDC 2015). The oseltamivir dosing regimen *is* listed in Table 2. This control treatment was based on consideration of safety, ethics, and efficacy for treatment of severe influenza and is consistent with guidelines for antiviral treatment of hospitalized patients with influenza (Harper et al. 2009, Fiore 2011).

Table 2 Oseltamivir Dosing Regimen

Neuraminidase Inhibitor	Dosing Regimen	Duration of Therapy
Oseltamivir	75 mg or 150 mg oral twice daily [a]	5 days [b]

[a] 75 mg or 150 mg dose at the discretion of the investigator, and dose must be documented. Capsules can be opened and the granules administered via nasogastric tube, if required. For renal dose adjustments, follow local standard of care practice/local package insert and document in the eCRF.

[b] Longer treatment times are at the discretion of the investigator (WHO 2005, Fiore 2011, CDC 2015).

If oseltamivir resistance is highly suspected or identified during treatment *or oseltamivir route of administration challenges are encountered, then* following discussion with the Sponsor medical representative, an alternative NAI to oseltamivir may be used.

From a safety standpoint there are no expected drug interactions between MHAA4549A, a monoclonal antibody, and any NAI, which are small molecule drugs that bind to a different viral protein than MHAA4549A. In the Phase 2a challenge study, all subjects that were dosed with MHAA4549A also received a 5-day course of oseltamivir starting on Day 7. There were no safety effects attributable to the combination when the drugs were present concurrently. The pharmacokinetics of oseltamivir and its potential interaction with MHAA4549A are being assessed from *the* Phase 2a *study*.

For this Phase 2b study, a combination of MHAA4549A and oseltamivir was determined to be the most clinically feasible treatment regimen, both from an ethical as well as a practical perspective. The treatment of all patients with oseltamivir ensures that all patients will receive *the* standard of care. *G*iven the high morbidity and mortality of hospitalized patients with influenza A along with guidelines from Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) *it is recommended that* NAIs are the standard of care for hospitalized patients with influenza A (Harper et al. 2009; CDC Website). Further*more*, pre-clinical efficacy data from a study using MHAA4549A and oseltamivir in combination showed a potential synergistic effect of both compounds which may be due to the different and potentially complementary mechanisms of action, i.e. targeting viral HA and neuraminidase (NA).

Dosing of MHAA4549A is confined to a treatment window designed for best expected treatment success and to ensure that any observed effects can be attributed to the study drug with high confidence. MHAA4549A shall only be dosed within 5 days of onset of *symptoms (including fever, chills, malaise, dry cough, loss of appetite, myalgias, coryza, or nausea),* no later than 48 hours after admission to the hospital*, and if a subject has taken less than a total of 6 doses (3 doses for peramivir) of approved anti-influenza therapy from onset of symptoms.* This proposed window is supported by data demonstrating that hospitalized influenza patients benefit from NAI treatment even at 5 days from onset *of symptoms* (Louie et al. 2012). *The patient must start*

standard-of-care oseltamivir no later than 8 hours after completion of MHAA4549A administration.

3.2.4 Rationale for MHAA4549A Dosage

A single IV dose of 3600 mg *MHAA4549A or a single IV dose* of *8400 mg* MHAA4549A was selected to assess the efficacy of MHAA4549A and to provide data for further clinical development. The selection of dose in this study for severely ill patients was based on the observed human pharmacokinetics in Phase 1 and the relationship between the pharmacokinetics, pharmacodynamics, and efficacy observed in a Phase 2a human challenge model of influenza. MHAA4549A was shown to be safe and well-tolerated at all dose levels (ranging from 1.5 mg/kg to 45 mg/kg for Phase 1 and 400-3600 mg for Phase 2a) through a follow-up period of 120 days post-dose in the Phase 1 and Phase 2a study. The dose *levels selected for* this study *were* determined following analysis of data from the Phase 2a study *(*GV28985*)*, which demonstrated the following:

- The 3600-mg dose demonstrated a significant decrease in viral shedding in upper respiratory samples. Based on current interim analysis data, there was a 97.5% (p=0.0051) decrease in *area under the viral load-time curve (*AUEC*)* and a 77.3% decrease in peak viral load by qPCR measurement compared to the placebo group.
- Symptom data in the Phase 2a study showed a decrease in the *area under the serum concentration-time curve (*AUC*)* of symptoms scores for the 3600-mg dose, as illustrated in Table 1, which is consistent with the virological results.
- *When compared to placebo, a decrease in viral shedding was observed at the 400 mg dose but not at the 1200 mg dose, which may be due to variability in the challenge model and differences in infection rate, infection peak, virus level in the nasopharynx, nasal pharmacokinetics, immune status, and other inter-subject differences.*
- There *were* no safety concerns at *any* dose level *associated with MHAA4549A.*
- Hospitalized patients generally have a longer duration of viral shedding and significantly more viral burden in the lower lung compartments; therefore, high concentrations of monoclonal antibody are likely needed to achieve sufficient occupancy of the virus binding sites in the upper and lower respiratory compartments. Furthermore, higher concentrations of monoclonal antibody may mitigate the risk of resistance for MHAA4549A, *supporting addition of the 8400 mg MHAA4549A treatment arm.*
- *Exploratory exposure-response analysis of GV28985 indicated that higher exposure appears to be associated with improved efficacy. Volunteers with nasal maximum concentration greater than the median value had shorter time to resolution of viral shedding compared with volunteers in the placebo group (median: 75.8 hours vs. 113.7 hours). However, volunteers with a nasal maximum concentration less than the median value had similar time to resolution of viral shedding compared with volunteers in the placebo group (median 113.7 hours vs 112.1 hours).*

The Phase 2a challenge study (GV28985) confirmed proof of activity in decreasing area under viral load-time curve, consistent with symptom data at the 3600-mg dose level. GV29216 will assess severely ill patients who may be infected with various influenza strains, have a higher viral burden and longer duration of viral shedding than the healthy volunteers in Study GV28985, and who may, therefore, require doses higher than 3600-mg. As a result, an ongoing, Phase 1 (GV29609) study was initiated to evaluate the safety and tolerability of two single IV doses of 8400 mg and 10800 mg MHAA4549A as compared to placebo when administered to 14 healthy volunteers. The starting dose of 8400 mg was selected based on simulations from a semi-quantitative PK model (Figure 2) developed from the Phase 2a challenge study, which suggests that 8400 mg may be the minimum dose that is expected to show a separation of nasal exposure from a dose of 3600 mg. This simulation assumes that pharmacokinetics can be extrapolated at doses above 3600 mg and that the PK profile in severely ill patients is similar to the PK profile of healthy volunteers in the Phase 2a challenge study. The highest proposed dose of 10800 mg was chosen in GV29609 to provide safety coverage for those exposures that might be reached in a 40-kg individual dosed with a flat dose of 8400 mg. Preliminary analysis of unblinded safety data up to day 57 shows that the 8400 mg and 10800 mg treatment groups are safe and well tolerated. In subjects who received 8400 mg MHAA4549A, 3 of 4 subjects reported 12 AEs. In subjects who received 10800 mg MHAA4549A, 4 of 4 subjects reported 7 AEs. In subjects who received placebo, 2 of 6 subjects reported 5 AEs. All AEs were reported as mild except for an unrelated moderate AE of an increase in creatinine kinase in one subject who received 10800 mg MHAA4549A. There were no SAEs and no subjects have discontinued the study for any reason. Headache was the most common adverse event. Headache was reported by 3 subjects (37.5%) who received 8400 mg MHAA4549A, 1 subject (12.5%) who received 10800 mg MHAA4549A, and 2 subjects (33.0%) who received placebo.

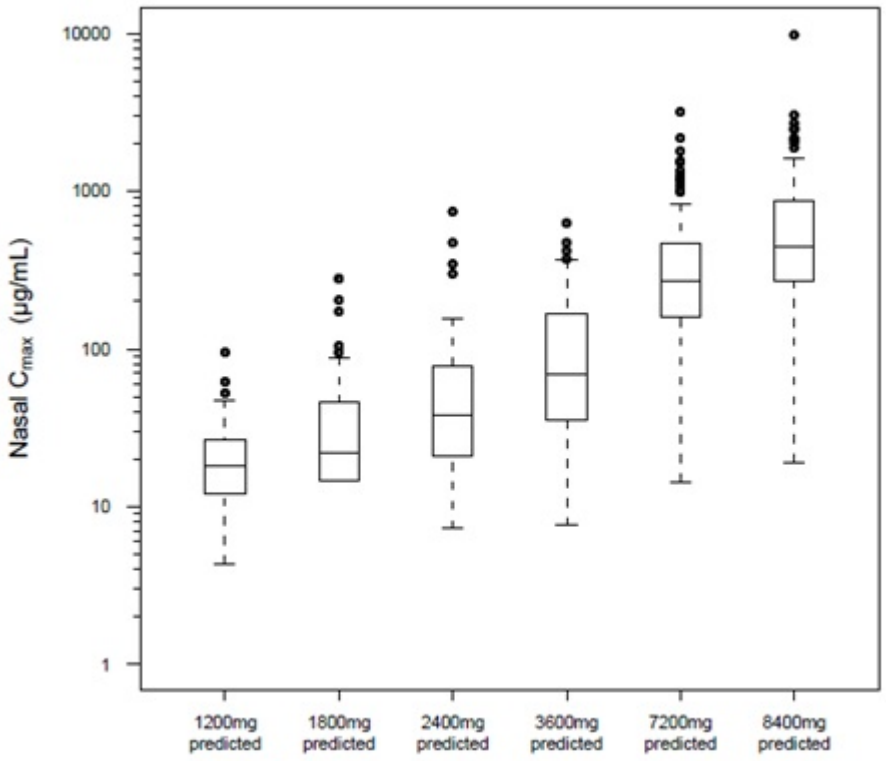
Nonclinical safety data do not show any expected or unexpected toxicity. Weekly administration of MHAA4549A (total of 5 doses) in Sprague-Dawley rats was well tolerated up to 150 mg/kg (the highest dose tested). Ex vivo tissue cross-reactivity study data showed no specific binding of MHAA4549A to any of the human or rat tissues examined.

Therefore, the 8400-mg dose is expected to be safe based upon previous nonclinical and clinical safety assessments and will be included in this Phase 2b study for further dose ranging.

*Although t*he *Phase 1 study (GV28916)* was conducted using body-weight based dosing, *the subsequent Phase 2a study (GV28985) and high-dose Phase 1 study GV29609 used* a fixed dosing strategy. Thus, the fixed dosing regimen will be used for this study, given the *comparable MHAA4549A PK profiles, the* practical advantages, and *the* positive safety profile of MHAA4549A to date. Further, fixed dosing is generally recommended

with monoclonal antibodies, due to their minimal PK variability (Bai et al. 2012). The PK variability introduced by different dosing regimens (i.e., body-weight based dosing versus fixed dosing) is moderate relative to the variability generally observed in pharmacodynamics, efficacy, and safety and would not be expected to be clinically meaningful.

Figure 2 *Predictions from a Semi-Quantitative Pharmacokinetic Model of Nasal Exposure*



Note: The bottom and top of the box represent the 25th and 75th percentile, and the band inside the box is the median. The upper whisker is the 1.5 interquartile range (IQR) of 75th percentile and the lower whisker is the 1.5 IQR of 25th percentile. The dot is an outlier.

3.2.5 Rationale for Biomarker Assessments

[redacted]

[redacted]

[redacted]

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- AEs and clinical laboratory abnormalities
- Vital signs, physical findings, ATAs, and clinical laboratory results during and following administration of MHAA4549A

3.3.2 Primary Efficacy Outcome Measures

The primary efficacy outcome measures for this study are as follows:

- Time to normalization of respiratory function defined as:
  - The time to cessation of O_2 support resulting in a stable $SpO_2 \geq 95\%$ (see Appendix 2 for details)

3.3.3 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- Clinical failure after 24 hours post-infusion of study drug; defined as:
  - Progression to increased O_2 requirement defined by an increase in oxygen supplementation from low flow oxygen (2 – 6 L/min) to high flow oxygen (> 6 L/min) or from oxygen supplementation alone to any PPV *or extracorporeal membrane oxygenation (ECMO)*
  - Progression to ICU
  - Prolonged ventilation or O_2 support defined by > 2 weeks, or
  - Death
- Time to clinical resolution of vital signs (3/5 criteria must be met):
  - $SpO_2 \geq 95\%$ without supplemental O_2
  - *Respiratory rate <24 breaths per minute without supplemental O_2*

  - Core temperature < 37.2°C immediately prior to receipt of any antipyretic drug, and at least 6-8 hours from the last dose of antipyretic or core temperature > 36°C in patients who are initially hypothermic
  - Heart rate (HR) < 100 $beats$/minute
  - Systolic blood pressure (SBP) > 90 mmHg
- All-cause mortality at Day 14, Day 30, and Day 60
- Influenza A viral load in nasopharyngeal samples
  - AUEC *(qPCR)*
  - Peak viral load *(qPCR)*
  - Time to resolution of infection *(qPCR)*
  - [redacted]
- Duration of hospitalization
- Duration of ICU stay
- Antibiotic usage for respiratory infections
- Complications of influenza:
  - Pneumonia (HAP/VAP)
  - Exacerbations of chronic lung disease
  - Myocarditis
  - ARDS
  - Otitis media
  - Other related complications
- All-cause readmission at Day 30 and Day 60
- Duration of ventilation

3.3.4 Pharmacokinetic Outcome Measures

The primary PK outcome measures for this study are as follows:

- PK parameters for MHAA4549A in serum including total exposure (i.e., AUC), maximum observed concentration (C_{max}), clearance, half-life, and volume of distribution, when appropriate, as data allow

The exploratory PK outcome measures for this study are as follows:

- [redacted]
- [redacted]

3.3.5 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

This study aims to enroll approximately *330* men and women and is designed to assess the safety and clinical activity of a single IV administration of *3600 mg MHAA4549A or a single IV administration of 8400 mg* MHAA4549A in adult patients hospitalized with severe influenza A.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Hospitalized men or women ≥ 18 years of age on the day of signing the informed consent or obtaining surrogate consent from an authorized representative

- Diagnosis of influenza A where *a Sponsor-approved influenza test is* used as *an aid in* diagnosis. *A Sponsor-approved influenza test includes:*
  - *Influenza antigen test –OR–*
  - Influenza PCR test
- One of the following markers of severity within 24 hours of hospital admission:
  - Requirement for PPV – OR –
  - Requirement for O_2 supplementation to maintain $SpO_2 > 92\%$
- A negative urine or serum pregnancy test for women of child-bearing potential
- Patients of reproductive potential must agree to use reliable means of contraception as described below as a minimum (adherence to more stringent local requirements may be required):
  - *For women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use two adequate methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment period and for at least 120 days after the last dose of study drug*

    Abstinence is only acceptable if it is in line with 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.*

    Barrier *methods must always be supplemented with the use of a spermicide.*

    Examples of contraceptive methods with a failure rate of *< 1% per year include tubal ligation, male sterilization, hormonal implants, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.*

    Male partners who have had a vasectomy should have the appropriate post-vasectomy documentation available of the absence of sperm in the ejaculate. The vasectomized male partner should be the sole partner for that patient.
  - *For men: agreement to remain abstinent or use a condom during the treatment period and for at least 30 days after the last dose of study drug and agreement to refrain from donating sperm during this same period*

    Men with a pregnant partner must agree to remain abstinent or use a condom for the duration of the pregnancy.

    Abstinence is only acceptable if it is in line with 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.
  - Non-reproductive potential is defined below (but could be superseded by local definitions, if they are more stringent):

Women who are postmenopausal (i.e., spontaneous amenorrhea for the past year confirmed by a *follicle stimulating hormone [*FSH*]* level greater than 40 mIU/mL unless the patient is receiving a hormonal therapy for their menopause)

Women who are surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)

Men who are surgically sterile (*i.e.,* castration)

4.1.2 Exclusion Criteria

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

- Pregnant or lactating, or intending to become pregnant during the study
  - Women who are not postmenopausal (*postmenopausal defined as* ≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 2 days prior to initiation of study drug.
- Hypersensitivity to monoclonal antibodies or to the active substance or any excipients of MHAA4549A study drug
- Hypersensitivity to the active substance or to any excipients of oseltamivir
- Investigational therapy within the 30 days prior to study treatment
- Received prior therapy with any anti-influenza monoclonal antibody therapy (including MHAA4549A) 8 months prior to study treatment
- Current treatment (within 7 days of dosing) with *probenecid*, amantadine, or rimantidine
- Patients who have taken more than a total of 6 doses (*3 doses of peramivir*) of anti-influenza therapy (e.g., oseltamivir, zanamivir*, peramivir*) in the period from onset of symptoms and prior to *study treatment*
- Admission > 48 hours prior to study treatment
- Onset of influenza symptoms *(including fever, chills, malaise, dry cough, loss of appetite, myalgias, coryza, or nausea)* > 5 days prior to study treatment
- Positive influenza B or influenza A + B infection within 2 weeks prior to study treatment
- High probability of mortality in the next 48 hours as determined by the investigator
- Patient requiring home or baseline oxygenation therapy
- Patient with history of chronic lung disease resulting in baseline $SpO_2 \leq 95\%$
- Patient on a chronic dose of corticosteroids exceeding 10 mg/day of prednisone or equivalent steroid dose for a duration of greater than 14 days within 30 days of entry into study
- *Creatinine clearance ≤10 mL/min*
- *Patients who received nasally administered influenza A vaccine within the last 7 days*

- Patients with the following significant immune suppression:
  - Bone marrow or solid organ transplant in the previous 12 months
  - Cancer chemotherapy in the previous 12 months
  - HIV infection with most recent CD4 $<$ 200 cells/mL
  - Other significant immune suppression as determined by the investigator in discussion with the Sponsor Medical Monitor or representative
- Patient on ECMO at time of randomization
- Any disease or condition that would, in the opinion of the site investigator or Sponsor, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The randomization of patients will be managed by a central Interactive Voice and Web Response System (IxRS) through use of a dynamic hierarchical algorithm *which includes a random component.* The treatment assignments will be unblinded to selected Sponsor personnel to facilitate ongoing monitoring of safety and tolerability, including members of the IMC and SOC.

All patients will be randomly assigned to receive *3600 mg* MHAA4549A*, 8400* mg *MHAA4549A,* or placebo at a 1:1*:1* ratio stratified by *country*, whether patient is on PPV vs supplemental O_2 at randomization, and whether the patient has suspected or confirmed bacterial pneumonia vs no bacterial pneumonia at randomization. *Initially GV29216 randomly assigned patients to receive either 3600 mg MHAA4549A, or placebo at a 1:1 ratio. The updated randomization scheme takes into account the numbers already allocated to these two arms and strata prior to allocating to the three arm design so that by the end of the study there will be an approximate 1:1:1 allocation between the three arms.*

All patients will receive oseltamivir (*as described in Table 2*) for a minimum of 5 days. Treatment for longer than 5 days is permitted based on local investigator discretion.

Unblinded personnel (i.e. unblinded site pharmacist or other designated, qualified unblinded study personnel) at each study site will prepare the IV infusions of study drug, as described in Section 4.3.3. The Sponsor will provide masking bags and blinded study personnel will administer the study drug. The other parties who are involved in the conduct of the study (i.e., patients and blinded site personnel) will remain blinded to patient-specific treatment assignments until the final database lock after the completion of the study.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this trial.

Bioanalytical laboratory personnel responsible for performing PK assays will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed. Samples from patients assigned to the comparator arm will not be analyzed except by request (e.g., to evaluate a possible error in study drug administration).

If unblinding is necessary for patient management (e.g., in the case of a SAE for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code in IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study drug for any other reason, they should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a SAE).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all suspected unexpected serious adverse reactions (SUSAR)(see Section 5.4) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 MHAA4549A and Placebo

The Sponsor will supply MHAA4549A *and* matching placebo. For information on the formulation, packaging, and handling of MHAA4549A and placebo, see the Pharmacy Manual and the MHAA4549A Investigator's Brochure.

The MHAA4549A vial delivers 10 mL (500 mg) of drug product solution, but may contain more (approximately 10.3 mL) than the stated volume to enable delivery of the entire 10 mL volume. MHAA4549A is formulated as 50 mg/mL in 10 mM sodium succinate, 240 mM sucrose, and 0.02% (w/v) polysorbate 20 at pH 5.5 and is contained in a 15 mL forma vitrum (USP/PH. Eur. Type 1) glass vial. The drug product is suitable for single use only and contains no preservatives.

Placebo for MHAA4549A has the same composition as the drug product (without MHAA4549A) and is supplied in an identical vial configuration. The placebo contains no preservatives and is suitable for single-use only. Placebo is formulated as 10 mM sodium succinate, 240 mM sucrose, and 0.02% polysorbate 20 at pH 5.5 in a total volume of 10 mL in a 15 mL forma vitrum (USP/PH. Eur. Type 1) glass vial.

MHAA4549A and placebo are supplied in identical blinded vials labeled with unique kit numbers. IxRS will assign kit numbers for each treatment arm; all treatment arms will be assigned the same total number of vials for each treatment, and the same preparation instructions. Placebo is identical to active MHAA4549A in formulation but does not contain active drug substance.

4.3.1.2 Oseltamivir (Tamiflu®)

Oseltamivir (Tamiflu®) is an influenza NAI indicated for treatment of acute, uncomplicated influenza. *The Sponsor will provide oseltamivir capsules for up to a 10-day treatment course.* For information on the formulation, packaging, and handling of oseltamivir; see the local prescribing information for oseltamivir.

Storage: Capsules should be stored at 25°C (77.7°F); excursions permitted to 15° to 30°C (59° to 86°F).

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 MHAA4549A and Placebo

The randomization of patients will be managed by a central IxRS. All patients will be randomly assigned to receive either a single dose of MHAA4549A 3600 mg IV or *MHAA4549A 8400 mg IV or* placebo IV at a 1:1*:1* ratio.

Administration of MHAA4549A or placebo will be performed in a setting with emergency medical equipment and personnel who are trained to monitor for and respond to medical emergencies. A qualified physician will be on site during study drug administration for all patients.

A single dose of MHAA4549A or placebo will be delivered by IV infusion following dilution in 0.9% normal saline over approximately *120* minutes. Study drug should be delivered using a 0.22 μm in-line filter. Compatibility testing has shown that MHAA4549A is stable when diluted in 0.9% normal saline in a polyvinylchloride *bag*, polyolefin bag, or ethylene vinyl acetate bag (EVA), at *concentrations* of 0.24 mg/mL up to 27.0 mg/mL. Study drug must be administered within the treatment window outlined in Section 3.1.1. Further detailed instructions for preparation of study drug can be found in the Pharmacy Manual.

There are no recommended dosage modifications for MHAA4549A since it is a single infusion. Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. General supportive measures will be taken to manage any AEs associated with overdose. Patients experiencing such AEs will be followed up clinically until the event has resolved.

Trained clinical site staff responsible for adequate and accurate study drug administration, accounting, and management will administer study drugs to patients. Study drug preparation and dosing instructions will be provided to each site. The exact times of study drug administration will be recorded in the relevant dispensing/administration logs and patient's source notes. Any noncompliance or problems with study drug administration will be recorded in the patient's source notes and reported to the Sponsor if appropriate.

4.3.2.2 Oseltamivir-Neuraminidase Inhibitor (NAI)

The Sponsor will *supply* oseltamivir (Tamiflu®) for this study for up to a 10-day course. Either 75 mg or 150 mg of oseltamivir will be administered twice daily as described in Section 3.1.1. Capsules can be opened and the granules administered via nasogastric tube, if required. *Doses should be captured in the eCRF.*

Any overdose or incorrect administration of oseltamivir should be noted on the oseltamivir Administration eCRF. AEs associated with an overdose or incorrect administration of oseltamivir should be recorded on the Adverse Event eCRF.

Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary, empty (used) oseltamivir packets and unused oseltamivir capsules to the study site at the next follow up visit. Patients will record the date and time when each oseltamivir capsule is administered.

4.3.3 Investigational Medicinal Product Accountability

Investigational medicinal products (IMPs) required for completion of this study (i.e., MHAA4549A and oseltamivir) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMP will be stored in a secure pharmacy or locked area with access limited to authorized personnel, in accordance with the details provided in the Investigator's Brochure and Pharmacy Manual. Upon receipt, MHAA4549A and placebo vials must be refrigerated at 2°C to 8°C until use. MHAA4549A does not contain antimicrobial preservatives; therefore, care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation. Dilute under appropriate aseptic conditions using 0.9% normal saline. The solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use should not exceed 24 hours at 2 to 8°C and/or 4 hours at ambient temperature (18°C – 24°C). If the dose solution is stored at 2°C – 8°C, it should be removed from refrigeration and allowed to reach room temperature prior to administration. If the infusion is interrupted and the combined ambient temperature storage and interruption time exceeds 4 hours, prepare a new dose solution to resume the infusion (see the Pharmacy Manual). Protect dose solutions from heat and intense light.

The total duration from the preparation of dose solutions to the end of infusion should not exceed 24 hours. Vials are intended for single use only; therefore, any remaining solution should be discarded (see the Pharmacy Manual).

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor or their delegate with the appropriate documentation. The site's method of IMP destruction must be agreed to by

the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.4 POST-TRIAL ACCESS TO MHAA4549A

As this is single dose administration, Genentech does not intend to provide MHAA4549A to patients after the conclusion of the study or any earlier withdrawal. Patients may or may not be eligible for any potential subsequent trials of MHAA4549A under a separate protocol.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:
http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.5 CONCOMITANT THERAPY AND FOOD

4.5.1 Permitted Therapy

Concomitant medication includes any medication (e.g., prescription drugs, over the counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 30 days prior to screening to the study completion/discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. For any NAIs (e.g., oseltamivir, peramivir, zanamivir, laninimavir) that have been taken prior to study drug therapy, the number of doses and duration of therapy must be recorded.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

All therapies required for management of the patient's acute illness are permitted except for those listed below in Section 4.5.2.

4.5.2 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 7 days prior to study treatment, unless otherwise specified below: probenecid, amantadine, or rimantidine.

Use of other NAIs, including but not limited to oseltamivir, zanamivir, and peramivir, are prohibited during the study, but allowed up to *a total of* 6 doses *(3 doses for peramivir) in the period from onset of symptoms and* prior to study treatment as outlined in the exclusion criteria. *Patients must start standard-of-care oseltamivir no later than 8 hours after completion of MHAA4549A administration.* If oseltamivir resistance is highly suspected or identified during treatment or *if oseltamivir route of administration*

challenges are encountered then, following discussion with the Sponsor's medical representative, an alternative NAI to oseltamivir may be used.

4.5.3 Prohibited Food

There are no prohibited foods for this study.

4.6 STUDY ASSESSMENTS

Please see Appendix 1a and Appendix 1b for the schedule of assessments performed during the study.

4.6.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study specific screening tests or evaluations. Informed consent by authorized representatives may be obtained only if allowed by and in accordance with local regulations and Independent Review Board (IRB)/Independent Ethics Committee (IEC) policies and procedures. Informed Consent Forms (ICF) 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 randomization. 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.

4.6.2 Diagnostic Testing for Enrollment

All hospitalized patients with severe influenza A must be assessed for disease confirmation prior to and enrollment into the study. A Sponsor-approved influenza test is required as an aid in the diagnosis of influenza A infection. This requires a nasopharyngeal swab be introduced into one nostril. Note that the influenza antigen test or influenza PCR test result must be available within the 48 hour screening window.

4.6.3 Medical History and Demographic Data

Medical history includes clinically significant diseases and procedures, including chronic respiratory disease, infections, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days prior to the screening visit. A careful assessment of the patient's baseline SpO_2 will be made especially if the patient has a history of severe chronic lung disease.

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

4.6.4 Priority of Assessments

When events warrant, or in the opinion of the investigator, safety issues become paramount, safety assessments will always have priority over all other measurements and procedures. Under routine circumstances, however, PK, nasal virological, and biomarker serum/plasma samples have priority over other measurements. The timing and number of safety measurements may be modified based on clinical evaluations.

Assessments on Day 1 must be concluded prior to dosing as specified in Appendix 1a. Any screening assessments completed prior to consent as standard of care do not need to be repeated if done within the screening period.

4.6.5 [redacted]

[redacted]

4.6.6 [redacted]

[redacted]

4.6.7 Physical Examinations

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

At protocol designated visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed which *include*, at a minimum, evaluation of general appearance, dermatological examination of the injection sites, evaluations directed by patient-reported symptoms, and any other evaluations that the investigator deems clinically relevant. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as AEs, if appropriate, on the adverse event eCRF.

4.6.8 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressures after the patient has been in a seated or supine position for > 5 *minutes*. Patients in intensive care may have vital signs assessed following local procedures, but those procedures should be captured in the eCRF in accordance with the eCRF instructions.

4.6.9 Oxygen Saturation Measurements

To ensure that the respiratory status is well recorded, the following daily measurements will be performed. Unless clinically contraindicated, all patients will have their SpO_2 and corresponding respiratory assessments recorded daily in the morning between 6 am – 12 pm local time. Patients on low flow O_2 will have a daily trial of their SpO_2 while on and off the supplementation, as outlined in Appendix 2, and both values will be recorded.

If the patient is on oxygen supplementation, SpO_2 measured by pulse oximetry and the corresponding respiratory assessments (e.g., FiO_2, flow rate) will be recorded. If the patient is on PPV, partial pressure of *arterial* O_2 (PaO_2) and the corresponding respiratory assessments (e.g., FiO_2, ventilator mode, ventilator respiratory rate, positive end expiratory pressure) will be recorded. *If clinically appropriate (i.e., the patient is on non-invasive PPV), the conversion table in Appendix 11 may be used for* PaO_2.

4.6.10 Laboratory, Biomarker, and Other Biological Samples

Samples for the laboratory tests listed in Table 3 and Table 4 will be sent to the study site's local laboratory for analysis at screening and during the study, respectively.

Table 3 Laboratory Tests at Screening

Hematology:	**Clinical Chemistry:**
Hemoglobin	Thyroid stimulating hormone (optional)
Hematocrit	
Erythrocyte count (RBC)	**Serology:**
Leukocytes (WBC)	HIV Serology
Neutrophils, segmented & bands	
Lymphocytes	**Misc:**
Monocytes	Pregnancy Test (urine or serum; women of child-bearing potential)
Eosinophils	
Basophils	
Platelets	

Note: Investigators must document their review of each laboratory report by signing (or initialing) and dating each report.

Table 4 Laboratory Tests During the Study

Hematology:	**Clinical Chemistry (Blood):**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Bicarbonate
Leukocytes (WBC)	Chloride
Neutrophils, segmented & bands	Calcium
Lymphocytes	Phosphorus
Monocytes	Magnesium
Eosinophils	Glucose
Basophils	Urea nitrogen (BUN) or urea
Platelets	Creatinine
	Total cholesterol
	Total protein
Coagulation:	Albumin
Activated partial thromboplastin time (APTT)	Total bilirubin
Prothrombin time (PT)	Alkaline phosphatase
International Normalized Ratio (INR)	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
Urinalysis:	Amylase
pH	Gamma-glutamyl transpeptidase (GGT) (if clinically indicated)
Specific gravity	
Glucose	C-reactive protein (CRP) (optional)
Protein	Erythrocyte Sedimentation Rate (ESR) (optional)
Ketones	
Blood	
Bilirubin	**Misc:**
Nitrite	Pregnancy Test (if clinically indicated)
Leukocyte esterase	
Microscopic examination (if clinically indicated)	

Note: Investigators must document their review of each laboratory report by signing (or initialing) and dating each report.

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

- [redacted]
- Serum samples for ATA testing (see Appendix 1a and Appendix 1b)

- [redacted]

Samples for exploratory research assays will be collected as described in the Schedule of Assessment (see Appendix 1a and Appendix 1b).

- [redacted]
- [redacted]
- [redacted]

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

4.6.11 Electrocardiograms

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

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

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The following should be recorded in the appropriate eCRF: HR, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5

minutes, and ECG monitoring should continue until QT interval corrected using Fridericia's formula (QTcF) has stabilized on two successive ECGs. The Medical Monitor should be notified. If QTcF is not available, QTcB may be recorded. Standard of care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 4.9.2. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, medications known to prolong the QT interval, severe bradycardia).

4.6.12 [redacted]

[redacted]

[redacted]

[redacted]

4.6.12.1 [redacted]

[redacted]

[redacted]

4.6.12.2 [redacted]

[redacted]

4.6.12.3 [redacted]

[redacted]

4.6.12.4 [redacted]

[redacted]

4.7 APACHE AND SOFA SCORES

Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) scores are for patients that are admitted into the ICU. These assessments are not required for study conduct or entry but should be collected if available. The initial scores for APACHE and SOFA should be taken within 24 hours of entry into the ICU and at *the* time points *specified* in Appendix 1a.

For the calculation of the initial APACHE and SOFA scores, the worst values in the first 24 hours of ICU admission should be used. SOFA scores are only for patients admitted into the ICU that have available data for calculation (i.e., partial pressure of arterial oxygen/fraction of inspired oxygen [PaO_2/FiO_2] in mmHg). See Appendix 7 for SOFA score calculation.

4.8 OSELTAMIVIR MEDICATION DIARY

Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary, empty (used) oseltamivir packets, and unused oseltamivir capsules to the study site at the next follow up visit.

Patients will record the date and time when each oseltamivir capsule is administered.

4.9 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.9.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.9.2 Study Treatment Discontinuation

Patients must discontinue MHAA4549A infusion and therefore treatment if they experience any of the following:

- *Life threatening infusion*-related reactions

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

- Pregnancy
- Serious skin/hypersensitivity reactions

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

The IMC and SOC may recommend to permanently discontinue dosing for all patients within one or both study arms in the event of a general safety concern.

4.9.3 Study Completion/Early Discontinuation Visit

Patients who complete all study visits through Day 60 are considered to have completed study. All patients who discontinue from the study early will be asked to complete all assessments for the early discontinuation visit. Please see Schedule of Assessments provided in Appendix 1a for assessments performed at the Study Completion/Early Discontinuation visit.

4.9.4 Study and Site Discontinuation

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

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

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study. The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

MHAA4549A is not approved and is currently in clinical development. Thus, the entire safety profile is not known at this time. The safety plan for this study is based upon preclinical data and the previous Phase 1 and Phase 2a (interim) studies and is designed to ensure patient safety. It will include specific eligibility criteria and monitoring assessments as detailed below and in Section 4.1.

The investigator, in consultation with the Sponsor, is responsible for assuring the safety of study participants who have entered this study and for taking appropriate action concerning any event that seems unusual, even if this event may be considered to be an unanticipated benefit to the study participant. The investigator will be responsible for a clinical assessment of the study participants before discharge from the study, and for the establishment of a discharge plan, if needed.

During the study, the incidence and nature of adverse events, serious adverse events, and laboratory abnormalities will be assessed. An ongoing blinded review of safety will be carried out by the Medical Monitor and a drug safety scientist. An unblinded review of safety will be performed on an ongoing regular basis by the IMC and SOC as described in the IMC and SOC agreement.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

Adverse events will be monitored throughout the entire study (enrollment through Day 60 or Early Discontinuation).

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Fatal (i.e., the adverse event actually causes or leads to death)

- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS); see Section 5.3.3, Appendix 8, and Appendix 9); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Non-serious adverse events of special interest (AESI) are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study 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 (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below
- Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in

a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- Adverse events associated with suspected cases of infusion-related reactions (IRR) which occur within 24 hours of study drug administration and may show the following signs and symptoms (for guidance on reporting AEs associated with IRR, see Section 5.3.5.1):
  - Fever and/or shaking chills
  - Flushing and/or itching
  - Alterations in heart rate and blood pressure
  - Dyspnea or chest discomfort
  - Back or abdominal pain
  - Nausea, vomiting, and/or diarrhea
  - Various types of skin rashes
  - Anaphylaxis

Anaphylaxis due to IV drugs most often presents with the following signs and symptoms:

- Cutaneous symptoms: flushing, itching, urticaria, and/or angioedema (usually of face, eyelids, or lips)
- Respiratory symptoms: repetitive cough, sudden nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and or change in voice quality due to laryngeal edema
- Cardiovascular symptoms: faintness, tachycardia (or less often bradycardia), tunnel vision, chest pain, hypotension, sense of impending doom, and/or loss of consciousness
- Gastrointestinal symptoms: such as nausea, vomiting, abdominal cramping, and diarrhea

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4–5.5.

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until the Day 60 visit or Early Discontinuation visit. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.5).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

Investigators will seek information on adverse events and serious adverse events at each patient contact. All adverse events, and serious adverse events, whether reported by the patient or noted by authorized study personnel, will be recorded.

The adverse event grading (severity) scale in the DAIDS v1.0 will be used for assessing adverse event severity (see Table 5).

Table 5 Adverse Event Grading (Severity) Scale

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical AE NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

AE = adverse event; DAIDS = Division of Acquired Immunodeficiency Syndrome.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or

not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

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

Table 6 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Other Adverse Events

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF, unless the severity increases. If a persistent adverse event becomes more severe, it should be recorded as a separate event on the Adverse Event eCRF. The initial (less severe) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became more severe. If a persistent adverse event becomes serious, it should be recorded as a separate event on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting

instructions). The initial (non-serious) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became serious.

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

5.3.5.4 Abnormal Laboratory Values

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

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment (laboratory abnormalities should be repeated at the first opportunity and only considered clinically significant if they persist on repeat assessment)

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event. Investigators should promptly repeat any abnormal assessment or clinically significant laboratory result. Only those findings that remain clinically significant upon a repeat assessment will be considered adverse events.

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology

changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

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

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of severe influenza or any related co-morbidities should be recorded on the Study Completion/Early Discontinuation eCRF. All other on study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF, and immediately reported to the Sponsor as an SAE (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of Influenza A Infection

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

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
- The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
- The patient has not experienced an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Adverse Events Associated with an Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No clinical safety data related to overdosing of MHAA4549A are available, however, overdoses with a monoclonal antibody theoretically could cause volume overload that can result in edema and/or heart failure.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (see Section 5.4.2 for further details)
- Non-serious adverse events of special interest (see Section 5.4.2 for further details)

- Pregnancies (see Section 5.4.3 for further details)

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

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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

[redacted] Medical Monitor contact information:

Primary Medical Monitor: [redacted]

Telephone Nos.: US Office: [redacted]

US Mobile: [redacted]

Secondary Medical Monitor: [redacted]

Telephone Nos.: US Office: [redacted]

US Mobile: [redacted]

Genentech Medical Monitor contact information for all sites if above medical monitor cannot be reached:

Medical Monitor: [redacted]

Telephone Nos.: US Office [redacted]

US Mobile [redacted]

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. A paper Serious Adverse Event / Adverse Event of Special Interest Reporting Form should be completed and faxed or scanned and emailed to the Sponsor's Safety Risk Management department or its designee immediately (i.e., no more than 24 hours after learning of the event), using the contact information below per region:

Region	Fax Number	Email Address
Asia Pacific	[redacted]	[redacted]
Europe	[redacted]	
Latin America	[redacted]	
North America	[redacted]	

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until the patient is at Day 60 or Early Discontinuation. Although the investigator is not required to actively monitor patients for adverse events after the patient has been discharged from the study, the Sponsor should be notified if the investigator becomes aware of any death or other serious adverse event that occurs after discharge from the study, if determined to be related to study drug by the investigator. The Sponsor should also be notified if the investigator becomes aware of a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug (see Section 5.4.3.3).

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

In the event that the EDC system is unavailable, a paper Serious Adverse Event / *Adverse Event of Special Interest* Reporting Form should be completed and faxed or scanned and emailed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the contact information provided to investigators (see Section 5.4.2.1). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.4.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 120 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, a paper Clinical Trial Pregnancy Reporting Form should be completed, faxed, or scanned and emailed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the contact information provided to investigators (see Section 5.4.2.1). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant within 30 days after the dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.2.1.

5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a serious adverse event,

recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.

5.5.2 Sponsor Follow-Up

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

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 60 days (see Section 5.3.1) after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to Roche, or its designee, either by faxing or by scanning and emailing the Serious Adverse Event / Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators (refer to site binder).

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

The Sponsor will promptly evaluate all serious adverse events including suspected unexpected serious adverse reactions (SUSARs) and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, IECs, and applicable health authorities based on applicable legislation.

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

- MHAA4549A Investigator's Brochure
- Local prescribing information for oseltamivir

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

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

Certain adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting. These anticipated events include, but are not limited to, the following:

- Asymptomatic elevations of ALT, AST, and or amylase without corresponding elevations of bilirubin have been shown to be increased during influenza A infection (Polakos 2006, *Yingying 2011*)
- Influenza associated disease and or complications of influenza

An IMC and SOC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

All efficacy analyses will be conducted according to the intent-to-treat principle and will include all patients who meet the following condition with patients allocated to the treatment arm to which they were randomized:

- Randomized patients who have confirmed influenza A infection as confirmed by a central PCR test from Day 1 samples

Safety analyses will include all patients who were included in the randomization and who received at least one dose of study medication, with patients allocated to the treatment arm associated with the regimen actually received.

No formal hypothesis testing will be done in this study. As a result, no adjustment for a type 1 error will be made to account for the multiplicity of analyses.

Results will be presented both for the MHAA4549A 3600 mg and 8400 mg treatment groups separately and combined for the purpose of comparison to standard of care.

Final efficacy and safety analyses of the total study population will be conducted at the end of the study after all patients have completed all study assessments and the database has been cleaned and closed. Further details of the analyses, including analysis of the exploratory endpoints, will be contained in the statistical analysis plan (SAP) which will be prepared and finalized before the first optional interim analysis (see Section 6.7) or the final efficacy and safety analysis, if no interim analysis takes place.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is estimation of the effect size and hypothesis generation regarding the effect of MHAA4549A on the time to normalization of respiratory function relative to the standard of care rather than hypothesis testing. Point and interval estimates will be obtained. *Approximately 330* patients will be enrolled. It is assumed that the median time to normalization of respiratory function in the control arm is 5 days. This sample size (approximately *110* patients per arm) provides *71*% power to detect a treatment difference of 1 day for the primary endpoint *in both MHAA4549A arms* assuming a 2-sided alpha of 0.2 *and no difference in efficacy between the two active arms. If the 3600-mg dose shows a treatment difference of 1 day and the 8400-mg dose shows a treatment difference of 1.5 days or more then this sample size provides > 86% power assuming a 2-sided alpha of 0.2.*

Operating characteristics (power) under other possible assumptions for 2-sided alpha of 0.2 and true differences of *0.5* to 2 days are provided in Table 7.

Table 7 Operating Characteristics for Proposed Study Design for Several Possible True Underlying Median Values

	True Underlying Median for MHAA4549A							
	3600 mg	*8400 mg*	*3600 mg*	*8400 mg*	*3600 mg*	*8400 mg*	*3600 mg*	*8400 mg*
	4 days	*4 days*	*4 days*	*3.5 days*	*4 days*	*3 days*	*4.5 days*	*4 days*
Hazard Ratio	*0.8*	*0.8*	*0.8*	*0.7*	*0.8*	*0.6*	*0.9*	*0.8*
Power of log-rank test [a]	*71.4%*		*86.6%*		*98.8%*		*56.2%*	

Note: Operating characteristics are based on the following assumptions: 330 evaluable patients, event times are exponentially distributed, median time to normalization of respiratory function in the control arm is 5 days, and patients are followed for 60 days.

a Two-sided $\alpha = 0.20$.

It should be noted that the study is underpowered for detection of minimally clinically meaningful differences at a 2-sided alpha of 0.05 such as a true hazard ratio of 0.80 *in both MHAA4549A arms*.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue (early discontinuation of treatment or early termination from the study), and complete the study will be tabulated by treatment group using descriptive statistics. Reasons for early discontinuation of treatment or early termination from the study will be listed and summarized by treatment group. Any eligibility criteria exceptions and other protocol deviations will also be summarized by treatment group.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics of the patient will be summarized for all randomized patients by treatment group by use of descriptive statistics. Baseline is defined as the last available value prior to study drug administration.

During the study patient disposition, concurrent treatment, and compliance with study treatment and visits will be summarized on the safety analysis population using descriptive statistics.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized patients who are confirmed to be influenza A infected, with patients grouped according to the treatment assigned at randomization.

Time to event data will be computed using Kaplan-Meier methodology and stratified Cox proportional hazards models and will be summarized using n, median when estimable, hazard ratios, and 95% confidence intervals. Patients who are lost to follow-up (while event free) will be censored at the time that they are last known to be event free.

Estimation of the treatment difference of proportions and its 95% confidence interval will be calculated using stratum-adjusted Mantel-Haenszel methodology (Koch et al. 1989). For continuous endpoints, Analysis of Covariance methods (after appropriate transformation of data) will be used to estimate treatment differences and 95% confidence intervals.

Other than censoring in the time to event analyses, no other imputation for missing data will be performed.

6.4.1 Primary Efficacy Endpoint

- Median time to normalization of respiratory function.

6.4.2 Secondary Efficacy Endpoints

- Proportion of patients with clinical failure after 24 hours post-infusion of study drug
- Median time to clinical resolution of vital signs
- Hazard ratio for mortality at Day 14, Day 30, and Day 60
- Mean and median AUC of viral load
- Mean and median peak viral load
- Median duration of viral shedding in nasopharyngeal samples
- Median duration of hospitalization
- Median duration of ICU stay
- Proportion of patients requiring antibiotics for respiratory indications during study
- Proportion of patients with influenza secondary complications
- Median duration of ventilation
- Proportion of patients who are readmitted by Day 30 and Day 60

6.4.3 Subgroup Analyses

Subgroup analyses will be performed to examine the consistency of the treatment estimates with use of the primary and selected secondary endpoints. Subgroups will include the stratification factors as well as patients who are identified at baseline as influenza A positive by the upper, lower, or both airways and by patients with bacterial co-infections at admission *as well as by the influenza season during which the patient was randomized*. Additional subgroups may be added following assessment of baseline characteristics as exploratory analyses.

6.5 SAFETY ANALYSES

The safety analyses will include all randomized patients who received study drug, with patients grouped according to the treatment actually received. Safety parameters to be evaluated include AEs (including deaths, SAEs, discontinuations due to AEs, and the incidence and severity of AEs), clinical laboratory tests, vital signs (including SpO_2 measurements), and ECGs.

All collected AE event data will be listed by study site and patient number. All AEs that occur on or after treatment on Day 1 will be summarized for each treatment group by mapped term, appropriate thesaurus levels, body system, and event within each body system, and toxicity grade. In addition, all SAEs, including deaths, will be listed separately and summarized. SAEs caused by a protocol mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) that occur between consent and first dose of study medication will be listed separately.

Laboratory data with values outside of the normal ranges will be identified. In addition, select laboratory data will be summarized by treatment group using descriptive summary statistics.

The absolute and percentage changes from baseline in vital sign parameters will be computed, and changes deemed clinically significant by the Investigator will be noted. Appropriate descriptive summary statistics will be provided for all vital sign parameters

6.6 PHARMACODYNAMIC ANALYSES

Individual and mean serum MHAA4549A concentration versus time data will be tabulated and plotted. The serum pharmacokinetics of MHAA4549A will be summarized by estimating total serum drug exposure (i.e., AUC), C_{max}, C_{min}, total serum clearance, half-life, and volume of distribution, as data allow. Estimates for these parameters will be tabulated and summarized (e.g., mean, standard deviation, coefficient of variation). Inter patient variability will be evaluated. MHAA4549A serum concentration–time data may be compared with available data from other MHAA4549A clinical studies.

6.7 OPTIONAL INTERIM ANALYSES

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

If conducted, an interim analysis would be for administrative purposes only (i.e., internal planning or decision making) and would not impact the conduct of the current study in any way. A nominal type I error penalty of 0.0001 will be taken.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline

(Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a US Investigational New Drug (IND) application will comply with US FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

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

The Consent Forms must be signed and dated by the patient or the patient's authorized representative as applicable and in accordance with local regulations, and IRB/IEC policies, before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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

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

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other

processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments (see Section 9.1).

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

8.4 CONFIDENTIALITY

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

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

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate, financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient, last visit [LPLV]).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/IEC in accordance with established IRB/IEC policies and procedures.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

Genentech, Inc., a member of the Roche group, is the Sponsor of this study. A clinical research organization (CRO) may provide clinical operations oversight, including but not limited to project management, clinical monitoring and site management, data quality support, medical monitoring, and some safety reporting and regulatory activities as specified in study management plans. Genentech will provide CRO oversight, develop the database and randomization scheme, and conduct statistical programming and analysis. An IMC and SOC will provide safety monitoring for the study in addition to the ongoing review of safety by the Medical Monitor and Safety Scientist.

EDC will be utilized for this study. An IxRS will be used to assign patient numbers, randomize patients into study through use of a dynamic hierarchical algorithm, and

manage site drug supply. A central laboratory will be used for sample management and storage until shipment to specialty laboratories or Genentech for analysis.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information from the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website: http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1a
Schedule of Assessments

Notes: Unless otherwise indicated, **all assessments on Day 1 should be performed prior to study drug administration**; x's within parentheses, i.e., (x), indicate optional assessments. Please refer to Follow-up Period table for visits to be completed after patient is discharged from hospital prior to Day 60. *Any screening assessments completed prior to consent as standard of care do not need to be repeated if done within the screening period. If a patient is unable to be present at the site for a follow-up visit, a telephone visit is permitted.*

	Screening	Hospitalized Days (only to be completed while patients are hospitalized)															D60
Day (D)	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D14	D20	D25	Hospital Discharge [a]	D30	Study Completion or Early Discontinuation while Hospitalized
Confirm study drug administration can occur within 48 hours of hospital admission																	
Informed consent [b]	x																
Sponsor-approved influenza test [c]	x																
Inclusion/exclusion criteria	x																
Medical history and demographic data	x																
Confirm onset of flu symptoms (≤ 5 days prior to study drug administration on Day 1)	x																
Confirm history of baseline $SpO_2 > 92\%$	x																
Pregnancy screening [d]	x																
Confirm O_2 requirement [e]	x																

Appendix 1a
Schedule of Assessments (cont.)

	Screening	Hospitalized Days (only to be completed while patients are hospitalized)													Hospital Discharge [a]	D30	D60 Study Completion or Early Discontinuation while Hospitalized
Day (D)	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D14	D20	D25			
Respiratory Assessment [f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [h]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
APACHE score [i]		(x [j])										(x)			(x)	(x)	(x)
SOFA score [k]		(x [j])						(x)				(x)			(x)	(x)	(x)
Electrocardiogram (12-lead) [l]		x				x						x			x	x	x
Randomization		x															
MHAA4549A administration [m]		x															
Oseltamivir administration [n]		x	x	x	x	x	(x)	(x)	(x)	(x)	(x)						
Complete physical examination [o]	x	(x)															
Limited, symptom-directed physical examination [p]			x	x	x	x						x			x	x	x
Weight & height [q]	x	x				x						x			x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [r]	x		x			x						x			x	x	x
Chemistry panel [r]	(x) [s]	x	x			x						x			x	x	x
Coagulation panel [r]		x				x						x			x	x	x

Appendix 1a
Schedule of Assessments (cont.)

Day (D)	Screening	Hospitalized Days (only to be completed while patients are hospitalized)													Hospital Discharge [a]	D30	D60 Study Completion or Early Discontinuation while Hospitalized
	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D14	D20	D25			
Erythrocyte sedimentation rate		(x)	(x)			(x)						(x)			(x)	(x)	(x)
C-reactive protein		(x)	(x)			(x)						(x)			(x)	(x)	(x)
Urinalysis [r, t]		x	x			x						x			x	x	x
Serology (HIV) [r, u]	x																
[redacted]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
[redacted]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Flu antibodies (HAI) [x]		x										x			x	x	x
[redacted]		x														x	x
Serum for MHAA4549A PK measurements [y]		x	x	x		x		x				x			x	x	x
[redacted]		x				x									(x) [aa]		
[redacted]		x	x	x		x		x			x	x	x	x	x	x	x
[redacted]		x	x	x		x		x			x	x	x	x	x	x	x
[redacted]		x													x	x	x
[redacted]		x														x	x

Appendix 1a
Schedule of Assessments (cont.)

	Screening	Hospitalized Days (only to be completed while patients are hospitalized)															
Day (D)	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D14	D20	D25	Hospital Discharge [a]	D30	D60 Study Completion or Early Discontinuation while Hospitalized
[redacted]		x													x	x	x
[redacted]		x													x	x	x
[redacted]															x		
Oseltamivir medication diary [dd]															x		

[redacted]; AE = adverse event; APACHE = Acute Physiology and Chronic Health Evaluation; ATA = Anti-therapeutic antibodies; D = day; Dx = diagnostics; eCFR = electronic Case Report Form; ECG = electrocardiogram; HAI = hemagglutinin inhibition; [redacted]; ICU = Intensive Care Unit; IRB/IEC = Independent Review Board/Independent Ethics Committee; NAI = neuraminidase inhibitor; NP = nasopharyngeal; O_2 = oxygen; PaO_2/FiO_2 = partial pressure of oxygen/fraction of inspired oxygen; PCR = polymerase chain reaction; PD = pharmacodynamics; PK = pharmacokinetic; PPV = positive pressure ventilation; qPCR = quantitative Polymerase Chain Reaction; RBCs = red blood cells; SOFA = Sequential Organ Failure Assessment; SpO_2 = oxygen saturation measured by pulse oximetry; WBCs = white blood cells.

oxygen/fraction of inspired oxygen; PCR = polymerase chain reaction; PD = pharmacodynamics; PK = pharmacokinetic; PPV = positive pressure ventilation; qPCR = quantitative Polymerase Chain Reaction; RBCs = red blood cells; SOFA = Sequential Organ Failure Assessment; SpO_2 = oxygen saturation measured by pulse oximetry; WBCs = white blood cells.

Appendix 1a
Schedule of Assessments (cont.)

[a] Assessments to be performed irrespective of day of discharge. Assessments on discharge day will supersede assessments for matching day except for the study completion/early discontinuation visit (e.g., If a patient is discharged from the hospital on Day X, use assessments under "hospital discharge" column instead of the Day X column and record under the hospital discharge folder in the eCRF. If a patient discontinues from the study early on Day X, complete all assessments under the "early discontinuation" column and record under the early discontinuation folder in the eCRF.

[b] Informed consent must be obtained from all patients. For patients who are unable to consent, an authorized representative may be used if allowed by local regulations and IRB/IEC policy.

[c] Sponsor-*approved* influenza test using *a* nasopharyngeal *swab in one nostril. A* Sponsor-*approved* influenza test *includes* influenza *antigen test or* influenza *polymerase chain reaction (PCR) test. Result must be available* within *the* 48-hour screening window.

[d] A urine pregnancy test should be *collected* only for women considered by the investigator to be of childbearing potential, see exclusion criteria. This result must be available *within 2 days* prior to *study treatment*. If urine testing is not available at the site, blood already collected from an existing sample may be tested for pregnancy.

[e] Confirm patient requires supplemental O_2 or PPV within 24 hours of hospital admission.

[f] All patients will have their on-study SpO_2 and corresponding respiratory assessments recorded daily in the morning between 6 am – 12 pm local time; screening SpO_2 may be taken outside this window. *From Day 1 onward post-study drug administration,* patients on low flow O_2 should have a daily trial of their SpO_2 while on and off the supplementation and both values will be recorded. If the patient is on oxygen supplementation, SpO_2 measured by pulse oximetry and the corresponding respiratory assessments (e.g., FiO_2, flow rate) will be recorded. If the patient is on PPV, PaO_2 and the corresponding respiratory assessments (e.g., FiO_2, ventilator mode, ventilator respiratory rate, positive end-expiratory pressure) will be recorded. *If clinically appropriate (i.e., the patient is on non-invasive PPV), the conversion table in Appendix 11 may be used.*

[g] Concomitant medications should be recorded for 30 days prior to screening, through the study completion/early discontinuation visit. See exclusion criteria in Section 4.5.2 for prohibited therapies.

[h] Vital signs will be collected within 1 hour before MHAA4549A infusion and within 1 hour after completion of MHAA4549A infusion and include temperature, respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure. Temperature should be measured using the same methodology throughout the study and should be measured prior to administration of any antipyretic drugs. In patients who have multiple vital signs taken during any day, the most abnormal value should be recorded from that 24-hour period. Temperature, blood pressure, respiratory rate, and heart rate will be completed after the patient has been in a seated or supine position for > 5 minutes. The worst/most abnormal value from the last 24-hour period should be recorded for patients who are in the ICU.

[i] APACHE scores are optional and only for patients that are in the ICU. For calculation of the screening APACHE score, the worst values in the preceding 24 hours should be used. APACHE scores are not required for study conduct or entry but should be collected if available.

Appendix 1a
Schedule of Assessments (cont.)

[j] *Assessment to be conducted based on entry into ICU; may vary from patient to patient.*

[k] SOFA scores are only for patients in the ICU that have available data such as PaO_2/FiO_2 (mmHg). See Appendix 7 for SOFA score calculation.

[l] Patient should rest in a supine position for 10 minutes prior.

[m] Patient will be a resident for at least 24 hours following administration of MHAA4549A.

[n] Oseltamivir must be given for a minimum of 5 days. Treatment longer than 5 days is permitted based on the discretion of the investigator [indicated by (x)].

[o] Complete physical examination includes evaluations of general appearance of head, eye, ear, nose, and throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as AEs, if appropriate. *Day 1 physical examination is optional if not done on Day -1 or -2.*

[p] Limited, symptom-directed physical examination includes, at a minimum, evaluation of general appearance, dermatological examination of the injection sites, evaluations directed by patient-reported symptoms, and any other evaluations that the investigator deems clinically relevant. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as AEs, if appropriate.

[q] Height will be obtained at screening only. Weight will be obtained at all indicated visits. Height and weight will be recorded in centimeters and kilograms, respectively.

[r] Local laboratory measurements should be utilized.

[s] For optional thyroid stimulating hormone test.

[t] Urinalysis includes pH, specific gravity, glucose, protein, ketones, blood, bilirubin, nitrite, and leukocyte esterase. Microscopic examination (e.g., sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) will be performed if clinically indicated.

[u] HIV serology result not needed for randomization *and a positive result does not require patient discontinuation.*

Appendix 1a
Schedule of Assessments (cont.)

[redacted]

[y] Day 1 serum PK samples are to be drawn 30 (±5) minutes pre-dose of MHAA4549A, 60 (± 15) minutes after the end of infusion. *Serum PK samples on Day 2 and after are to be drawn immediately before oseltamivir dosing.* PK samples will be drawn from the contralateral arm from that used for drug infusion and must be labeled with the exact time of draw.

[redacted]

[aa] *If patient is discharged on or before Day 5, the oseltamivir PK samples are to be taken on the discharge day.*

[redacted]

[dd] Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary, empty (used) oseltamivir packets and unused oseltamivir capsules to the study site at the next follow up visit. Patients will record the date and time when each oseltamivir capsule is administered.

Appendix 1b
Schedule of Assessments: Follow-Up Period

- If a patient is discharged prior to Day 14, he/she will need to complete the following assessments for Day 14, Day 30, and Day 60 below.
- If a patient is discharged *after Day 14 but* prior to Day 30, he/she will need to complete the following assessments for Day 30 and Day 60 below.
- If a patient is discharged *after Day 30, but* prior to Day 60, he/she will need to complete the following assessments for Day 60 below.
- If patient is hospitalized for Day 14, Day 30, and/or Day 60, please refer to Appendix 1a.

Day (D)	D14 ± 1 (If discharged BEFORE D*ay* 14)	D30 ± 4 (If discharged BEFORE D*ay* 30)	Day 60 ± 4 (Study Completion) or Early Discontinuation
Concomitant medications [a]	x	x	x
Vital signs [b]	x	x	x
Electrocardiogram (12-lead) [c]	x	x	x
Weight & height, BMI [d]	x	x	x
Adverse events	x	x	x
Hematology [e]	x	x	x
Chemistry panel [e]	x	x	x
Coagulation panel [e]	x	x	x
Urinalysis [e]	x	x	x
Flu antibodies (HAI)	x	x	x
[redacted]		x	x
Serum for MHAA4549A PK measurements [f]	x	x	x
[redacted]	x	x	x
[redacted]	x	x	x
[redacted]		x	x
[redacted]		x	x
[redacted]		x	x
[redacted]		x	x

Appendix 1b
Schedule of Assessments: Follow-Up Period (cont.)

[redacted]; ATA = Anti-therapeutic antibodies; BMI = body mass index; D = day; Dx = diagnostics; eCFR = electronic Case Report Form; ECG = electrocardiogram; HAI = hemagglutinin inhibition; [redacted]; PD = pharmacodynamics; PK = pharmacokinetic.

[a] Concomitant medications should be recorded for 30 days prior to screening, through the study completion/early discontinuation visit. See exclusion criteria in Section 4.1.2 for prohibited therapies.

[b] Vital signs include temperature, respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure. Temperature should be measured using the same methodology throughout the study and should be measured prior to study drug administration of any antipyretic drugs. In patients who have multiple vital signs taken during any day, the most abnormal value should be recorded from that 24-hour period. Temperature, blood pressure, respiratory rate, and heart rate will be completed after the patient has been *in a seated or* supine *position* for > 5 minutes.

[c] ECG should be recorded after the patient has rested in a supine position for 10 minutes.

[d] Height will be obtained at screening only. Weight will be obtained at all indicated visits. Height and weight will be recorded in meters and kg, respectively.

[e] Local laboratory measurements should be used.

[f] PK samples must be labeled with the exact time of draw.

[redacted]

Appendix 2
Time to Normalization of Respiratory Function

For the purposes of this study, the time to normalization of respiratory function will be defined as the time to removal of the patient from O_2 supplementation in order to maintain an $SpO_2 \geq 95\%$.

Patients who are on low flow O_2 (2-6L/min) should receive a daily trial off O_2 in the morning between 6 am – 12 pm as described below.

1. Patient should be resting or sitting.
2. Patient should be fitted with pulse oximeter, and their SpO_2 should be checked once while on O_2 and then again 3 – 5 minutes after turning off O_2 supplementation.
3. If the $SpO_2 \geq 95\%$, then the time and reading should be recorded. Notify the study doctor so that he/she can make a clinical judgment to determine whether the O_2 can be removed.
4. The recorded time for the endpoint corresponds with the initial discontinuation of O_2 and reading.

Appendix 3

[redacted]

Appendix 4

[redacted]

Appendix 5

[redacted]

Appendix 6

[redacted]

Appendix 7
SOFA Score Calculation

Variables	SOFA Score				
	0	**1**	**2**	**3**	**4**
Respiratory (PaO_2/FiO_2, mmHg)	>400	≤ 400	≤ 300	≤ 200[a]	≤ 100[a]
Coagulation (Platelets x $10^3/\mu L$) [b]	>150	≤ 150	≤ 100	≤ 50	≤ 20
Liver (Bilirubin, mg/dL) [b]	<1.2	$1.2-1.9$	$2.0-5.9$	$6.0-11.9$	>12.0
Cardiovascular (Hypotension)	No hypotension	MAP <70 mmHg	Dop ≤ 5 or dob (any dose) [c]	Dop >5, epi ≤ 0.1, or norepi ≤ 0.1[c]	Dop >15, epi >0.1, or norepi >0.1[c]
Central Nervous System (Glasgow Coma Score Scale)	15	$13-14$	$10-12$	$6-9$	<6
Renal (Creatinine, mg/dL or urine output, mL/day) [d]	<1.2	$1.2-1.9$	$2.0-3.4$	$3.5-4.9$ or <500	>5.0 or <200

Norepi = norepinephrine; Dob = dobutamine; Dop = dopamine; Epi = epinephrine; FiO_2 = fraction of inspired oxygen; MAP = mean arterial pressure; PaO_2 = partial pressure of $arterial$ oxygen.

[a] Values are with respiratory support.

[b] To convert bilirubin from mg/dL to μmol/L, multiply by 17.1.

[c] Adrenergic agents administered for at least 1 hour (doses given are in μg/kg per minute).

[d] To convert creatinine from mg/dL to μmol/L, multiply by 88.4.

References for Appendix 7:

Ferreira FL, Bota DP, Bross A et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001; 286(14):1754–1758

Vincent JL, de Mendonca A, Cantraine F et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;26(11): 1793–1800.

Appendix 8
DAIDS Toxicity Grading Tables for Clinical Abnormalities

From the FDA Guidance document 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials' (September 2007)

Vital Signs [a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) [b] (°F)*	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40.0 102.1 – 104.0	>40 >104
Tachycardia – beats per minute	101- 115	116 – 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia – beats per minute [c]	50 – 54	45 – 49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) – mmHg	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mmHg	91 – 95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mmHg	85 – 89	80 – 84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	>25	Intubation

[a] Subject should be at rest for all vital sign measurements.

[b] Oral/tympanic temperature; no recent hot or cold beverages or smoking.

[c] When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Appendix 8 (cont'd)
DAIDS Toxicity Grading Tables for Clinical Abnormalities

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/ vomiting	No interference with activity or 1 – 2 episodes/ 24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 g/ 24 hours	4 – 5 stools or 400 – 800 g/ 24 hours	5 or more watery stools or > 800 g/ 24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity no requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Appendix 9
DAIDS Toxicity Grading Tables for Laboratory Abnormalities

Adapted from Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007 DRAFT and FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials

Abbreviations used in the table:
[redacted]; CPK = creatine phosphokinase; Dec = Decreased; IV = Intravenous; LLN = Lower limit of normal; Mod = Moderate; Req = Required; Rx = Therapy; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = Upper limit of normal.

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 – 10.5 g/dL	8.0 – 9.4 g/dL	6.5 – 7.9 g/dL	<6.5 gm/dL
Absolute Neutrophil Count	1,000 – 1,500/mm^3	750 – 999/mm^3	500 – 749/mm^3	<500/mm^3
*Platelets	125,000 – 140,000/mm^3	100,000 – 124,999/mm^3	25,000 – 99,999/mm^3	<25,000/mm^3
WBCs	11,000 – 13,000/mm^3	13,000 – 15,000/mm^3	15,000 – 30,000/mm^3	>30,000 or <1,000/mm^3
*Lymphocytes Decrease – cell/mm^3	750 – 1,000	500 – 749	250 – 499	<250
*Eosinophils – cell/mm^3	650 – 1500	1501 – 5000	>5000	Hypereosinophilic
Abnormal Fibrinogen	Low: 100 – 200 mg/dL High: 400 – 600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: <50 mg/dL	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20 – 40 mcg/mL	41 – 50 mcg/mL	51 – 60 mcg/mL	>60 mcg/mL
Prothrombin Time (PT)	1.01 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin Time (APTT)	1.01 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3 x ULN	>3 x ULN
Methemoglobin	5.0 – 9.9%	10.0 – 14.9%	15.0 – 19.9%	>20.0%

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

Appendix 9 (cont'd)
DAIDS Toxicity Grading Tables for Laboratory Abnormalities

CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130 – 135 mEq/L	123 – 129 mEq/L	116 – 122 mEq/L	<116 mEq/L or abnormal sodium with mental status changes or seizures
Hypernatremia	146 – 150 mEq/L	151 – 157 mEq/L	158 – 165 mEq/L	>165 mEq/L or abnormal sodium with mental status changes or seizures
Hypokalemia	3.0 – 3.4 mEq/L	2.5 – 2.9 mEq/L	2.0 – 2.4 mEq/L or intensive replacement therapy or hospitalization required	<2.0 mEq/L or abnormal potassium with paresis ileus or life-threatening arrhythmia
Hyperkalemia	5.6 – 6.0 mEq/L	6.1 – 6.5 mEq/L	6.6 – 7.0 mEq/L	>7.0 mEq/L or abnormal potassium with life-threatening arrhythmia
Hypoglycemia	55 – 64 mg/dL	40 – 54 mg/dL	30 – 39 mg/dL	<30 mg/dL or abnormal glucose with mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 – 160 mg/dL	161 – 250 mg/dL	251 – 500 mg/dL	>500 mg/dL or abnormal glucose with ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 – 7.8 mg/dL	7.7 – 7.0 mg/dL	6.9 – 6.1 mg/dL	<6.1 mg/dL or abnormal calcium with life threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6 – 11.5 mg/dL	11.6 – 12.5 mg/dL	12.6 – 13.5 mg/dL	>13.5 mg/dL or abnormal calcium with life-threatening arrhythmia
Hypomagnesemia	1.4 – 1.2 mEq/L	1.1 – 0.9 mEq/L	0.8 – 0.6 mEq/L	<0.6 mEq/L or abnormal magnesium with life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 – <1.25 x ULN	1.25 – <1.5 x ULN	1.5 – 1.75 x ULN	>1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 – <1.5 x ULN	1.5 – <2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Appendix 9 (cont'd)
DAIDS Toxicity Grading Tables for Laboratory Abnormalities

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 × ULN	2.0 - <3.0 × ULN	3.0 – 8.0 × ULN	>8.0 × ULN
ALT (SGPT)	1.1 - <2.0 × ULN	2.0 - <3.0 × ULN	3.0 – 8.0 × ULN	>8.0 × ULN
GGT	1.1 - <2.0 × ULN	2.0 - <3.0 × ULN	3.0 – 8.0 × ULN	>8.0 × ULN
Alkaline Phosphatase	1.1 - <2.0 × ULN	2.0 - <3.0 × ULN	3.0 – 8.0 × ULN	>8.0 × ULN
Amylase	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.1 – 5.0 × ULN	>5.1 × ULN
Lipase	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.1 – 5.0 × ULN	>5.1 × ULN
*CPK – mg/dL	1.25 – 1.5 × ULN	1.6 – 3.0 × ULN	3.1 – 10.0 × ULN	>10 × ULN

* From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg – 1 g loss/day	2-3+ or 1-2 g loss/day	4+ or 2-3.5 g loss/day	Nephrotic syndrome or >3.5 g loss/day
Hematuria	Microscopic only <10 RBC/hpf	Gross, no clots >10 RBC/hpf	Gross, with or without clots, OR red blood casts	Obstructive or required transfusion
*Glucose	Trace	1+	2+	Hospitalization for hyperglycemia

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

Appendix 10
Anaphylaxis Precautions and Management

Administration of MHAA4549A will be performed in a setting with emergency medical equipment and personnel who are trained to monitor for and respond to medical emergencies. A qualified physician will be on site during study drug administration for all patients.

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Airway management equipment
- O_2
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion.
- Maintain an adequate airway.
- Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix 11
Respiratory Conversion Table for PaO_2

Estimating PaO_2 from a given oxygen saturation

Oxygen Saturation (%)	*PaO_2 (mmHg)*
80	*44*
81	*45*
82	*46*
83	*47*
84	*49*
85	*50*
86	*52*
87	*53*
88	*55*
89	*57*
90	*60*
91	*62*
92	*65*
93	*69*
94	*73*
95	*79*
96	*86*
97	*96*
98	*112*
99	*145*

From The Extended Study of Prevalence of Infection in Intensive Care:
http://www.intensive.org/epic2/Documents/Estimation%20of%20PO2%20and%20FiO2.pdf

PROTOCOL

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY, IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION**
PROTOCOL NUMBER:	GV29216
VERSION NUMBER:	7 (Global)
EUDRACT NUMBER:	2014-000461-43
IND NUMBER:	117,318
TEST PRODUCT:	MHAA4549A
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	30 May 2014
DATES AMENDED:	Version 2: 14 August 2014 Version 3 (VHP Only): 25 September 2014 Version 4 (Russia Only): 5 February 2015 Version 5 (Global): 20 March 2015 Version 6 (Russia Only): 11 April 2015 Version 7 (Global): See electronic date stamp below.

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	16-May-2016 15:31:18

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PROTOCOL AMENDMENT, VERSION 7:
RATIONALE

There are currently no validated clinical endpoints for evaluating clinical efficacy of therapeutics for patients hospitalized with severe influenza. Possible endpoints have been proposed which include mortality, duration of hospitalization stay, virology, clinical signs and symptoms, time to normalization of vital signs, time to normalization of oxygen, and requirements for supplemental oxygen or ventilation. Each of these outcomes will be assessed in this study.

This Version 7 amendment adds an additional secondary endpoint to compare the clinical status of patients using an ordinal outcome with 6 clinical statuses. Patients will be categorized into 1 of the following 6 mutually exclusive categories (death; in the intensive care unit [ICU]; non-ICU hospitalization, requiring supplemental oxygen; non-ICU hospitalization, not requiring supplemental oxygen; not hospitalized, but unable to resume normal activities; or not hospitalized with full resumption of normal activities) on Days 1-7, 14, and 30. An ordinal outcome is hypothesized to have greater statistical power than a binary clinical outcome because it uses more information. Ordinal outcomes have been used in other studies of seriously ill patients (Roozenbeek B et al. 2011).

This amendment also contains:

- Updates to MHAA4549A background information
- Updates to clinical safety and efficacy background
- Revised initial oseltamivir dosing from 8 hours to 12 hours after completion of study drug administration
- Allowing a medically qualified designee to be present during MHAA4549A administration
- Clarification to inclusion criteria of “any supplemental O_2 to maintain oxygen saturation >92%”
- Expanded Day 60 follow up window from ± 4 to ± 7 days to allow more operational flexibility
- Clarification around renal dose adjustments for oseltamivir
- Clarification that only 75 mg oseltamivir capsules are supplied by IxRS for 75 mg twice a day (BID) and 150 mg BID regimens
- Removed requirement for FSH test
- Clarification that patients with a history of chronic lung disease with a documented $SpO_2 < 95\%$ off oxygen are excluded
- Clarification that a lower respiratory tract sample may be used if appropriate for the sponsor-approved local PCR test for influenza diagnosis
- Clarification of daily trial off oxygen

- Update to emergency medical contacts
- Update to contact information for reporting serious adverse events and non-serious adverse events of special interest
- Update to efficacy analyses in Section 6.4 to support the addition of the new ordinal secondary endpoint
- Revision to Schedule of Activities to support the addition of the new ordinal secondary endpoint
- Revision to Schedule of Activities to ensure that daily trial off oxygen are captured every day up to Day 30 when patients are hospitalized
- Additional appendix on clinical status assessment to aid in assessing the new ordinal secondary endpoint
- Updates to remove repetition

PROTOCOL AMENDMENT, VERSION 7:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.1: BACKGROUND ON INFLUENZE

Influenza infection is an upper and lower respiratory disease with a broad spectrum of presentations that can result in fever, shortness-of-breath, pneumonia, respiratory failure, secondary respiratory infections, and even death. The standard of care therapy for patients hospitalized with influenza consists of supportive measures and administration of available antiviral agents, primarily neuraminidase inhibitors (NAI) that include but are not limited to oseltamivir, zanamivir, *laninamivir,* and peramivir. However, a significant unmet medical need still exists in the severely ill patient population, as evidenced by the considerable degree of morbidity and mortality in this setting. To address this need, the Sponsor is developing a highly-specific anti-influenza A (MHAA4549A) antibody therapy for treatment of hospitalized patients with severe influenza.

SECTION 1.2.1: Nonclinical Background

MHAA4549A is a human monoclonal IgG1 antibody that binds to the influenza A virus and is cloned from a single-human plasmablast cell isolated from an influenza vaccinated donor (Nakamura et al. 2013). This antibody binds to a highly conserved epitope on the influenza A hemagglutinin (HA) stalk region~~, which allows broad neutralization of the influenza A virus by~~*,* blocking *fusion of the viral envelope with* the ~~HA mediated,~~*host target cell endosomal* membrane ~~fusion event in the late endosome~~ *and preventing viral replication.*

In vitro, MHAA4549A is capable of neutralizing all ~~current clinically relevant~~*human seasonal* influenza A strains *tested.* In vivo, efficacy of MHAA4549A has been demonstrated in mouse models of influenza A infection, both as a single agent and in combination with oseltamivir. ~~MHAA4549A specifically targets an~~ *In the absence of influenza infection, the* epitope on the human influenza A HA glycoprotein~~, which does~~ *targeted by MHAA4549A is* not ~~appear to be~~ endogenously expressed ~~on~~*in* human or rat tissues and, therefore, is unlikely to be present in the absence of ~~viral infection.~~ *influenza infection. Ex vivo tissue cross-reactivity study data showed no specific binding of MHAA4549A to any of the human or rat tissues examined.* Weekly *intravenous* administration of MHAA4549A (total of 5 doses) in Sprague-Dawley rats was well tolerated up to the maximum feasible dose of 150~~ mg/kg. Ex vivo tissue cross-reactivity study data showed no specific binding of MHAA4549A to any of the human or rat tissues examined~~ *mg/kg.*

SECTION 1.2.2: Clinical Safety Background

To date, MHAA4549A has been shown to be safe and well tolerated in ~~two~~*three* clinical studies, which altogether enrolled ~~122~~*84* healthy volunteers *who were dosed with MHAA4549A.*

SECTION 1.2.2.1: Phase 1 Entry-into-Human Study (GV28916)

~~The first study was a~~ *In the* Phase 1 *entry-into-human (EIH)* study (GV28916~~) in~~*),* 21 healthy volunteers ~~where~~*were given* single *IV* doses of *placebo (n =5) or MHAA4549A (n =16) at* 1.5, 5, 15, ~~and~~*or* 45 mg/kg *and followed for 120 days.*

A total of 23 treatment-emergent adverse events (TEAEs) were ~~tested~~*reported by 13 of the 21 subjects (61.9%) who received one dose of the study medication. Nineteen of these TEAEs were reported by 10 of the 16 subjects (62.5%) who had received MHAA4549A and four TEAEs were reported by 3 of the 5 subjects (60.0%) who received placebo. The total number of TEAEs reported was similar in all dosing cohorts (four TEAEs per cohort),* with ~~an extended follow up period of 120 days. MHAA4549A~~ *the exception of the 5-mg/kg cohort, where seven TEAEs were observed. Overall, no notable trends were observed among dose levels or between subjects who received MHAA4549A and those who received placebo.*

The most commonly reported TEAEs in subjects receiving MHAA4549A were headache (4 subjects) and oropharyngeal pain (2 subjects). The severity of TEAEs was ~~safe and well tolerated~~*primarily mild,* with ~~no~~ *only two moderate TEAEs. No* serious adverse events ~~(SAEs). All adverse events (AEs) were mild or mild~~*or dose-limiting toxicities were reported. Two clinical laboratory values were considered TEAEs (an increase in ALT in 1 subject who received 5 mg/kg MHAA4549A and an increase in creatinine phosphokinase [CK] in 1 subject who received placebo). Both results returned* to ~~moderate and resolved fully before the end of the study's follow up period. No~~*normal within 10 days.*

No safety issues were observed with respect to vital signs results or ECG measurements. For all clinical laboratory results, no relevant differences in mean values or deviations from baseline over time were observed in subjects receiving MHAA4549A doses as compared to placebo. No drug-emergent anti-therapeutic antibodies (ATAs) were detected in this study.

SECTION 1.2.2.2: *Phase 1 High-Dose Safety Study (GV29609)*

In the Phase 1 high-dose study (GV29609), 14 healthy volunteers were given single IV doses of placebo (n =6) or MHAA4549A (n =8) at 8400 mg (Cohort A) or 10800 mg (Cohort B) and were followed for 120 days.

A total of 34 TEAEs were reported by 12 of the 14 subjects (85.7%) who received one dose of the study medication or placebo (safety population). Of these 34 TEAEs, 24 TEAEs were reported by 7 of the 8 subjects (87.5%) who had received MHAA4549A

and 10 TEAEs were reported by 5 of the 6 subjects (83.3%) who received placebo. TEAEs were reported by 3 of the 4 subjects receiving 8400 mg MHAA4549A and all 4 subjects receiving 10800 mg MHAA4549A. No notable trends in types of TEAEs or laboratory results were observed between dose levels or between subjects who received MHAA4549A versus placebo.

The most commonly reported TEAEs were headache (4 subjects who received MHAA4549A [3 subjects in Cohort A, 1 subject in Cohort B]) and nasopharyngitis (3 subjects who received MHAA4549A [1 subject in Cohort A, 2 subjects in Cohort B]). All other TEAEs were each reported by no more than 1 subject who received MHAA4549A. The severity of TEAEs was primarily mild, with only three moderate TEAEs reported (a bacterial infection observed in 1 subject who received 8400 mg MHAA4549A, and elevations of blood creatine phosphokinase [CK] observed twice in 1 subject who received 10800 mg MHAA4549A). No serious adverse events or dose-limiting toxicities were reported.

No safety issues were observed with respect to vital sign results and ECG measurements. Overall, no relevant differences in mean values and changes or shifts from baseline over time were observed with respect to dose levels or MHAA4549A compared to placebo. No subjects in the study developed an ATA response following study drug administration.

SECTION 1.2.2.3: Phase 2a Influenza Nasal Challenge Study (GV28985)

~~The second study was a~~ *In the* Phase 2a challenge study (GV28985~~) in~~*),* 101 healthy volunteers ~~infected~~*were nasally inoculated* with ~~a~~*the* H3N2 (A/Wisconsin/67/2005) strain of influenza virus. ~~Sixty~~*At 24 to 36 hours after inoculation, 60* subjects received *single IV* doses of 400, 1200, or 3600 mg MHAA4549A; *8 subjects received oseltamivir as an active comparator;* and 32 ~~subjects received placebo following nasal inoculation~~ *subjects received placebo. All subjects, regardless of initial treatment, received oseltamivir on Days 7–11 to mitigate risk of late shedding and/or further transmission of virus.*

Adverse events were collected from time of influenza A ~~virus one day earlier. Eight subjects received oseltamivir starting on~~ *inoculation (*Day ~~1. One subject~~ *0). Consistent with the Phase 1 studies (GV28916 and GV29609), there* was *no evidence of a dose-related pattern of TEAEs in MHAA4549A-treated subjects. Expected influenza-related symptoms and AEs were observed in inoculated subjects; these influenza-related AEs were similar in subjects who received MHAA4549A or placebo. Of the 101 subjects inoculated* ~~and inoculated, but not dosed.~~ *, 23 subjects experienced at least 1 adverse event following virus inoculation but prior to the first dose of study medication. The most common adverse events seen prior to the administration of study drug were headache (4 subjects), elevated blood pressure (4 subjects), dizziness (3 subjects), and procedural hemorrhage (3 subjects).*

Following administration of the study drug, there were 207 TEAEs in 86 of the 100 safety-evaluable subjects (86%), which occurred in a similar pattern across all treatment groups. Thirty-six of the 86 subjects (42%) experienced at least 1 study drug-related TEAE. Study drug-related TEAEs occurred in a similar proportion and in a similar pattern across all treatment groups. The most common TEAEs were elevations in ALT, AST, and amylase, which were reported in 15 of 25 TEAEs (60%) in subjects receiving placebo (n =32) or oseltamivir (n =8) and in 26 of 33 TEAEs (79%) in subjects receiving MHAA4549A (n =60). Similar elevations have been seen previously following influenza infection (Polakos et al. 2006; Yingying 2011). There were no clinically significant changes in vital signs, spirometry, or electrocardiograms and no pattern of study drug-related effects in these parameters. There were no observed adverse events or safety events that were considered attributable to interactions between oseltamivir and MHAA4549A.

No subject experienced a serious adverse event prior to the first dose of study drug. Three treatment-unrelated serious adverse events were reported by 2 subjects: 1 subject who received placebo reported symptoms of major depression on Day 15; and 1 subject who received 3600 mg MHAA4549A reported a lower limb fracture on Day 109 and a post-operative wound infection on Day 133 after study drug administration.

One subject in the placebo group tested positive for ATAs at baseline as well as post-baseline. The immunogenicity incidence rate among the 60 subjects who received MHAA4549A was 0%.

~~Most AEs appeared to reflect symptoms of an active influenza infection and occurred primarily within the first 21 days after patients received their virus inoculation and dose of MHAA4549A or placebo (123 of 213: 58%). Following the resolution of the influenza symptoms, even though levels of MHAA4549A remained relatively high, the number of AEs dropped and remained low throughout the remainder of the study: 59 of 213 (28%) of all AEs occurred between Study Days 22 and 60, and 31 of 213 (15%) of all AEs occurred between Study Days 61 and 120. Differences between treatment groups in the number and severity of AEs during the first 22 days appeared to reflect variability in the extent and severity of the influenza infection. Throughout the entire study, the pattern of AEs did not differ substantially between subjects who received placebo and subjects who received any dose of MHAA4549A.~~

~~The percentage of AEs that investigators judged to be related to study drug treatment was 12/33 (36%) for the 400 mg group, 10/40 (25%) for the 1200 mg group, 11/52 (21%) for the 3600 mg group, and 25/88 (28%) for subjects receiving placebo. Of those AEs considered related, however, 15 of 25 (60%) in the placebo cohort and 26 of 33 (79%) in all MHAA4549A cohorts consisted of elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or amylase. These laboratory abnormalities have been shown to be associated with the influenza infection (Polakos et al 2006;~~

Yingying 2011) and were not observed in either the previous or subsequent Phase 1 studies (i.e., GV28916, GV29609) where MHAA4549A was administered to subjects without influenza infection.

There were 3 SAEs in Study GV28985, none of which were assessed as related to MHAA4549A. One was in a subject hospitalized with a depressive psychosis. Due to his previous history of depression and the known association of psychosis with influenza infections, the Investigator considered this event unrelated to study drug. The other 2 SAEs were in one subject who fell and required a surgical repair of a fractured tibial plateau. This same subject was subsequently hospitalized for her second SAE, which was a post surgical wound infection. Neither of these events was considered related to study treatment.

In GV28985, the immunogenicity incidence rate amongst the 60 subjects who received MHAA4549A was 0%. One subject tested positive for ATAs. This subject tested positive for ATA at baseline and post baseline. This subject was in the placebo group, which included 32 other subjects, resulting in an immunogenicity prevalence rate (ATA positive rate at baseline) of 3.1% and an immunogenicity incidence rate (ATA titers post baseline) of 3.1%, as well, within the placebo group. Overall, study GV28985 had an immunogenicity prevalence rate of 1%.

SECTION 1.2.2.4: Phase 1 High Dose Safety Study GV29609

A Phase 1 (GV29609) study was initiated to evaluate the safety and tolerability of a single intravenous (IV) doses at 8400 mg or 10800 mg MHAA4549A as compared to placebo when administered to 14 healthy volunteers. The starting dose of 8400 mg was based on simulations from a semi-quantitative pharmacokinetic model (Figure 2) developed from the Phase 2a challenge study (GV28985), which suggests that the 8400 mg may be the minimum dose that is expected to show a separation of nasal exposure from a dose of 3600 mg. The simulation assumes that pharmacokinetics can be extrapolated at doses above 3600 mg and that the PK profile in severely ill patients is similar to the PK profile of healthy volunteers in the Phase 2a challenge study. The highest proposed dose of 10800 mg was chosen in GV29609 to provide safety coverage for those exposures that might be reached in a 40-kg individual dosed with a flat dose of 8400 mg.

GV29609 is currently on-going, but preliminary analysis of unblinded safety data up to day 57 shows that the 8400 mg and 10800 mg treatment groups are safe and well tolerated.

- In subjects who received 8400 mg MHAA4549A (N=4):

  3 of 4 subjects reported 12 AEs

6 AEs were reported as related to 8400 mg MHAA4549A: 3 headaches, pruritus, 1 peripheral swelling, and 1 nasal congestion

- ~~In subjects who received 10800 mg MHAA4549A (N=4):~~

  ~~4 of 4 subjects reported 7 AEs~~

  ~~3 AEs reported as related to the 10800 mg MHAA4549A treatment group: 1 nausea, 1 headache, and 1 asthenia~~

- ~~In subjects who received placebo (N=6):~~

  ~~2 of 6 subjects reported 5 AEs~~

  ~~1 AE was reported as related to study drug: 1 headache~~

~~All AEs were reported as mild except for an unrelated moderate AE of an increase in creatinine kinase in one subject who received 10800 mg MHAA4549A. There were no SAEs and no subjects have discontinued the study for any reason.~~

~~As in both previous studies, headache was the most common AE. Headache was reported by 3 subjects (37.5%) who received 8400 mg MHAA4549A; 1 subject (12.5%) who received 10800 mg MHAA4549A and 2 subjects (33.0%) who received placebo.~~

~~Based on this data, MHAA4549A is considered generally safe and well tolerated.~~

SECTION 1.2.3: ~~Clinical Efficacy Background~~*Clinical Pharmacokinetics*

The Phase 1 *EIH* study (GV28916) demonstrated that MHAA4549A *serum* pharmacokinetics were ~~generally~~ dose proportional~~.~~ *with a mean half-life of approximately 23 days (range: 21.9–24.6 days).* The *pharmacokinetic (*PK*)* profile appeared consistent with that of a human IgG1 antibody that lacks known endogenous host targets~~.~~ *(Bai et al. 2012; Ishida et al. 2015).*

~~In the Phase 2a challenge study (GV28985), 101 healthy volunteers were inoculated with influenza virus 24-36 hours prior to dosing with MHAA4549A. Following inoculation, 60 subjects received doses of 400 mg, 1200 mg, or 3600 mg MHAA4549A, 32 subjects received placebo, 8 subjects received a 5-day course of oseltamivir, and 1 subject was not dosed. The interim efficacy analysis~~ *In the Phase 2a influenza nasal challenge study (GV28985), serum MHAA4549A concentrations exhibited a biphasic disposition with an initial rapid distribution phase followed by a slow elimination phase, which was also observed in the Phase 1 EIH study (GV28916). MHAA4549A demonstrated linear pharmacokinetics. The group mean maximum observed concentration (C_{max}) increased in a dose-proportional manner, at 116 µg/mL for the 400-mg dose group and 1110 µg/mL for the 3600-mg dose group. Similarly, the group mean area under the curve from zero to infinity ($AUC_{0\text{-}infinity}$) was 1800 and 18100 day •µg/mL for the 400- and 3600-mg dose groups, respectively, and was approximately dose proportional. PK data from the Phase 2a study (GV28985) are consistent with those observed in the Phase 1 EIH study (GV28916), with MHAA4549A demonstrating a mean half-life of approximately 23 days (range: 22.5–23.7 days).*

In the Phase 1 high-dose study (GV29609), MHAA4549A showed linear pharmacokinetics, with a mean half-life of approximately 21.5 days (range: 21.4–21.6 days). For the 8400- and 10800-mg dose groups, the mean apparent clearance (CL) and the mean volume of distribution at steady state (V_{ss}) ranged from 151 to 167 mL/day and from 4590 to 4170 mL, respectively. PK data from the Phase 1 high-dose study (GV29609) is consistent with those observed in the Phase 1 EIH study (GV28916) and Phase 2a study (GV28985).

SECTION 1.2.4: *Clinical Efficacy Background*

The virologic efficacy analysis for the Phase 2a influenza nasal challenge study (GV28985), presented in ~~Table 1 included~~*Table 1, includes* the Intent-to-Treat infected (ITTI) population~~ followed until at least Day 29~~ who received 400 mg MHAA4549A (n=11), 1200 mg MHAA4549A (n=13), 3600 mg MHAA4549A (n=14), *oseltamivir alone (n =2), or* placebo (n=21). *The ITTI population included all subjects who were randomized, inoculated with challenge virus,* and ~~oseltamivir (N = 2). Analysis~~*had laboratory confirmed evidence* of ~~efficacy~~*influenza infection as defined by one or more of the following:*

- *A positive cell culture assay by 50% tissue culture infectious dose ($TCID_{50}$) at least once during quarantine postchallenge virus inoculation*

  Or

- *At least two positive detections by any quantitative polymerase chain reaction (qPCR) assay between virus inoculation and day of discharge* from ~~the 3600~~ *quarantine*

  Or

- *Seroconversion (≥4-fold rise in titer compared to baseline)*

SECTION 1.2.4.1: *Virologic Efficacy*

The 400 mg dose ~~level~~ demonstrated a ~~statistically significant~~ decrease in viral shedding ~~from the upper respiratory tract as measured by the area under the curve (97.5%~~ *(*reduction *in median viral area under the curve [AUC]* by ~~quantitative polymerase chain reaction~~ [qPCR]) ~~and peak viral load (77% reduction by qPCR). All subjects have completed dosing, and interim PK and efficacy data are available in the Investigator's Brochure and upon request.~~ *by 46% (p =0.05) and peak viral load (reduction in median peak viral load by qPCR) by 20.4% (p =0.02). The 1200-mg dose showed a decrease in viral shedding by 3.0% (p =0.90) and peak viral load by 0.3% (p =1.00). The 3600-mg dose level demonstrated a significant decrease in viral shedding by 97.5% (p =0.01) and peak viral load by 77.3% (p =0.002) [Table 1]. The decreased efficacy observed in the 1200-mg dose group is thought to be due to the variability from the challenge model and intersubject differences.*

~~In the GV28985 study, all subjects received oseltamivir started on Day 7 for a 5-day course, and there were no observed AEs or imbalances in safety events that were considered attributable to interactions between oseltamivir and MHAA4549A. The PK profile of MHAA4549A and oseltamivir in GV28985 are being analyzed to exclude potential drug-drug interactions, and this analysis will be available before the start of this study (GV29216).~~

SECTION 1.2.4.2: *Symptomatic Efficacy*

The A/Wisconsin/67/2005 virus induced mild symptoms that were predominantly ~~captured in the upper respiratory tract symptoms that included runny nose, stuffy nose, and sneezing.~~

~~The~~ *limited to the upper respiratory tract, including rhinorrhea, nasal congestion, and sneezing. The duration and severity of influenza-related symptoms (rhinorrhea, nasal congestion, sneezing, sore throat, earache, malaise, cough, shortness of breath, headache, and muscle/joint ache) were collected on a self-reported* Symptom Diary ~~Cards used~~*Card. The cards grade the symptoms on* a scale of 0–3, where Grade 0 is absence, Grade 1 is just noticeable, Grade 2 is bothersome but does not prevent participation in activities, and Grade 3 is bothersome and interferes with activities. Composite clinical symptom scores ~~from Study GV28985~~ for the ~~ITT infected (~~ITTI~~)~~ population are shown in Table 1.

~~Given the variability of the symptom scores the results were not statistically significant. However~~*Consistent with the virological results*, there was a *trend toward a* decrease in the ~~AUEC of~~ symptoms scores for the 3600-mg dose~~, which is consistent with the virological results described in Table 1. Data from the oseltamivir treated group is also shown, but it should be noted that only 2 subjects were in the ITT infected population.~~*with a mean reduction of the composite symptom score of 82% (Table 1).*

The responses observed in the Phase 2a study (GV28985) suggest that ~~a~~ higher ~~dose~~*doses of MHAA4549A* may ~~provide better~~*improve virological and symptomatic* efficacy in a population with ~~established~~*influenza* infection. ~~An~~*Because of this, an* 8400-mg dose will be ~~included~~*assessed* in this ~~Phase 2b~~ study ~~for further dose ranging. The rationale for selected dosages is further explained in Section 3.2.4.~~

~~See the MHAA4549A Investigator's Brochure for additional details on nonclinical and clinical studies~~.

SECTION 1.3.1: Study Rationale

Two Phase 1 (GV28916, GV29609) studies have demonstrated that MHAA4549A is safe and well tolerated to date in healthy volunteers at doses up to ~~8400~~*10800* mg. Data from a Phase 2a study (GV28985) ~~demonstrates safety in healthy subjects inoculated with influenza virus and provides evidence~~*demonstrated* that the3600 mg ~~dose of~~ MHAA4549A *dose* is *safe, well tolerated, and* effective in reducing viral titers *as compared*

to placebo in healthy volunteers inoculated with influenza ~~A virus.~~ *virus. No MHAA4549A-specific TEAEs have been identified in any of our clinical studies.* When combined with ~~previous~~ nonclinical studies *demonstrating* that ~~showed~~ MHAA4549A ~~to have~~*has a well-tolerated safety profile and* in vitro and in vivo efficacy~~, a well tolerated safety profile, and anti viral activity~~ *against influenza virus*, these findings support further ~~clinical~~ development of MHAA4549A.

~~In this Phase 2b study (GV29216), MHAA4549A is being evaluated in combination with the current standard of care (oseltamivir), to decrease the severity and duration of viral infection with influenza A virus with the ultimate goal of reducing the clinical symptoms of infection as compared to oseltamivir with placebo.~~ *Initially, this GV29216 Phase 2b study enrolled patients in a two-arm treatment study comparing 3600 mg MHAA4549A with oseltamivir versus placebo with oseltamivir. This current Phase 2b study has added an additional arm to evaluate the improvement in outcome of a combination therapy of 3600 mg MHAA4549A with oseltamivir or of 8400 mg MHAA4549A with oseltamivir versus placebo with oseltamivir for additional dose-response information. All patients will receive oseltamivir, which is part of the recommended standard of care for hospitalized influenza patients. Therefore, at a minimum, all patients will be treated with standard of care for influenza.* There are three primary goals for this Phase 2b study:

- Demonstrate the safety and efficacy of MHAA4549A in combination with oseltamivir in hospitalized influenza A patients
- [redacted]
- Demonstrate and evaluate the optimal endpoints for study in hospitalized patients with influenza A, given the lack of precedence for approval in patients hospitalized with influenza infection, an area of high unmet medical need

~~Initially, this GV29216 Phase 2b study enrolled patients in a two-arm treatment study comparing 3600 mg MHAA4549A with oseltamivir versus placebo with oseltamivir.~~

~~This current Phase 2b study has added an additional arm to evaluate the improvement in outcome of a combination therapy of 3600 mg MHAA4549A with oseltamivir or of 8400 mg MHAA4549A with oseltamivir versus placebo with oseltamivir. All patients will receive oseltamivir, which is part of the recommended standard of care. In addition, and as discussed above, MHAA4549A is a human monoclonal antibody that has, to date, shown an acceptable safety profile, a PK profile consistent with that of a IgG1 human antibody that lacks known endogenous host targets, and demonstrated antiviral activity at the planned dose level of 3600 mg.~~

~~This study (GV29216) will assess severely ill patients who may be infected with various influenza A strains, have a higher viral burden and longer duration of viral shedding than the healthy volunteers in GV28985, and who may, therefore, require doses higher than 3600 mg. A Phase 1 (GV29609) study is currently on going to assess the safety, tolerability, and pharmacokinetics of 8400 mg and 10800 mg doses of MHAA4549A. The starting dose of 8400 mg was selected based on simulations from a semi-quantitative PK model developed from the Phase 2a challenge study (GV28985), suggesting that 8400 mg MHAA4549A may be the minimum dose that is expected to show a separation of nasal exposure from a dose of 3600 mg. This simulation assumes that pharmacokinetics can be extrapolated at doses above 3600 mg and that the PK profile in severely ill patients is similar to the PK profile of healthy volunteers in Phase 2a challenged with influenza A virus. The 10800 mg dose was chosen to provide assurance of safety for the increased MHAA4549A levels that may be reached in smaller individuals who received 8400 mg.~~

~~A preliminary, unblinded analysis of the safety data from GV29609 up to Day 57 has shown that the 8400 mg and 10800 mg treatment groups are safe and well tolerated. In subjects who received 8400 mg MHAA4549A, 3 of 4 subjects reported 12 AEs. In subjects who received 10800 mg MHAA4549A, 4 of 4 subjects reported 7 AEs. In subjects who received placebo, 2 of 6 subjects reported 5 AEs. All AEs were reported as mild, except for one unrelated moderate AE of an increase in creatinine kinase in one subject who received 10800 mg MHAA4549A. There were no SAEs and no subjects have discontinued the study for any reason. As in previous studies, headache was the most common AE, and was reported by 3 subjects (37.5%) who received 8400 mg MHAA4549A, 1 subject (12.5%) who received 10800 mg MHAA4549A, and 2 subjects (33.0%) who received placebo. As a result, the Sponsor feels that the 8400 mg dose is safe to include in Study GV29216.~~

~~The 8400 mg dose is also expected to be safe based upon previous nonclinical and clinical safety assessments. Nonclinical safety data do not show any expected or unexpected toxicity.~~

SECTION 1.3.2.1: ~~Treatment in Combination with Oseltamivir~~

~~All patients in the study will receive oseltamivir as the current standard of care treatment, either with or without MHAA4549A. Therefore, at a minimum, all patients will be treated with the standard of care for influenza. Given that MHAA4549A is an antibody, the potential for a drug-drug interaction with oseltamivir is very low. In the Phase 2a challenge study (GV28985), study subjects received MHAA4549A followed by oseltamivir with no AEs attributable to the combination therapy noted to date. In addition, in this Phase 2b study the PK profile of oseltamivir in concomitantly treated subjects will be assessed.~~

SECTION 1.3.2.2: ~~Drug Mechanism and Preclinical Studies~~

~~The available pre-clinical data suggest that there is low risk for drug target related safety events in healthy humans since MHAA4549A specifically targets an epitope on a viral protein (i.e., the human influenza A virus HA glycoprotein), which is not endogenously expressed in human tissues. Furthermore, there were no adverse MHAA4549A related findings demonstrated in nonclinical studies at doses up to 150 mg/kg administered weekly for 5 weeks and no evidence of target present in host tissues.~~

SECTION 1.3.2.3: ~~Rationale for Selection of Phase 2b Study Population~~

~~The target patient population of hospitalized patients with severe influenza A requiring oxygen (O_2) or positive pressure ventilation (PPV) is considered an appropriate population to test MHAA4549A for the following reasons:~~

- ~~Nonclinical safety data does not show any expected or unexpected toxicity.~~
- ~~Clinical safety data for MHAA4549A demonstrate a well tolerated safety profile:~~
  - ~~AEs in the Phase 1 study (GV28916) were mild and did not show a dose relationship; there were no ATAs detected in patients treated with MHAA4549A after 120 day follow up visit.~~
  - ~~All AEs in GV29609 from a preliminary analysis of unblinded safety data up to day 57 were reported as mild except for an unrelated moderate AE of an increase in creatinine kinase in one subject who received 10800 mg MHAA4549A. There were no SAEs and no subjects have discontinued the study for any reason.~~

~~In the Phase 2a study (GV28985), MHAA4549A was generally well tolerated. A few subjects in all treatment groups were observed to have transient elevations in ALT, AST, and amylase levels. There was no dose dependent relationship of the ALT/AST/amylase elevations with MHAA4549A and the overall event rate was in line with published rates associated with the influenza challenge model regardless of treatment arm: 27/100 [27%] in GV28985 vs. approximately 26% in previous challenge studies (Polakos 2006, Yingying 2011). There were no SAEs related to study drug. There were a total of 3 SAEs unrelated to MHAA4549A in two subjects. One subject reported depressive psychosis associated with influenza. The second subject reported a broken knee with a subsequent infection following a surgical procedure.~~

Although there has been no benefit demonstrated for MHAA4549A in the setting of hospitalized influenza, there is a possibility that patients may have improved clinical outcomes from this therapy.

Potential risks of MHAA4549A include immunogenicity and infusion-related reactions. Theoretically, any biologic agent may evoke these responses. To date, MHAA4549A has not been associated with the development of allergic or anaphylactic reactions or infusion-related reactions in nonclinical or clinical studies. In the three

clinical trials conducted so far, none of the subjects dosed with MHAA4549A developed an ATA response. No adverse events have been identified that are specific to MHAA4549A.

SECTION 1.3.2.1: Patient Monitoring and Supervision

MHAA4549A will be administered to enrolled patients in a hospital environment under close medical supervision by *a* physician ~~investigators~~*or medically qualified designee*. Medical staff will be available for prompt evaluation and treatment of any AEs. Emergency resuscitation equipment and emergency facilities will be readily available. Patients will undergo screening assessments to confirm eligibility, will be closely monitored during the administration of MHAA4549A, and will be resident for at least 24 hours following the administration of MHAA4549A. Furthermore, safety laboratory tests relating to the blood chemistries, including liver function tests will be conducted.

An internal monitoring committee (IMC) in combination with a scientific oversight committee (SOC) will provide safety monitoring for the study in addition to the ongoing review of safety by the Medical Monitor and Safety Scientist. See Section 3.1.2 for more information.

In addition to the regularly scheduled safety reviews of the patient data by the IMC and SOC, an additional sentinel safety cohort of the first 30 patients or patients after the first influenza season, whichever occurs first, will be assessed by the IMC and SOC.

The 120-day follow-up period in the Phase 1 and 2a studies allowed for monitoring of subjects for approximately 5 half-lives of MHAA4549A. No *treatment-induced* ATAs were detected in ~~the~~*both* Phase 1 ~~study, while one~~*studies. One* subject who received placebo in the Phase 2a study tested positive for ATAs at baseline and post-baseline timepoints as described in Section 1.2.2. The Phase 2b study will also include a safety follow-up period of 60 days and an unlimited collection of all SAEs believed related to MHAA4549A.

Based on the above data and design of this study, the Sponsor concludes that the benefit-risk profile of MHAA4549A in the population with severe influenza is favorable.

SECTION 2.3: SECONDARY EFFICACY OBJECTIVES

The secondary efficacy objectives for this study are as follows:

- *To compare the clinical status of patients at Days 1–7, 14, and 30 using an ordinal outcome with six clinical statuses. Patients will be categorized into one of the following six mutually exclusive categories on Days 1–7, 14, and 30*
    1. *Death;*
    2. *In the ICU;*
    3. *Non-ICU hospitalization, requiring supplemental oxygen;*
    4. *Non-ICU hospitalization, not requiring supplemental oxygen;*

5. *Not hospitalized, but unable to resume normal activities; or*
6. *Not hospitalized with full resumption of normal activities*

- To measure clinical failure, as defined in Section 3.3.3, after 24 hours post infusion of study drug
- To determine the time to clinical resolution of *abnormal* vital signs
- To measure mortality in patients
- To determine changes in the extent and duration of viral ~~shedding~~*burden* in nasopharyngeal samples as a measure of the pharmacodynamic response
- ~~To identify any potential viral resistance to MHAA4549A in influenza A isolates from upper respiratory samples~~

SECTION 2.5: EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

SECTION 3.1.1: Overview of Study Design

This is a Phase 2b (GV29216), randomized, double-blind, placebo-controlled study designed to assess the safety and clinical activity of a single IV dose of 3600 mg MHAA4549A or a single IV dose of 8400 mg MHAA4549A in hospitalized patients with severe influenza A in combination with oseltamivir versus a comparator arm of placebo with oseltamivir. *A Sponsor-approved influenza test that includes influenza antigen test or influenza polymerase chain reaction (PCR) test must be used to diagnose influenza A infection for study eligibility.* This study is planned to take place in approximately 170 study centers globally.

Initially, GV29216 targeted enrollment into two treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir or a single IV dose of placebo with oseltamivir.

In this version of the protocol, patients will be randomized 1:1:1 into three treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir, a single IV dose of 8400 mg of MHAA4549A with oseltamivir, or a single IV dose of placebo with oseltamivir. *Patients will be stratified by country, PPV versus supplemental O_2 at randomization, and suspected or confirmed bacterial pneumonia versus no bacterial pneumonia based on the status at randomization.* All patients *must begin study drug infusion within 48 hours of hospital admission. In addition, all patients* will receive oseltamivir~~, a NAI,~~ as standard therapy for a minimum of 5 days ~~after study drug administration. Oseltamivir at~~ *(10* doses ~~of 75 mg twice a day (BID) or 150 mg BID is permitted in order to be consistent with local standard of care practice.~~ *) starting no later than 12 hours after completion of study drug administration. Oseltamivir t*~~T~~reatment for longer than 5 days is permitted based on local investigator discretion. ~~The patient must start oseltamivir no later than 8 hours after completion of study drug administration. The study has a planned enrollment of approximately 330 patients globally.~~

Hospitalized patients with an O_2 or PPV requirement will be evaluated for influenza A infection. Enrollment in this study requires ongoing treatment within 24 hours of hospital admission with one of the following:

- any PPV or
- any supplemental O_2 to maintain oxygen saturation (SpO_2) $>$ 92% (Section 3.3.2)

Patients on PPV should not exceed *approximately* 45% of the total patients enrolled *in the study*.

~~A Sponsor-approved influenza test that includes influenza antigen test or influenza polymerase chain reaction (PCR) test must be used as an aid in the diagnosis of influenza A infection.~~

[redacted]

~~At the time of randomization, patients who are eligible for enrollment, as described above, will be randomized to receive 3600 mg MHAA4549A or 8400 mg MHAA4549A or placebo. Patients will be stratified by country, PPV versus supplemental O2 at randomization, and suspected or confirmed bacterial pneumonia versus no bacterial pneumonia based on the status at randomization.~~

~~Eligible patients who are enrolled into the study will receive a single IV infusion of 3600 mg MHAA4549A or a single IV infusion of 8400 mg MHAA4549A or a single IV infusion of placebo on Day 1. All patients must begin study drug infusion within 48 hours of hospital admission or sooner if possible. All patients will receive oseltamivir for a minimum of 5 days (10 doses), starting on Day 1, beginning no later than 8 hours after completion of study drug administration.~~

All patients will be followed and evaluated at minimum on a daily basis for the duration of their hospital stay consistent with the planned schedule of ~~assessments~~*activities*. Any suspicion of bacterial superinfection should be thoroughly evaluated including microbiological confirmation, if possible. A follow-up study visit should occur on Day 14 $\pm$1 (if discharged before Day 14); Day 30$\pm$4 days (if discharged before Day 30); ~~and~~ Day 60$\pm$4*7* days (if discharged before Day 60).

Safety evaluations will also be provided by an IMC and SOC, as defined in the IMC and SOC agreement (see Section 3.1.2). If after review of available study data, the IMC and SOC conclude that there is a significant toxicity or worsening disease associated with MHAA4549A, they may recommend stopping further enrollment in the study.

An additional safety cohort of the first 30 patients, or patients from the first influenza season (whichever occurs first), will be assessed by the IMC and SOC. A review of chemistry laboratory test results, AEs, SAEs, vital signs, and deaths will be assessed.

A schedule of ~~assessments~~*activities* is provided in Appendix 1a and Appendix 1b. A diagram of the study design is presented in Figure 1.

SECTION 3.1.2: Internal Monitoring Committee and Scientific Oversight Committee

A combined approach with both an IMC and a SOC is proposed to enhance patient safety. The IMC consists of Sponsor representatives from the following functions: Clinical Science, Drug Safety, Biostatistics, and Statistical Programming and Analysis*,*

and may invite representatives from other functional areas on an ad-hoc basis when additional expertise is required (e.g., Clinical Pharmacology, Research, etc). The IMC members will be unblinded to patient treatment and assignment. The Clinical Science representative on the IMC (IMC Chair) will be a person other than the Study Medical Monitor and will not be involved in the conduct of the study or have any contact with study investigators or site staff. The Study Medical Monitor will remain blinded to individual treatment assignments, unless, in exceptional cases, specific circumstances require Study Medical Monitor unblinding after IMC Chair approval. The Drug Safety Scientist on the IMC will also not be involved in the conduct of the study or have any contact with the study investigators. The Biostatistician and Statistical Programmer are the only IMC members involved in the conduct of the study; however, they do not have any contact with study investigators, and all discussion within the IMC are kept confidential. All other Sponsor and Contract Research Organization personnel involved in the conduct of the study will remain blinded to individual treatment assignments.

SECTION 3.2.2: Rationale for Patient Population and Primary Endpoint

Severe influenza, for the purpose of this study, is defined as requiring one of the following treatments: any supplemental O_2 to maintain an $SpO_2 > 92\%$ or PPV. PPV is defined as any mechanical positive pressure device to maintain oxygenation; this can include positive pressure mask and intubation. ~~A Sponsor-approved influenza test, which includes influenza antigen test or influenza PCR test, must be used as an aid in the diagnosis of influenza A infection.~~

SECTION 3.2.3: Rationale for Control Group and Treatment Window

In this study, the standard of care regimen for the control or comparator group *(hospitalized influenza A patients)* is oseltamivir, an NAI. In the treatment groups, MHAA4549A will be dosed in addition to oseltamivir. ~~Either 75 mg or 150 mg orally BID oseltamivir~~*Oseltamivir* for a minimum of 5 days is permitted following treatment with MHAA4549A. Treatment for longer than 5 days is permitted based on local investigator discretion (WHO 2005; Fiore et al. 2011; ~~CDC 2015~~*CDC 2016*). The oseltamivir dosing regimen is listed in Table 2. This control treatment was based on consideration of safety, ethics, and efficacy for treatment of severe influenza and is consistent with guidelines for antiviral treatment of hospitalized patients with influenza (Harper et al. 2009; Fiore et al. 2011).

If oseltamivir resistance is highly suspected or identified ~~during treatment~~ or oseltamivir route of administration challenges are encountered, then following discussion with the Sponsor ~~medical representative~~*Medical Monitor*, an alternative NAI to oseltamivir may be used. *For renal dose adjustments, local standard-of-care practice/local package insert should be followed and documented in the eCRF. Capsules other than 75 mg (for 75 mg twice a day [BID] or 150 mg BID regimens) cannot be provided through the study Interactive Voice and Web Response System (IxRS). In these instances, the study site may supply the appropriate dose and be reimbursed by the Sponsor.*

From a safety standpoint there are no expected drug interactions between MHAA4549A, a monoclonal antibody, and any NAI, which are small molecule drugs that bind to a different viral protein than MHAA4549A. In the Phase 2a challenge study, all subjects that were dosed with MHAA4549A also received a 5-day course of oseltamivir starting on Day 7. There were no safety effects attributable to the combination when the drugs were present concurrently. ~~The pharmacokinetics~~*In the Phase 2a challenge study, MHAA4549A treatment did not appear to impact the exposure* of oseltamivir and its ~~potential~~*active metabolite oseltamivir carboxylate. There was no suggestion of PK drug-drug* interaction ~~with~~*between* MHAA4549A ~~are being assessed from the Phase 2a study.~~*and oseltamivir.*

For this Phase 2b study, a combination of MHAA4549A and oseltamivir was determined to be the most clinically feasible treatment regimen, both from an ethical as well as a practical perspective. The treatment of all patients with oseltamivir ensures that all patients will receive the standard of care. Given the high morbidity and mortality of hospitalized patients with influenza A along with guidelines from Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) it is recommended that NAIs are the standard of care for hospitalized patients with influenza A (Harper et al. 2009; *CDC 2016*~~CDC Website~~). Furthermore, pre-clinical efficacy data from a study using MHAA4549A and oseltamivir in combination showed a potential synergistic effect of both compounds which may be due to the different and potentially complementary mechanisms of action, i.e. targeting viral HA and neuraminidase (NA).

Dosing of MHAA4549A is confined to a treatment window designed for best expected treatment success and to ensure that any observed effects can be attributed to the study drug with high confidence. MHAA4549A shall only be dosed within 5 days of onset of symptoms (including fever, chills, malaise, dry cough, loss of appetite, myalgias, coryza, or nausea), no later than 48 hours after admission to the hospital, and if a subject has taken less than a total of 6 doses (3 doses for peramivir) of approved anti-influenza therapy from onset of symptoms. This proposed window is supported by data demonstrating that hospitalized influenza patients benefit from NAI treatment even at 5 days from onset of symptoms (Louie et al. 2012). The patient must start standard-of-care oseltamivir no later than ~~8~~*12* hours after completion of MHAA4549A administration.

SECTION 3.2.4: Rationale for MHAA4549A Dosage

~~A single~~*Single* IV ~~dose~~*doses* of 3600 ~~mg MHAA4549A or a single IV dose of~~ *and* 8400 mg ~~MHAA4549A was~~ *were* selected to assess the *safety,* efficacy~~-~~*, and pharmacokinetics* of MHAA4549A and to provide data for further clinical development. The selection of dose in this study ~~for severely ill patients~~ was based on *nonclinical efficacy data from* the ~~observed human~~*in vivo mouse influenza A infection models, the* pharmacokinetics in ~~Phase 1~~*clinical studies,* and the relationship between the pharmacokinetics, pharmacodynamics, and efficacy observed in ~~a~~*the* Phase 2a ~~human~~

challenge *study* ~~model of influenza. MHAA4549A was shown to be safe and well tolerated at all dose levels (ranging from 1.5 mg/kg to 45 mg/kg for Phase 1 and 400-3600 mg for Phase 2a) through a follow-up period of 120 days post dose in the Phase 1 and Phase 2a study.~~ *in influenza A (GV28985).*

The dose ~~levels selected for this study were determined following analysis of data from~~*3600 mg is based on* the Phase 2a *challenge* study (GV28985), which demonstrated ~~the following:~~

- ~~The 3600 mg dose demonstrated~~ *both* a significant decrease in viral shedding in *the* upper respiratory ~~samples. Based on current interim analysis data, there was a 97.5% (p = 0.0051)~~ *tract and a* decrease in ~~area under the viral load time curve (AUEC) and a 77.3% decrease in peak viral load by qPCR measurement compared to~~ the ~~placebo group.~~
- ~~Symptom data in the Phase 2a study showed a decrease in the area under the serum concentration time curve (~~AUC~~)~~ of symptoms scores ~~for~~*in patients who received* the 3600-mg dose~~,~~ *of MHAA4549A* as ~~illustrated in Table 1, which is consistent with the virological results.~~
- ~~When~~ compared to *patients who received* placebo~~, a decrease in viral shedding was observed at the 400 mg dose but not at the 1200 mg dose, which may be due to variability in the challenge model and differences in infection rate, infection peak, virus level in the nasopharynx, nasal pharmacokinetics, immune status, and other inter-subject differences.~~
- ~~There were no safety concerns at any dose level associated with MHAA4549A.~~
- ~~Hospitalized patients generally have a longer duration of viral shedding and significantly more viral burden in the lower lung compartments; therefore, high concentrations of monoclonal antibody are likely needed to achieve sufficient occupancy of the virus binding sites in the upper and lower respiratory compartments. Furthermore, higher concentrations of monoclonal antibody may mitigate the risk of resistance for MHAA4549A, supporting addition of the 8400 mg MHAA4549A treatment arm.~~
- ~~Exploratory~~ *(see Section 1.2.4). An exploratory* exposure-response analysis of ~~GV28985 indicated that higher exposure appears to be associated with improved efficacy. Volunteers with nasal maximum concentration~~*this group demonstrated that subjects with nasal viral loads* greater than the median ~~value~~*viral load* had shorter time to resolution of viral shedding *as* compared with ~~volunteers in~~ the placebo group (median: 75.8 hours vs. 113.7 hours~~). However, volunteers~~*), whereas subjects* with ~~a~~ nasal ~~maximum concentration~~*viral loads* less than the median ~~value~~*viral load* had similar time to resolution of viral shedding compared with ~~volunteers in~~ the placebo group (median*: 112.1 hours vs.* 113.7 hours ~~vs 112.1 hours~~).

~~The Phase 2a challenge study (GV28985) confirmed proof of activity in decreasing area under viral load time curve, consistent with symptom data at the 3600 mg dose level.~~

~~GV29216 will assess severely ill patients who may be infected with various influenza strains, have a higher viral burden and longer duration of viral shedding than the healthy volunteers in Study GV28985, and who may, therefore, require doses higher than 3600 mg. As a result, an ongoing, Phase 1 (GV29609) study was initiated to evaluate the safety and tolerability of two single IV~~ *Thus, at higher viral loads, higher* doses of ~~8400 mg and 10800 mg MHAA4549A as compared to placebo when administered to 14 healthy volunteers. The starting dose of 8400 mg was selected based on simulations from a semi-quantitative PK model (Figure 2) developed from the Phase 2a challenge study, which suggests that 8400 mg may be the minimum dose that is expected to show a separation of nasal exposure from a dose of 3600 mg. This simulation assumes that pharmacokinetics can be extrapolated at doses above 3600 mg and that the PK profile in severely ill patients is similar to the PK profile of healthy volunteers in the Phase 2a challenge study. The highest proposed dose of 10800 mg was chosen in GV29609 to provide safety coverage for those exposures that might be reached in a 40 kg individual dosed with a flat dose of 8400 mg. Preliminary analysis of unblinded safety data up to day 57 shows that the 8400 mg and 10800 mg treatment groups are safe and well tolerated. In subjects who received 8400 mg MHAA4549A, 3 of 4 subjects reported 12 AEs. In subjects who received 10800 mg MHAA4549A, 4 of 4 subjects reported 7 AEs. In subjects who received placebo, 2 of 6 subjects reported 5 AEs. All AEs were reported as mild except for an unrelated moderate AE of an increase in creatinine kinase in one subject who received 10800 mg MHAA4549A. There were no SAEs and no subjects have discontinued the study for any reason. Headache was the most common adverse event. Headache was reported by 3 subjects (37.5%) who received 8400 mg MHAA4549A, 1 subject (12.5%) who received 10800 mg MHAA4549A, and 2 subjects (33.0%) who received placebo.~~*MHAA4549A are expected to be more efficacious.*

~~Nonclinical safety data do not show any expected or unexpected toxicity. Weekly administration of MHAA4549A (total of 5 doses) in Sprague-Dawley rats was well tolerated up to 150 mg/kg (the highest dose tested). Ex vivo tissue cross-reactivity study data showed no specific binding of MHAA4549A to any of the human or rat tissues examined.~~

~~Therefore, the 8400 mg dose is~~ *The 8400-mg dose was selected based on the hypothesis that severely ill patients hospitalized with influenza infection (the target population of MHAA4549A) are likely to have high viral loads and longer durations of viral shedding and require increased doses of MHAA4549A. Simulations from a semi-quantitative pharmacokinetic model developed from the Phase 2a challenge study (GV28985) suggest that 8400 mg is the minimum dose that will show a separation of nasal exposure from a dose of 3600 mg (Figure 2).*

Both the 3600- and 8400-mg doses of MHAA4549A are expected to be safe based ~~upon~~*on* previous ~~nonclinical and~~ clinical ~~safety assessments and will be included in this Phase 2b study for further dose ranging.~~

~~Although the~~ Phase 1 ~~study (GV28916) was conducted using body weight based dosing, the subsequent Phase 2a study (GV28985) and high dose Phase 1 study GV29609 used a fixed dosing strategy. Thus, the fixed dosing regimen will be used for this study, given the comparable MHAA4549A PK profiles, the practical advantages,~~ and ~~the positive safety profile of MHAA4549A to date. Further, fixed dosing is generally recommended with monoclonal antibodies, due to their minimal PK variability (Bai et al. 2012). The PK variability introduced by different dosing regimens (i.e., body weight based dosing versus fixed dosing) is moderate relative to the variability generally observed in pharmacodynamics, efficacy, and safety and would not be expected to be clinically meaningful.~~ *Phase 2a studies.*

SECTION 3.2.5: Rationale for Biomarker Assessments

[redacted]

SECTION 3.3.3: Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- *Clinical status of patient at Days 1–7, 14, and 30. This is an ordinal outcome with six mutually exclusive categories:*
  1. *Death;*
  2. *In the ICU;*
  3. *Non-ICU hospitalization, requiring supplemental oxygen;*
  4. *Non-ICU hospitalization, not requiring supplemental oxygen;*
  5. *Not hospitalized, but unable to resume normal activities; or*
  6. *Not hospitalized with full resumption of normal activities*
- Clinical failure after 24 hours post-infusion of study drug; defined as:
  - Progression to increased O_2 requirement defined by an increase in oxygen supplementation from low flow oxygen (i.e., 2–6 L/min) to high flow oxygen (~~>~~*(i.e., >*6 L/min) or from oxygen supplementation alone to any PPV or extracorporeal membrane oxygenation (ECMO)
  - Progression to ICU
  - Prolonged ventilation or O_2 support defined by >2 weeks, or
  - Death
- Time to clinical resolution of *abnormal* vital signs (3/5 criteria must be met):
  - $SpO_2 \geq 95\%$ without supplemental O_2
  - Respiratory rate <24 breaths per minute without supplemental O_2
  - Core temperature <37.2°C immediately prior to receipt of any antipyretic drug, and at least 6-8 hours from the last dose of antipyretic or core temperature >36°C in patients who are initially hypothermic
  - Heart rate (HR) <100 beats/minute
  - Systolic blood pressure (SBP) >90 mmHg
- All-cause mortality at Day 14, Day 30, and Day 60
- Influenza A viral load in nasopharyngeal samples
  - AUEC (qPCR)
  - Peak viral load (qPCR)
  - ~~Time to resolution~~*Duration* of ~~infection~~ *viral shedding* (qPCR)
  - ~~Identification of potential viral resistance~~
- Duration of hospitalization
- Duration of ICU stay
- Antibiotic usage for respiratory infections

- Complications of influenza:
  - Pneumonia (HAP/VAP)
  - Exacerbations of chronic lung disease
  - Myocarditis
  - ARDS
  - Otitis media
  - Other related complications
- All-cause readmission at Day 30 and Day 60
- Duration of ventilation

SECTION 3.3.5: Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- [redacted]

[redacted]

SECTION 4.1.1: Inclusion Criteria

Patients must meet the following criteria for study entry:

- Hospitalized men or women ≥ 18 years of age on the day of signing the informed consent or obtaining surrogate consent from an authorized representative
- Diagnosis of influenza A where a Sponsor-approved influenza test is used as an aid in diagnosis. A Sponsor-approved influenza test includes:
  - Influenza antigen test –OR–
  - Influenza PCR test
- One of the following markers of severity within 24 hours of hospital admission:
  - Requirement for PPV –OR–
  - Requirement for O_2 supplementation to maintain $SpO_2 > 92\%$ *(Source documentation should show that the patient's SpO_2 was less than 92% off oxygen. Source documentation may consist of either a SpO_2 off oxygen with a value below 92% or a documentation of the Investigator's rationale in lieu of this SpO_2 documentation.)*
- A negative urine or serum pregnancy test for women of child-bearing potential
- Patients of reproductive potential must agree to use reliable means of contraception as described below as a minimum (adherence to more stringent local requirements may be required):
  - For women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use two adequate methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment period and for at least 120 days after the ~~last~~ dose of study drug

    Abstinence is only acceptable if it is in line with 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.

    Barrier methods must always be supplemented with the use of a spermicide.

    Examples of contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, hormonal implants, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.

Male partners who have had a vasectomy should have the appropriate post-vasectomy documentation available of the absence of sperm in the ejaculate. The vasectomized male partner should be the sole partner for that patient.

- For men: agreement to remain abstinent or use a condom during the treatment period and for at least 30 days after the ~~last~~ dose of study drug and agreement to refrain from donating sperm during this same period

  Men with a pregnant partner must agree to remain abstinent or use a condom for the duration of the pregnancy.

  Abstinence is only acceptable if it is in line with 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.

- Non-reproductive potential is defined below (but could be superseded by local definitions, if they are more stringent):

  Women who are postmenopausal ~~(i.e., spontaneous~~*(≥12 months of non-therapy-induced* amenorrhea~~ for the past year confirmed by a follicle stimulating hormone [FSH] level greater than 40 mIU/mL unless the patient is receiving a hormonal therapy for their menopause)~~ *)*

  Women who are surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)

  Men who are surgically sterile (i.e., castration)

SECTION 4.1.2: Exclusion Criteria

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

- Pregnant or lactating, or intending to become pregnant during the study
  - Women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative ~~serum~~ pregnancy test result within 2 days prior to initiation of study drug.
- Hypersensitivity to monoclonal antibodies or to ~~the active substance or~~ any ~~excipients~~*constituents (sodium succinate, sucrose, polysorbate 20)* of MHAA4549A study drug
- Hypersensitivity to the active substance or to any excipients of oseltamivir
- Investigational therapy within the 30 days prior to study treatment
- Received prior therapy with any anti-influenza monoclonal antibody therapy (including MHAA4549A) *within* 8 months prior to study treatment
- Current treatment (within 7 days of dosing) with probenecid, amantadine, or rimantidine

- Patients who have taken more than a total of 6 doses (3 doses of peramivir) of anti-influenza therapy (e.g., oseltamivir, zanamivir, *laninamivir,* peramivir) in the period from onset of symptoms and prior to study treatment
- Admission > 48 hours prior to study treatment
- Onset of influenza symptoms (including fever, chills, malaise, dry cough, loss of appetite, myalgias, coryza, or nausea) > 5 days prior to study treatment
- Positive influenza B or influenza A + B infection within 2 weeks prior to study treatment
- High probability of mortality in the next 48 hours as determined by the investigator
- Patient requiring home or baseline oxygenation therapy
- Patient with history of chronic lung disease ~~resulting in baseline~~*with a documented* $SpO_2 < 95\%$ *off oxygen*
- Patient on a chronic dose of corticosteroids exceeding 10 mg/day of prednisone or equivalent steroid dose for a duration of greater than 14 days within 30 days of entry into study
- Creatinine clearance ≤ 10 mL/min
- Patients who received nasally administered influenza A vaccine within ~~the last~~ 7 days *prior to screening*
- Patients with the following significant immune suppression:
  - Bone marrow or solid organ transplant in the previous 12 months
  - Cancer chemotherapy in the previous 12 months
  - HIV infection with most recent CD4 < 200 cells/mL
  - Other significant immune suppression as determined by the investigator in discussion with the Sponsor Medical Monitor ~~or representative~~
- Patient on ECMO at time of randomization
- Any disease or condition that would, in the opinion of the site investigator or Sponsor, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol

SECTION 4.3.1.1: MHAA4549A and Placebo

~~The Sponsor will supply~~ MHAA4549A ~~and matching~~*will be supplied by the Sponsor in a sterile, preservative-free liquid solution in a single-use 15-mL USP/Ph. Eur. Type 1 glass vials filled to deliver 10 mL (500 mg) of MHAA4549A solution.*

MHAA4549A placebo~~.~~ *will be provided as a clear, colorless, sterile, preservative-free liquid solution and has the same vial configuration as the drug product.*

For information on the formulation~~, packaging,~~ and handling of MHAA4549A ~~and placebo~~, see the ~~Pharmacy Manual~~*pharmacy manual* and the ~~MHAA4549A Investigator's~~*Investigator's* Brochure.

~~The MHAA4549A vial delivers 10 mL (500 mg) of drug product solution, but may contain more (approximately 10.3 mL) than the stated volume to enable delivery of the entire 10 mL volume. MHAA4549A is formulated as 50 mg/mL in 10 mM sodium succinate, 240 mM sucrose, and 0.02% (w/v) polysorbate 20 at pH 5.5 and is contained in a 15 mL forma vitrum (USP/PH. Eur. Type 1) glass vial. The drug product is suitable for single use only and contains no preservatives.~~

~~Placebo for MHAA4549A has the same composition as the drug product (without MHAA4549A) and is supplied in an identical vial configuration. The placebo contains no preservatives and is suitable for single use only. Placebo is formulated as 10 mM sodium succinate, 240 mM sucrose, and 0.02% polysorbate 20 at pH 5.5 in a total volume of 10 mL in a 15 mL forma vitrum (USP/PH. Eur. Type 1) glass vial.~~

~~MHAA4549A and placebo are supplied in identical blinded vials labeled with unique kit numbers. IxRS will assign kit numbers for each treatment arm; all treatment arms will be assigned the same total number of vials for each treatment, and the same preparation instructions. Placebo is identical to active MHAA4549A in formulation but does not contain active drug substance.~~

SECTION 4.3.1.2: Oseltamivir (Tamiflu®)

Oseltamivir (Tamiflu®) is an influenza NAI indicated for treatment of acute, uncomplicated influenza. The Sponsor will provide *75-mg capsules of* oseltamivir ~~capsules~~ for up to a 10-day treatment course~~.~~ *(for 75- or 150-mg BID regimens). For renal dose adjustments, follow local standard-of-care practice/local package insert and document in the eCRF. Capsules other than 75 mg (for 75- or 150-mg BID regimens) cannot be provided through the study IxRS. In these instances, the study site may supply the appropriate dose and be reimbursed by the Sponsor.*

SECTION 4.3.2.1: MHAA4549A and Placebo

~~The randomization of patients will be managed by a central IxRS. All patients will be randomly assigned to receive either a single dose of MHAA4549A 3600 mg IV or MHAA4549A 8400 mg IV or placebo IV at a 1:1:1 ratio.~~

Administration of MHAA4549A or placebo will be performed in a setting with emergency medical equipment and personnel who are trained to monitor for and respond to medical emergencies. A qualified physician *or medically qualified designee* will be on site during study drug administration for all patients.

A single dose of MHAA4549A or placebo will be delivered by IV infusion following dilution in 0.9% normal saline over approximately 120 minutes. Study drug should be delivered using a 0*.20- to 0.22-*μm in-line filter. Compatibility testing has shown that MHAA4549A is stable when diluted in 0.9% normal saline in a polyvinylchloride bag, polyolefin bag, or ethylene vinyl acetate bag (EVA), at concentrations of 0.24 mg/mL up to 27.0 mg/mL. Study drug must be administered within the treatment window outlined

in Section 3.1.1. Further detailed instructions for preparation of study drug can be found in the Pharmacy Manual.

Subjects who experience a moderate-to-severe infusion-related reaction should have their infusion stopped. The infusion should not be restarted. The infusion will be discontinued in the event that the subject experiences a serious reaction and further dosing of subjects will be halted until the safety of the drug is assessed.

SECTION 4.3.2.2: Oseltamivir-Neuraminidase Inhibitor (NAI)

The Sponsor will supply *75-mg* oseltamivir (Tamiflu®) *capsules* for this study for up to a 10-day course~~. Either~~ *(for 75-* or 150-mg ~~of oseltamivir~~*BID regimens). Oseltamivir* will be administered twice daily as described in Section 3.1.1. Capsules can be opened and the granules administered via nasogastric tube, if required. Doses should be captured in the eCRF. *For renal dose adjustments, follow local standard-of-care practice/local package insert and document in the eCRF. Capsules other than 75 mg (for 75- or 150-mg BID regimens) cannot be provided through the study IxRS. In these instances, the study site may supply the appropriate dose and be reimbursed by the Sponsor.*

SECTION 4.3.3: Investigational Medicinal Product Accountability

Investigational medicinal products (IMPs) required for completion of this study (i.e., MHAA4549A and *75-mg* oseltamivir *capsules*) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced.

SECTION 4.5: CONCOMITANT THERAPY AND FOOD

Concomitant medication includes any medication (e.g., prescription drugs, over the counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 30 days prior to screening to the study completion/*early* discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. For any NAIs (e.g., oseltamivir, peramivir, zanamivir, laninamivir) that have been taken prior to study drug therapy, the number of doses and duration of therapy must be recorded.

SECTION 4.5.2: Prohibited Therapy

Use of other NAIs, including but not limited to oseltamivir, zanamivir, *laninamivir,* and peramivir, are prohibited during the study, but allowed up to a total of 6 doses (3 doses for peramivir) in the period from onset of symptoms and prior to study treatment as outlined in the exclusion criteria. Patients must start standard-of-care oseltamivir no later than ~~8~~*12* hours after completion of MHAA4549A administration. If oseltamivir resistance is highly suspected or identified ~~during treatment~~ or if oseltamivir route of administration challenges are encountered then, following discussion with the Sponsor's *Medical Monitor*~~medical representative~~, an alternative NAI to oseltamivir may be used.

SECTION 4.6.1: Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study ~~specific screening tests or evaluations.~~ *-related procedures.* Informed consent by authorized representatives may be obtained only if allowed by and in accordance with local regulations and Independent Review Board (IRB)/Independent Ethics Committee (IEC) policies and procedures. Informed Consent Forms (ICF) for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

SECTION 4.6.2: Diagnostic Testing for Enrollment

All hospitalized patients with severe influenza A must be assessed for disease confirmation prior to and enrollment into the study. A Sponsor-approved influenza test is required as an aid in the diagnosis of influenza A infection. This requires a nasopharyngeal swab be introduced into one nostril. *A lower respiratory tract sample may be used if appropriate for the Sponsor-approved local PCR test.* Note that the influenza antigen test or influenza PCR test result must be available within the 48-hour screening window.

SECTION 4.6.5: [redacted]

SECTION 4.6.6: [redacted]

SECTION 4.6.7: Physical Examinations

Day 1 physical examination is optional if already completed on Day -1 or -2.

SECTION 4.6.8: Vital Signs

Vital signs will include measurements of respiratory rate, *heart*~~pulse~~ rate, temperature, and systolic and diastolic blood pressures after the patient has been in a seated or supine position for >5 minutes. *Temperature should be measured using the same methodology throughout the study and should be measured prior to administration of*

any antipyretic drugs. Patients in intensive care may have vital signs assessed following local procedures, but those procedures should be captured in the eCRF in accordance with the eCRF instructions.

SECTION 4.6.9: Oxygen Saturation Measurements

To ensure that the respiratory status is well recorded, the following daily measurements will be performed. ~~Unless clinically contraindicated, all~~*All* patients will have their SpO_2 and corresponding respiratory assessments recorded daily in the morning between 6:00 a.m. and 12:00 noon local time. ~~Patients~~*Unless clinically contraindicated*, patients* on low flow O_2 will have a daily trial of their SpO_2 while on and off the supplementation, as outlined in ~~Appendix 2, and both values will be recorded.~~ *Appendix 2, and both values will be recorded. If a patient is clinically able to be removed from oxygen outside the time window above (6:00 a.m. to 12:00 noon), the trial-off data should be recorded as an unscheduled visit.*

If the patient is on oxygen supplementation, SpO_2 measured by pulse oximetry and the corresponding respiratory assessments (e.g., FiO_2, flow rate) will be recorded. If the patient is on PPV, partial pressure of arterial O_2 (PaO_2) and the corresponding respiratory assessments (e.g., FiO_2, ventilator mode, ventilator respiratory rate, positive end expiratory pressure) will be recorded. If clinically appropriate (i.e., the patient is on non-invasive PPV), the conversion table in Appendix 11 may be used for PaO_2.

**If a patient has an SpO_2 <95% while on oxygen supplementation, he/she shall be considered to be "clinically contraindicated" from requiring a trial off oxygen; however, corresponding respiratory assessments should be recorded.*

SECTION 4.6.10: Laboratory, Biomarker, and Other Biological Samples

[redacted]

SECTION 4.6.11: Electrocardiograms

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

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

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The following should be recorded in the appropriate eCRF: HR, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF *(or QTcB if QTcF is not available)* based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean ~~QTcF~~*corrected QT interval* is > 500 ms and/or > 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until *the corrected* QT interval ~~corrected using Fridericia's formula (QTcF)~~ has stabilized on two successive ECGs. The Medical Monitor should be notified. ~~If QTcF is not available, QTcB may be recorded.~~ Standard of care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on ~~study drug~~ discontinuation should be made, as described in Section 4.9.2. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, medications known to prolong the QT interval, severe bradycardia).

SECTION 4.9.4: Study and Site Discontinuation

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

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

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study. The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

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

SECTION 4.10: ***Assay Methods***

[redacted]

SECTION 5.1.1: ***Risks Associated with MHAA4549A***

There are no known risks associated with MHAA4549A based on completed Phase 1 (GV28916 and GV29609) and Phase 2a (GV28985) studies.

SECTION 5.1.1.1: ***Immunogenicity***

MHAA449A is a monoclonal antibody-based therapeutic. As with any recombinant monoclonal antibody, MHAA4549A may elicit an immune response in patients with the development of antibodies against MHAA4549A. Subjects will be closely monitored for any potential immune response to MHAA4549A. Screening, confirmatory, and characterization assays with appropriate sensitivity and therapeutic tolerance will be employed to assess ATAs before and after treatment with MHAA4549A.

SECTION 5.3.1: Adverse Event Reporting Period

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until *study completion at* the Day 60 visit or *until an* Early Discontinuation visit. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

SECTION 5.3.5.1: Diagnosis versus Signs and Symptoms Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than *an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than* a diagnosis of ~~allergic~~*infusion-related* reaction or ~~infusion~~*anaphylactic* reaction~~.~~*).*

SECTION 5.3.5.7: Deaths

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

SECTION 5.4.1: Emergency Medical Contacts ~~Medical Monitor Contact Information~~

[redacted] ~~Medical Monitor contact information:~~

~~Primary Medical Monitor:~~ [redacted]

~~Telephone Nos.:~~ ~~US Office:~~ [redacted]

~~US Mobile:~~ [redacted]

~~Secondary Medical Monitor:~~ [redacted]

~~Telephone Nos.:~~ ~~US Office:~~ [redacted]

~~US Mobile:~~ [redacted] ***24-Hour Safety Hotline***

- *North America:* [redacted]
- *EMEA/APAC:* [redacted]
- *Latin America:* [redacted]

Genentech Medical Monitor contact information for all sites if above ~~medical monitor~~ *contact* cannot be reached:

Medical Monitor: [redacted]

Telephone Nos.: US Office [redacted]

US Mobile [redacted]

Email Address: [redacted]

SECTION 5.4.2.2: Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until the patient ~~is~~*completes the study* at Day 60 or ~~Early Discontinuation. Although the investigator is not required to actively monitor patients for adverse events after the patient has been discharged from the study, the Sponsor should be notified if the investigator becomes aware of any death or other serious adverse event that occurs after discharge from the study, if determined to be related to study drug by the investigator. The Sponsor should also be notified if the investigator~~

~~becomes aware of a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug (see Section 5.4.3.3).~~

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

In the event that the EDC system is unavailable, a paper *Clinical Trial* Serious Adverse Event/Adverse Event of Special Interest Reporting Form should be completed and faxed or scanned and emailed to *the Sponsor*~~Safety Risk Management~~ or its designee immediately (i.e., no more than 24 hours after learning of the event), using the contact information provided to investigators (see Section 5.4.2.1). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

SECTION 5.4.3.1: Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 120 days ~~after the last dose~~ of study drug~~.~~ *administration.* A *paper Clinical Trial* Pregnancy ~~Report eCRF~~*Reporting Form* should be completed ~~by the investigator~~*and submitted to the Sponsor or its designee* immediately (i.e., no more than 24 hours after learning of the pregnancy~~) and submitted via~~*), either by faxing or by scanning and emailing the form using* the ~~EDC system. A pregnancy report will automatically be generated and sent to Safety Risk Management~~*fax number or email address provided in Section 5.4.2.1.* Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. *In addition, the Investigator will submit a paper Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.*

~~In the event that the EDC system is unavailable, a paper Clinical Trial Pregnancy Reporting Form should be completed, faxed, or scanned and emailed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the contact information provided to investigators (see Section 5.4.2.1). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.~~

SECTION 5.4.3.2: Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant *during the study or* within 30 days ~~after the dose~~ of study drug~~.~~ *administration.* A *paper Clinical Trial* Pregnancy

~~Report eCRF~~*Reporting Form* should be completed ~~by~~ *and submitted to* the ~~investigator~~*Sponsor or its designee* immediately (i.e., no more than 24 hours after learning of the pregnancy~~) and submitted via~~*), either by faxing or by scanning and emailing* the ~~EDC system.~~*form using the fax number or email address provided in Section 5.4.2.1.* Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. ~~Once~~*After* the authorization has been signed, the investigator will ~~update the~~*submit a paper Clinical Trial* Pregnancy ~~Report eCRF with additional~~*Reporting Form when updated* information on the course and outcome of the pregnancy *becomes available*. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

~~In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.2.1.~~

SECTION 5.5.1: Investigator Follow-Up

All pregnancies reported during the study should be followed until pregnancy outcome. ~~If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.~~

SECTION 5.6: POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 60 days ~~(see Section 5.3.1)~~ after the ~~last~~ dose of study drug), if the event is believed to be related to prior study drug treatment.

~~The~~*These events should be reported through the use of the Adverse Event eCRF and submit the report via the EDC system. However, if the EDC system is not available, the* investigator should report these events directly to ~~Roche,~~*the Sponsor* or its designee, either by faxing or by scanning and emailing ~~the~~ *a paper Clinical Trial* Serious Adverse Event / Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators (refer to site binder).

SECTION 6.4: EFFICACY ANALYSES

Time to event data will be *analyzed*~~computed~~ using Kaplan-Meier methodology and stratified Cox proportional hazards models and will be summarized using n, median when estimable, hazard ratios, and 95% confidence intervals. Patients who are lost to follow-up (while event free) will be censored at the time that they are last known to be event free.

The ordinal outcomes will be analyzed using a proportional odds model. To supplement the overall summary odds ratio, separate odds ratios will be estimated for each dichotomized definition of improvement that can be formulated from the components of the ordinal outcome. A test for the proportionality assumption will also be made. Patients discharged from the hospital to a rehabilitation facility will be included in category 5. Patients discharged from the hospital to a nursing home will also be included in category 5, unless the patient lived in a nursing home prior to admission to the hospital, in which case the patient will be characterized based on resumption of normal activities.

Estimation of the treatment difference of proportions and *the corresponding* ~~its~~ 95% confidence interval*s* will be calculated using stratum-adjusted Mantel-Haenszel methodology (Koch et al. 1989). For continuous endpoints, Analysis of Covariance methods (after appropriate transformation of data) will be used to estimate treatment differences and 95% confidence intervals.

SECTION 6.4.2: Secondary Efficacy Endpoints

- *Clinical status at Days 1-7, 14, and 30 categorizing proportion of patients in each of the 6 pre-defined categories*
- Proportion of patients with clinical failure after 24 hours post-infusion of study drug
- Median time to clinical resolution of vital signs
- Hazard ratio for mortality at Day 14, Day 30, and Day 60
- Mean and median AUC of viral load
- Mean and median peak viral load
- Median duration of viral shedding in nasopharyngeal samples
- *Proportion of patients with detectable infection*
- Median duration of hospitalization
- Median duration of ICU stay
- Proportion of patients requiring antibiotics for respiratory indications during study
- Proportion of patients with influenza secondary complications
- Median duration of ventilation
- Proportion of patients who are readmitted by Day 30 and Day 60

SECTION 6.6: ~~Pharmacodynamic~~*Pharmacokinetic* Analyses

This heading was updated.

SECTION 6.7: *IMMUNOGENICITY ANALYSES*

The immunogenicity analyses will include patients with at least one predose and one postdose ATA assessment, with patients grouped according to treatment received.

The numbers and proportions of ATA-positive patients and ATA-negative patients during the treatment and follow-up periods will be summarized by treatment group. Patients are considered to be ATA positive if they are ATA negative at baseline but develop an ATA response following study drug administration (treatment-induced ATA response), or if they are ATA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., ≥0.60 titer units) than the titer of the baseline sample (treatment-enhanced ATA response). Patients are considered to be ATA negative if they are ATA negative at baseline and all post-baseline samples are negative, or if they are ATA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ATA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

SECTION 6.8: *Biomarker Analyses*

[redacted]

SECTION 6.9: *Exploratory Pharmacokinetics Analyses*

[redacted]

SECTION 8.4: CONFIDENTIALITY

Given the exploratory nature of the biomarker analyses, data derived from exploratory biomarker specimens 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 Sponsor policy on study data publication (see Section 9.5).

FIGURE 1: Phase 2b Study Design (GV29216)

Figure 1 has been revised to clarify the timing of assessments and division of assessment periods.

TABLE 3: Laboratory Tests at Screening

Table 3 has been revised for consistency with Section 4.6.10.

TABLE 1: Interim Efficacy Results from Phase 2a Challenge Study (GV28985)

Table 1 has been deleted. Subsequent tables have been renumbered accordingly.

TABLE 1: ***GV28985 Efficacy Results from Intent-to-Treat Infected Population***

Table 1 has been added. Subsequent tables have been renumbered accordingly.

APPENDIX 1a: Schedule of Activities

The schedule of assessments has been revised to reflect the changes to the protocol.

APPENDIX 1b: Schedule of Activities: Follow-Up Period

The schedule of assessments has been revised to reflect the changes to the protocol.

APPENDIX 2: Time to Normalization of Respiratory Function

Appendix 2 has been revised for consistency with the other changes in the protocol.

APPENDIX 12: ***Clinical Status Assessment***

Appendix 12 has been added. Subsequent appendices have been renumbered accordingly.

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY, IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION**
PROTOCOL NUMBER:	GV29216
VERSION NUMBER:	7 (Global)
EUDRACT NUMBER:	2014-000461-43
IND NUMBER:	117,318
TEST PRODUCT:	MHAA4549A
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION**
PROTOCOL NUMBER:	GV29216
VERSION NUMBER:	7 (Global)
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IND NUMBER:	117,318
TEST PRODUCT:	MHAA4549A
INDICATION:	INFLUENZA A
SPONSOR:	Genentech, Inc.

Objectives

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety of MHAA4549A in combination with oseltamivir compared with placebo and oseltamivir in patients with severe influenza A, focusing on the nature, frequency, and severity of serious and non-serious adverse events (AEs), as well as effects on laboratory values, vital signs, electrocardiogram (ECG) parameters, anti-therapeutic antibodies (ATA), and other safety biomarkers

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To determine the time to normalization of respiratory function of patients dosed with MHAA4549A in combination with oseltamivir compared to patients dosed with placebo and oseltamivir

The secondary efficacy objectives for this study are as follows:

- *To compare the clinical status of patients at Days 1-7, 14, and 30 using an ordinal outcome with six clinical statuses. Patients will be categorized into one of the following six mutually exclusive categories on Days 1-7, 14, and 30*
    1. *Death;*
    2. *In the ICU;*
    3. *Non-ICU hospitalization, requiring supplemental oxygen;*
    4. *Non-ICU hospitalization, not requiring supplemental oxygen;*
    5. *Not hospitalized, but unable to resume normal activities; or*
    6. *Not hospitalized with full resumption of normal activities*
- To measure clinical failure after 24 hours post-infusion of study drug
- To determine the time to clinical resolution of *abnormal* vital signs
- To measure mortality in patients
- To determine changes in the extent and duration of viral *burden* in nasopharyngeal samples as a measure of pharmacodynamic response

- To measure the duration of hospital and/or intensive care unit (ICU) stay
- To measure antibiotic usage for respiratory infections
- To measure the frequency and severity of the following secondary complications of influenza:
  - Pneumonia (hospital acquired pneumonia [HAP]/ ventilator acquired pneumonia [VAP])
  - Exacerbations of chronic lung disease
  - Myocarditis
  - Acute respiratory distress syndrome (ARDS)
  - Otitis media
  - Other related complications
  - Readmission rates at 30 and 60 days after study treatment
- To measure duration of positive pressure ventilation (PPV)
- To measure readmission rates

Pharmacokinetic Objectives

The major pharmacokinetic (PK) objective for this study is as follows:

- To characterize the PK profile of MHAA4549A in serum

The exploratory PK objectives for this study are as follows:

[redacted]

Exploratory Objectives

The exploratory objectives for this study are as follows:

[redacted]

Study Design

Description of Study

This is a Phase 2b (GV29216), randomized, double-blind, placebo-controlled study designed to assess the safety and clinical activity of a single intravenous (IV) dose of 3600 mg MHAA4549A

or a single IV dose of 8400 mg MHAA4549A in hospitalized patients with severe influenza A in combination with oseltamivir versus a comparator arm of oseltamivir with placebo. *A Sponsor-approved influenza test that includes influenza antigen test or influenza polymerase chain reaction (PCR) test must be used to diagnose influenza A infection for study eligibility.*

Initially, GV29216 enrolled and randomized patients into two treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir or a single IV dose of placebo with oseltamivir.

Patients will be randomized 1:1:1 into three treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir, a single IV dose of 8400 mg of MHAA4549A with oseltamivir, or a single IV dose of placebo with oseltamivir.

All patients must begin study drug infusion within 48 hours of hospital admission; therefore, screening must be completed within this window. All patients will receive oseltamivir for a minimum of 5 days (10 doses), starting on Day 1 beginning no later than *12* hours after completion of study drug administration. All patients will be followed for 60 days from the time of study drug administration.

Number of Patients

The study has a planned enrollment of approximately 330 patients (adult men and women) globally. Patients will receive 3600 mg MHAA4549A, 8400 mg, or placebo in 1:1:1 ratio. The number of patients on PPV should not exceed 45% of the total enrolled patients.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Men or women ≥ 18 years of age on day of signing informed consent or obtaining surrogate consent from an authorized representative
- Diagnosis of influenza A where a Sponsor-approved influenza test is used as an aid in diagnosis. A Sponsor-approved influenza test includes:
  - Influenza antigen test –OR–
  - Influenza polymerase chain reaction (PCR) test
- One of the following markers of severity within 24 hours of hospital admission:
  - Requirement for PPV, OR
  - Requirement for O_2 supplementation to maintain $SpO_2 > 92\%$ *(Source documentation should show that the patient's SpO2 was less than 92% off oxygen. Source documentation may consist of either a SpO2 off oxygen with a value below 92% or a documentation of the Investigator's rationale in lieu of this SpO2 documentation.)*
- A negative urine or serum pregnancy test for women of childbearing potential
- Patients of reproductive potential must agree to use reliable means of contraception as described below as a minimum (adherence to more stringent local requirements may be required):
  - For women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use two adequate methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment period and for at least 120 days after the dose of study drug

    Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

    Barrier methods must always be supplemented with the use of a spermicide.

Examples of contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, hormonal implants, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.

- For men: agreement to remain abstinent or use a condom during the treatment period and for at least 30 days after the dose of study drug and agreement to refrain from donating sperm during this same period

  Men with a pregnant partner must agree to remain abstinent or use a condom for the duration of the pregnancy.

  Abstinence is only acceptable if it is in line with 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.

Non-reproductive potential is defined below (but could be superseded by local definitions, if they are more stringent):

- Women who are postmenopausal *(≥ 12 months of non-therapy-induced* amenorrhea)
- Women who are surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)
- Men who are surgically sterile (castration)

Exclusion Criteria

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

- Pregnant or lactating, or intending to become pregnant during the study
  - Women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non-therapy-induced amenorrhea) or who are not surgically sterile must have a negative pregnancy test result within 2 days prior to study treatment
- Hypersensitivity to monoclonal antibodies or to any *constituents (sodium succinate, sucrose, polysorbate 20)* of MHAA4549A study drug
- Hypersensitivity to the active substance or to any excipients of oseltamivir
- Investigational therapy within the 30 days prior to study treatment
- Received prior therapy with any anti-influenza monoclonal antibody therapy (including MHAA4549A) *within* 8 months prior to study treatment
- Current treatment (within 7 days of dosing) with probenecid, amantadine, or rimantidine
- Patients who have taken more than a total of 6 doses (3 doses for peramivir) of anti-influenza therapy (e.g., oseltamivir, zanamivir, *laninamivir,* peramivir) in the period from onset of symptoms and prior to study treatment
- Admission > 48 hours prior to study treatment
- Onset of influenza symptoms (including fever, chills, malaise, dry cough, loss of appetite, myalgias, coryza, or nausea) > 5 days prior to study treatment
- Positive influenza B or influenza A + B infection within 2 weeks prior to study treatment
- High probability of mortality in the next 48 hours as determined by the investigator
- Patient requiring home or baseline oxygenation therapy
- Patient with history of chronic lung disease *with a documented* $SpO_2 < 95\%$ *off oxygen*
- Patient on chronic dose of corticosteroids exceeding 10 mg/day of prednisone or equivalent steroid dose for a duration of greater than 14 days within 30 days of entry into study
- Creatinine clearance ≤10 mL/min
- Patients who received nasally administered influenza A vaccine within 7 days *prior to screening*

- Patients with the following significant immune suppression:
  - Bone marrow or solid organ transplant in the previous 12 months
  - Cancer chemotherapy in the previous 12 month
  - Human immunodeficiency virus (HIV) infection with most recent CD4 $<$ 200 cells/mL
  - Other significant immune suppression as determined by the investigator in discussion with the Sponsor Medical Monitor
- Patient on extracorporeal membrane oxygenation (ECMO) at time of randomization
- Any disease or condition that would, in the opinion of the site investigator or Sponsor, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol

Length of Study

This study will consist of the following study periods:

- A screening period of 48 hours, beginning at time of hospital admission
- A treatment period of 1 day, during which patients will receive a single dose of MHAA4549A or placebo and a minimum of 5 days of oseltamivir.
- A follow-up period beginning at hospital discharge through 60 days post study drug (MHAA4549A/placebo) administration

End of Study

The end of the study is defined as the first day when all patients have had a study completion visit or early termination visit or have otherwise been discontinued from the study.

Outcome Measures

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- AEs and clinical laboratory abnormalities
- Vital signs, physical findings, ATAs, and clinical laboratory results during and following administration of MHAA4549A

Efficacy Outcome Measures

The primary outcome measure for this study is as follows:

- Time to normalization of respiratory function defined as:
  - The time to cessation of O_2 support resulting in a stable $SpO_2 \geq 95\%$

The secondary efficacy outcome measures for this study are as follows:

- *Clinical status of patient at Days 1-7, 14, and 30. This is an ordinal outcome with six mutually exclusive categories:*
  1. *Death;*
  2. *In the ICU;*
  3. *Non-ICU hospitalization, requiring supplemental oxygen;*
  4. *Non-ICU hospitalization, not requiring supplemental oxygen;*
  5. *Not hospitalized, but unable to resume normal activities; or*
  6. *Not hospitalized with full resumption of normal activities*
- Clinical failure after 24 hours post-infusion of study drug defined as:
  - Progression to increased O_2 requirement defined by an increase in oxygen supplementation from low flow oxygen (*i.e.,* 2 – 6 L/min) to high flow oxygen (*i.e.,* $>$ 6 L/min) or from oxygen supplementation alone to any PPV or ECMO
  - Progression to ICU
  - Prolonged ventilation or O_2 support defined by $>$ 2 weeks, or
  - Death

- Time to clinical resolution of *abnormal* vital signs (3/5 criteria must be met):
  - $SpO_2 \geq 95\%$ without supplemental O_2
  - Respiratory rate < 24 breaths per minute without supplemental O_2
  - Core temperature $< 37.2°C$ immediately prior to receipt of any antipyretic drug, and at least 6-8 hours from the last dose of antipyretic or core temperature $> 36°C$ in patients who are initially hypothermic
  - Heart rate (HR) < 100 beats/minute
  - Systolic blood pressure (SBP) > 90 mmHg
- All-cause mortality at Day 14, Day 30, and Day 60
- Influenza A viral load in nasopharyngeal samples
  - Area under viral load-time curve (AUEC; qPCR)
  - Peak viral load (qPCR)
  - *Duration* of *viral shedding* (qPCR)
- Duration of hospitalization
- Duration of ICU stay
- Antibiotic usage for respiratory infections
- Complications of influenza:
  - Pneumonia (HAP/VAP)
  - Exacerbations of chronic lung disease
  - Myocarditis
  - ARDS
  - Otitis media
  - Other related complications
- All-cause readmission at Day 30 and Day 60
- Duration of ventilation

Pharmacokinetic Outcome

The primary PK outcome measures for this study are as follows:

- PK parameters for MHAA4549A in serum including total exposure (i.e., area under the curve [AUC]), maximum observed concentration (C_{max}), clearance, half-life, and volume of distribution, when appropriate, as data allow

The exploratory PK outcome measures for this study are as follows:

[redacted]

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

[redacted]

[redacted]

Investigational Medicinal Products

An investigational medicinal product (IMP) is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, excluding marketed products unless the product is 1) used or assembled (formulated or packaged) differently than the authorized form, 2) used for an unauthorized indication, or 3) used to gain further information about the authorized form (Directive 2001/20/EC Article 2[d]). A non-investigational medicinal product (NIMP) is a medicinal product that is intended for use in a clinical trial per the protocol but does not fall under the definition of IMP. Further details can be found in the following European Union (EU) guidance: Guidance on Investigational Medicinal Products and Non-Investigational Medicinal Products (effective March 2011).

MHAA4549A and Placebo

A single 3600-mg dose of MHAA4549A or a single 8400-mg dose of MHAA4549A or dose of placebo will be delivered by IV infusion following dilution in 0.9% normal saline over approximately 120 minutes. Study drug should be delivered using a 0.20-0.22 μm in-line filter. Placebo will be identical to active MHAA4549A in formulation, but will not contain active drug substance.

Oseltamivir (Tamiflu®)

Oseltamivir (Tamiflu®) 75 mg or 150 mg will be administered BID for a minimum of 5 days. Capsules can be opened and the granules administered via nasogastric tube, if required.

Statistical Methods

Primary Analysis

All efficacy analyses will be conducted according to the intent-to-treat principle and will include all patients who meet the following condition with patients allocated to the treatment arm to which they were randomized:

- Randomized patients who have confirmed influenza A infection by a central PCR test from Day 1 samples.

The primary and secondary efficacy analyses will include all randomized patients who are confirmed to be influenza A infected, with patients grouped according to the treatment assigned at randomization.

Time to event data will be computed using Kaplan-Meier methodology and stratified Cox proportional hazards models and will be summarized using n, median when estimable, hazard ratios, and 95% confidence intervals. Patients who are lost to follow-up (while event free) will be censored at the time that they are last known to be event free.

Estimation of the treatment difference of proportions and its 95% confidence interval will be calculated using stratum-adjusted Mantel-Haenszel methodology. For continuous endpoints, Analysis of Covariance methods (after appropriate transformation of data) will be used to estimate treatment differences at 95% confidence intervals.

Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

If conducted, an interim analysis would be for administrative purposes only (i.e., internal planning or decision making) and would not impact the conduct of the current study in any way. A nominal type I error penalty of 0.0001 will be taken. In addition, as discussed below, the Sponsor will conduct interim safety analyses separate from and in conjunction with the above.

Determination of Sample Size

A total of 330 patients will be enrolled in this study. It is assumed that the median time to normalization of respiratory function in the control arm is 5 days

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
[redacted]	[redacted]
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
APAC	Asia-Pacific
APACHE	Acute Physiology and Chronic Health Evaluation
APTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
ATA	Anti-therapeutic antibody
AUC	Area under serum concentration-time curve
$AUC_{0\text{-infinity}}$	Area under the curve from zero to infinity
AUEC	Area under viral load-time curve
BID	Twice a day
°C	Celsius
CDC	Centers for Disease Control and Prevention
CL	clearance
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CPK	Creatine phosphokinase
CRO	Contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECMO	Extracorporeal membrane oxygenation
EDC	Electronic data capture
EIH	Entry-into-human
ELISA	Enzyme-linked immunosorbent assay
EMEA	Europe, Middle East, and Africa
ESR	Erythrocyte sedimentation rate
EU	European Union
EVA	Ethylene vinyl acetate
FDA	Food and Drug Administration

FiO_2	Fraction of inspired oxygen
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HA	Hemagglutinin
HAI	Hemagglutinin inhibition
HAP	Hospital Acquired Pneumonia
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
hMPV	Human metapneumovirus
HPLC	High-performance liquid chromatography
HR	Heart rate
HRP	Horseradish peroxidase
HRV	Human rhinovirus
[redacted]	[redacted]
IC_{50}	Concentration required for 50% inhibition
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
IMC	Internal Monitoring Committee
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalization ratio
IQR	Interquartile range
IRB	Institutional Review Board
IRR	Infusion-related reactions
ITT	Intent-to-treat
ITTI	Intent-to-treat infected
IV	Intravenous
IxRS	Interactive voice and web response system
LFTs	Liver function tests
LLN	Lower limit of normal
LPLV	Last patient, last visit
NA	Neuraminidase
NAI	Neuraminidase inhibitor

NIMP	Non-investigational medicinal product
O_2	Oxygen
PaO_2	Partial pressure of arterial oxygen
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PE	Paired end
PK	Pharmacokinetic
PIV	Parainfluenza virus
PPV	Positive pressure ventilation
PT	Prothrombin time
qPCR	Quantitative polymerase chain reaction
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SOA	Schedule of activities
SOC	Scientific Oversight Committee
SOFA	Sequential Organ Failure Assessment
SpO_2	Oxygen saturation by pulse oximetry
SUSAR	Suspected unexpected serious adverse reactions
$TCID_{50}$	50% tissue culture infectious dose
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
UVTM	Universal viral transport medium
VAP	Ventilation Acquired Pneumonia
WBC	White blood cell

1. BACKGROUND

1.1 BACKGROUND ON INFLUENZA

Influenza A is a membrane-enveloped RNA virus that causes significant morbidity and mortality. Currently, there is a great need in hospitalized influenza patients for a parenteral therapeutic option that is well tolerated, can rapidly resolve influenza-related signs and symptoms, decrease mortality, reduce hospital and intensive care unit (ICU) stays, as well as have a prolonged window for initiation of treatment beyond the current standard of care (i.e., within 48 hours of the onset of flu symptoms).

Approximately 200,000 to 278,000 patients are hospitalized with severe influenza infections annually in the United States (US) (Thompson et al. 2004; Zhou et al. 2012), and assuming the same rate reported in the US, an estimated 319,000 to 445,000 patients are hospitalized in the European Union (EU). Hospitalization due to severe influenza is associated with high mortality (4%–8%), ICU admission (5%–17%; Lee and Ison 2012), mechanical ventilation support in an ICU setting (7%–11%; Doshi et al. 2011), and prolonged hospital stays (5–9 days; Lee and Ison 2012). 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).

Influenza infection is an upper and lower respiratory disease with a broad spectrum of presentations that can result in fever, shortness-of-breath, pneumonia, respiratory failure, secondary respiratory infections, and even death. The standard of care therapy for patients hospitalized with influenza consists of supportive measures and administration of available antiviral agents, primarily neuraminidase inhibitors (NAI) that include but are not limited to oseltamivir, zanamivir, *laninamivir,* and peramivir. However, a significant unmet medical need still exists in the severely ill patient population, as evidenced by the considerable degree of morbidity and mortality in this setting. To address this need, the Sponsor is developing a highly-specific anti-influenza A (MHAA4549A) antibody therapy for treatment of hospitalized patients with severe influenza.

1.2 BACKGROUND ON MHAA4549A

1.2.1 Nonclinical Background

MHAA4549A is a human monoclonal IgG1 antibody that binds to the influenza A virus and is cloned from a single-human plasmablast cell isolated from an influenza vaccinated donor (Nakamura et al. 2013). This antibody binds to a highly conserved epitope on the influenza A hemagglutinin (HA) stalk region, blocking *fusion of the viral envelope with* the *host target cell endosomal* membrane *and preventing viral replication*.

In vitro, MHAA4549A is capable of neutralizing all *human seasonal* influenza A strains *tested*. In vivo, efficacy of MHAA4549A has been demonstrated in mouse models of

influenza A infection, both as a single agent and in combination with oseltamivir. *In the absence of influenza infection, the* epitope on the human influenza A HA glycoprotein *targeted by MHAA4549A is* not endogenously expressed *in* human or rat tissues and, therefore, is unlikely to be present in the absence of *influenza infection. Ex vivo tissue cross-reactivity study data showed no specific binding of MHAA4549A to any of the human or rat tissues examined.* Weekly *intravenous* administration of MHAA4549A (total of 5 doses) in Sprague-Dawley rats was well tolerated up to the maximum feasible dose of 150 mg/kg.

1.2.2 Clinical Safety Background

To date, MHAA4549A has been shown to be safe and well tolerated in *three* clinical studies, which altogether enrolled *84* healthy volunteers *who were dosed with MHAA4549A*.

1.2.2.1 Phase 1 Entry-into-Human Study (GV28916)

In the Phase 1 *entry-into-human (EIH)* study (GV28916*),* 21 healthy volunteers *were given* single *IV* doses of *placebo (n =5) or MHAA4549A (n =16) at* 1.5, 5, 15, *or* 45 mg/kg *and followed for 120 days.*

A total of 23 treatment-emergent adverse events (TEAEs) were *reported by 13 of the 21 subjects (61.9%) who received one dose of the study medication. Nineteen of these TEAEs were reported by 10 of the 16 subjects (62.5%) who had received MHAA4549A and four TEAEs were reported by 3 of the 5 subjects (60.0%) who received placebo. The total number of TEAEs reported was similar in all dosing cohorts (four TEAEs per cohort),* with *the exception of the 5-mg/kg cohort, where seven TEAEs were observed. Overall, no notable trends were observed among dose levels or between subjects who received MHAA4549A and those who received placebo.*

The most commonly reported TEAEs in subjects receiving MHAA4549A were headache (4 subjects) and oropharyngeal pain (2 subjects). The severity of TEAEs was *primarily mild,* with *only two moderate TEAEs. No* serious adverse events *or dose-limiting toxicities were reported. Two clinical laboratory values were considered TEAEs (an increase in ALT in 1 subject who received 5 mg/kg MHAA4549A and an increase in creatinine phosphokinase [CK] in 1 subject who received placebo). Both results returned* to *normal within 10 days.*

No safety issues were observed with respect to vital signs results or ECG measurements. For all clinical laboratory results, no relevant differences in mean values or deviations from baseline over time were observed in subjects receiving MHAA4549A doses as compared to placebo. No drug-emergent anti-therapeutic antibodies (ATAs) were detected in this study.

1.2.2.2 *Phase 1 High-Dose Safety Study (GV29609)*

In the Phase 1 high-dose study (GV29609), 14 healthy volunteers were given single IV doses of placebo (n =6) or MHAA4549A (n =8) at 8400 mg (Cohort A) or 10800 mg (Cohort B) and were followed for 120 days.

A total of 34 TEAEs were reported by 12 of the 14 subjects (85.7%) who received one dose of the study medication or placebo (safety population). Of these 34 TEAEs, 24 TEAEs were reported by 7 of the 8 subjects (87.5%) who had received MHAA4549A and 10 TEAEs were reported by 5 of the 6 subjects (83.3%) who had received placebo. TEAEs were reported by 3 of the 4 subjects receiving 8400 mg MHAA4549A and all 4 subjects receiving 10800 mg MHAA4549A. No notable trends in types of TEAEs or laboratory results were observed between dose levels or between subjects who received MHAA4549A versus placebo.

The most commonly reported TEAEs were headache (4 subjects who received MHAA4549A [3 subjects in Cohort A, 1 subject in Cohort B]) and nasopharyngitis (3 subjects who received MHAA4549A [1 subject in Cohort A, 2 subjects in Cohort B]). All other TEAEs were each reported by no more than 1 subject who received MHAA4549A. The severity of TEAEs was primarily mild, with only three moderate TEAEs reported (a bacterial infection observed in 1 subject who received 8400 mg MHAA4549A, and elevations of blood creatine phosphokinase [CK] observed twice in 1 subject who received 10800 mg MHAA4549A). No serious adverse events or dose-limiting toxicities were reported.

No safety issues were observed with respect to vital sign results and ECG measurements. Overall, no relevant differences in mean values and changes or shifts from baseline over time were observed with respect to dose levels or MHAA4549A compared to placebo. No subjects in the study developed an ATA response following study drug administration.

1.2.2.3 Phase 2a Influenza Nasal Challenge Study (GV28985)

In the Phase 2a challenge study (GV28985*),* 101 healthy volunteers *were nasally inoculated* with *the* H3N2 (A/Wisconsin/67/2005) strain of influenza virus. *At 24 to 36 hours after inoculation, 60* subjects received *single IV* doses of 400, 1200, or 3600 mg MHAA4549A; *8 subjects received oseltamivir as an active comparator;* and 32 *subjects received placebo. All subjects, regardless of initial treatment, received oseltamivir on Days 7–11 to mitigate risk of late shedding and/or further transmission of virus.*

Adverse events were collected from time of influenza A *inoculation (*Day *0). Consistent with the Phase 1 studies (GV28916 and GV29609), there* was *no evidence of a dose-related pattern of TEAEs in MHAA4549A-treated subjects. Expected influenza-related symptoms and AEs were observed in inoculated subjects; these influenza-related AEs were similar in subjects who received MHAA4549A or placebo. Of the 101 subjects*

inoculated, 23 subjects experienced at least 1 adverse event following virus inoculation but prior to the first dose of study medication. The most common adverse events seen prior to the administration of study drug were headache (4 subjects), elevated blood pressure (4 subjects), dizziness (3 subjects), and procedural hemorrhage (3 subjects).

Following administration of the study drug, there were 207 TEAEs in 86 of the 100 safety-evaluable subjects (86%), which occurred in a similar pattern across all treatment groups. Thirty-six of the 86 subjects (42%) experienced at least 1 study drug-related TEAE. Study drug-related TEAEs occurred in a similar proportion and in a similar pattern across all treatment groups. The most common TEAEs were elevations in ALT, AST, and amylase, which were reported in 15 of 25 TEAEs (60%) in subjects receiving placebo (n =32) or oseltamivir (n =8) and in 26 of 33 TEAEs (79%) in subjects receiving MHAA4549A (n =60). Similar elevations have been seen previously following influenza infection (Polakos et al. 2006; Yingying 2011). There were no clinically significant changes in vital signs, spirometry, or electrocardiograms and no pattern of study drug-related effects in these parameters. There were no observed adverse events or safety events that were considered attributable to interactions between oseltamivir and MHAA4549A.

No subject experienced a serious adverse event prior to the first dose of study drug. Three treatment-unrelated serious adverse events were reported by 2 subjects: 1 subject who received placebo reported symptoms of major depression on Day 15; and 1 subject who received 3600 mg MHAA4549A reported a lower limb fracture on Day 109 and a postoperative wound infection on Day 133 after study drug administration.

One subject in the placebo group tested positive for ATAs at baseline as well as post-baseline. The immunogenicity incidence rate among the 60 subjects who received MHAA4549A was 0%.

1.2.3 ***Clinical Pharmacokinetics***

The Phase 1 *EIH* study (GV28916) demonstrated that MHAA4549A *serum* pharmacokinetics were dose proportional *with a mean half-life of approximately 23 days (range: 21.9–24.6 days).* The *pharmacokinetic (*PK*)* profile appeared consistent with that of a human IgG1 antibody that lacks known endogenous host targets *(Bai et al. 2012; Ishida et al. 2015).*

In the Phase 2a influenza nasal challenge study (GV28985), serum MHAA4549A concentrations exhibited a biphasic disposition with an initial rapid distribution phase followed by a slow elimination phase, which was also observed in the Phase 1 EIH study (GV28916). MHAA4549A demonstrated linear pharmacokinetics. The group mean maximum observed concentration (C_{max}) increased in a dose-proportional manner, at 116 µg/mL for the 400-mg dose group and 1110 µg/mL for the 3600-mg dose group. Similarly, the group mean area under the curve from zero to infinity ($AUC_{0\text{-}infinity}$) was

1800 and 18100 day • µg/mL for the 400- and 3600-mg dose groups, respectively, and was approximately dose proportional. PK data from the Phase 2a study (GV28985) are consistent with those observed in the Phase 1 EIH study (GV28916), with MHAA4549A demonstrating a mean half-life of approximately 23 days (range: 22.5–23.7 days).

In the Phase 1 high-dose study (GV29609), MHAA4549A showed linear pharmacokinetics, with a mean half-life of approximately 21.5 days (range: 21.4–21.6 days). For the 8400- and 10800-mg dose groups, the mean apparent clearance (CL) and the mean volume of distribution at steady state (V_{ss}) ranged from 151 to 167 mL/day and from 4590 to 4170 mL, respectively. PK data from the Phase 1 high-dose study (GV29609) is consistent with those observed in the Phase 1 EIH study (GV28916) and Phase 2a study (GV28985).

1.2.4 *Clinical Efficacy Background*

The virologic efficacy analysis for the Phase 2a influenza nasal challenge study (GV28985), presented in *Table 1, includes* the Intent-to-Treat infected (ITTI) population who received 400 mg MHAA4549A (n=11), 1200 mg MHAA4549A (n=13), 3600 mg MHAA4549A (n=14), *oseltamivir alone (n =2), or* placebo (n=21). *The ITTI population included all subjects who were randomized, inoculated with challenge virus,* and *had laboratory confirmed evidence* of *influenza infection as defined by one or more of the following:*

- *A positive cell culture assay by 50% tissue culture infectious dose ($TCID_{50}$) at least once during quarantine postchallenge virus inoculation*

  Or

- *At least two positive detections by any quantitative polymerase chain reaction (qPCR) assay between virus inoculation and day of discharge* from *quarantine*

  Or

- *Seroconversion (≥4-fold rise in titer compared to baseline)*

1.2.4.1 *Virologic Efficacy*

The 400 mg dose demonstrated a decrease in viral shedding *(*reduction *in median viral area under the curve [AUC]* by qPCR) *by 46% (p =0.05) and peak viral load (reduction in median peak viral load by qPCR) by 20.4% (p =0.02). The 1200-mg dose showed a decrease in viral shedding by 3.0% (p =0.90) and peak viral load by 0.3% (p =1.00). The 3600-mg dose level demonstrated a significant decrease in viral shedding by 97.5% (p =0.01) and peak viral load by 77.3% (p =0.002) [Table 1]. The decreased efficacy observed in the 1200-mg dose group is thought to be due to the variability from the challenge model and intersubject differences.*

1.2.4.2 *Symptomatic Efficacy*

The A/Wisconsin/67/2005 virus induced mild symptoms that were predominantly *limited to the upper respiratory tract, including rhinorrhea, nasal congestion, and sneezing. The duration and severity of influenza-related symptoms (rhinorrhea, nasal congestion, sneezing, sore throat, earache, malaise, cough, shortness of breath, headache, and muscle/joint ache) were collected on a self-reported* Symptom Diary *Card. The cards grade the symptoms on* a scale of 0–3, where Grade 0 is absence, Grade 1 is just noticeable, Grade 2 is bothersome but does not prevent participation in activities, and Grade 3 is bothersome and interferes with activities. Composite clinical symptom scores for the ITTI population are shown in Table 1.

Consistent with the virological results, there was a *trend toward a* decrease in the symptoms scores for the 3600-mg dose*, with a mean reduction of the composite symptom score of 82% (Table 1).*

Table 1 GV28985 Efficacy Results from Intent-to-Treat Infected Population

Endpoint	MHAA4549A				
	Placebo (n = 21)	400 mg (n = 11) % reduction (p-value)	1200 mg (n = 13) % reduction (p-value)	3600 mg (n = 14) % reduction (p-value)	Oseltamivir (n = 2) % reduction (p-value)
Median qPCR AUC (log_{10} vc/mLxhour)	458.1	247.2 46.0% (0.0455)	444.4 3.0% (0.9020)	11.3 97.5% (0.0051)	57.4 87.5% (0.0558)
Median cell culture AUC (log_{10} $TCID_{50}$ • hour)	186.8	70.3 62.4% (0.0087)	224.5 -20.2% (0.8742)	0.0 100% (0.0023)	28.8 84.6% (0.0558)
Median qPCR peak (log_{10} vc/mL)	6.38	5.08 20.4% (0.0187)	6.36 0.3% (1.0000)	1.45 77.3% (0.0024)	2.30 63.9% (0.0947)
Median cell culture peak (log_{10} $TCID_{50}$)	4.25	1.75 58.8% (0.0220)	4.00 5.9% (0.9578)	0.00 100% (0.0023)	1.25 70.6% (0.1150)
Median composite symptom score AUC	207.7	87.5 57.9% (0.2000)	192.1 7.5% (0.8743)	37.7 81.8% (0.2887)	8.1 96.1% (0.0855)

AUC=area under the curve; qPCR=quantitative polymerase chain reaction; $TCID_{50}$=50% tissue culture infectious dose; vc=viral copies.

Note: Comparison of 400, 1200, and 3600 mg and oseltamivir to placebo using nonparametric Wilcoxon rank-sum test. % Reduction is calculated as 100% ×[(the median of placebo−the median of active) / the median of placebo]. All p-values are unadjusted for multiple testing.

The responses observed in the Phase 2a study (GV28985) suggest that higher *doses of MHAA4549A* may *improve virological and symptomatic* efficacy in a population with *influenza* infection. *Because of this, an* 8400-mg dose will be *assessed* in this study.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

Two Phase 1 (GV28916, GV29609) studies have demonstrated that MHAA4549A is safe and well tolerated to date in healthy volunteers at doses up to *10800* mg. Data from a Phase 2a study (GV28985) *demonstrated* that the3600 mg MHAA4549A *dose* is *safe, well tolerated, and* effective in reducing viral titers *as compared to placebo* in healthy volunteers inoculated with influenza *virus. No MHAA4549A-specific TEAEs have been identified in any of our clinical studies.* When combined with nonclinical studies

demonstrating that MHAA4549A *has a well-tolerated safety profile and* in vitro and in vivo efficacy *against influenza virus*, these findings support further development of MHAA4549A.

Initially, this GV29216 Phase 2b study enrolled patients in a two-arm treatment study comparing 3600 mg MHAA4549A with oseltamivir versus placebo with oseltamivir. This current Phase 2b study has added an additional arm to evaluate the improvement in outcome of a combination therapy of 3600 mg MHAA4549A with oseltamivir or of 8400 mg MHAA4549A with oseltamivir versus placebo with oseltamivir for additional dose-response information. All patients will receive oseltamivir, which is part of the recommended standard of care for hospitalized influenza patients. Therefore, at a minimum, all patients will be treated with standard of care for influenza. There are three primary goals for this Phase 2b study:

- Demonstrate the safety and efficacy of MHAA4549A in combination with oseltamivir in hospitalized influenza A patients
- [redacted]
- Demonstrate and evaluate the optimal endpoints for study in hospitalized patients with influenza A, given the lack of precedence for approval in patients hospitalized with influenza infection, an area of high unmet medical need

1.3.2 Benefit-Risk Assessment

Although there has been no benefit demonstrated for MHAA4549A in the setting of hospitalized influenza, there is a possibility that patients may have improved clinical outcomes from this therapy. Potential risks of MHAA4549A include immunogenicity and infusion-related reactions. Theoretically, any biologic agent may evoke these responses. To date, MHAA4549A has not been associated with the development of allergic or anaphylactic reactions or infusion-related reactions in nonclinical or clinical studies. In the three clinical trials conducted so far, none of the subjects dosed with MHAA4549A developed an ATA response. No adverse events have been identified that are specific to MHAA4549A.

1.3.2.1 Patient Monitoring and Supervision

MHAA4549A will be administered to enrolled patients in a hospital environment under close medical supervision by *a* physician *or medically qualified designee*. Medical staff will be available for prompt evaluation and treatment of any AEs. Emergency resuscitation equipment and emergency facilities will be readily available. Patients will undergo screening assessments to confirm eligibility, will be closely monitored during the administration of MHAA4549A, and will be resident for at least 24 hours following the administration of MHAA4549A. Furthermore, safety laboratory tests relating to the blood chemistries, including liver function tests will be conducted.

An internal monitoring committee (IMC) in combination with a scientific oversight committee (SOC) will provide safety monitoring for the study in addition to the ongoing review of safety by the Medical Monitor and Safety Scientist. See Section 3.1.2 for more information.

In addition to the regularly scheduled safety reviews of the patient data by the IMC and SOC, an additional sentinel safety cohort of the first 30 patients or patients after the first influenza season, whichever occurs first, will be assessed by the IMC and SOC.

The 120-day follow-up period in the Phase 1 and 2a studies allowed for monitoring of subjects for approximately 5 half-lives of MHAA4549A. No *treatment-induced* ATAs were detected in *both* Phase 1 *studies. One* subject who received placebo in the Phase 2a study tested positive for ATAs at baseline and post-baseline timepoints as described in Section 1.2.2. The Phase 2b study will also include a safety follow-up period of 60 days and an unlimited collection of all SAEs believed related to MHAA4549A.

Based on the above data and design of this study, the Sponsor concludes that the benefit-risk profile of MHAA4549A in the population with severe influenza is favorable.

2. OBJECTIVES

2.1 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety of MHAA4549A in combination with oseltamivir compared with placebo and oseltamivir in patients with severe influenza A, focusing on the nature, frequency, and severity of serious and non-serious AEs as well as effects on laboratory values, vital signs, electrocardiogram (ECG) parameters, ATAs, and other safety biomarkers

2.2 PRIMARY EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To determine the time to normalization of respiratory function of patients dosed with MHAA4549A in combination with oseltamivir compared to patients dosed with placebo and oseltamivir.

2.3 SECONDARY EFFICACY OBJECTIVES

The secondary efficacy objectives for this study are as follows:

- *To compare the clinical status of patients at Days 1–7, 14, and 30 using an ordinal outcome with six clinical statuses. Patients will be categorized into one of the following six mutually exclusive categories on Days 1–7, 14, and 30*
    1. *Death;*
    2. *In the ICU;*

3. *Non-ICU hospitalization, requiring supplemental oxygen;*
4. *Non-ICU hospitalization, not requiring supplemental oxygen;*
5. *Not hospitalized, but unable to resume normal activities; or*
6. *Not hospitalized with full resumption of normal activities*

- To measure clinical failure, as defined in Section 3.3.3, after 24 hours post infusion of study drug
- To determine the time to clinical resolution of *abnormal* vital signs
- To measure mortality in patients
- To determine changes in the extent and duration of viral *burden* in nasopharyngeal samples as a measure of the pharmacodynamic response
- To measure the duration of hospital and/or ICU stay
- To measure antibiotic usage for respiratory infections
- To measure the frequency and severity of the following secondary complications of influenza:
  - Pneumonia (hospital acquired pneumonia [HAP]/ ventilator acquired pneumonia [VAP])
  - Exacerbations of chronic lung disease
  - Myocarditis
  - Acute respiratory distress syndrome (ARDS)
  - Otitis media
  - Other related complications
  - Readmission rates at 30 and 60 days after study treatment
- To measure duration of PPV
- To measure readmission rates

2.4 PHARMACOKINETIC OBJECTIVES

The PK objectives for this study are as follows:

- To characterize the PK profile of MHAA4549A in serum

The exploratory PK objectives for this study are as follows:

- [redacted]
- [redacted]

2.5 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a Phase 2b (GV29216), randomized, double-blind, placebo-controlled study designed to assess the safety and clinical activity of a single IV dose of 3600 mg MHAA4549A or a single IV dose of 8400 mg MHAA4549A in hospitalized patients with severe influenza A in combination with oseltamivir versus a comparator arm of placebo with oseltamivir. *A Sponsor-approved influenza test that includes influenza antigen test or influenza polymerase chain reaction (PCR) test must be used to diagnose influenza A infection for study eligibility.* This study is planned to take place in approximately 170 study centers globally.

Initially, GV29216 targeted enrollment into two treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir or a single IV dose of placebo with oseltamivir.

In this version of the protocol, patients will be randomized 1:1:1 into three treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir, a single IV dose of 8400 mg of MHAA4549A with oseltamivir, or a single IV dose of placebo with oseltamivir. *Patients will be stratified by country, PPV versus supplemental O_2 at randomization, and suspected or confirmed bacterial pneumonia versus no bacterial*

pneumonia based on the status at randomization. All patients *must begin study drug infusion within 48 hours of hospital admission. In addition, all patients* will receive oseltamivir as standard therapy for a minimum of 5 days *(10* doses*) starting no later than 12 hours after completion of study drug administration. Oseltamivir t*reatment for longer than 5 days is permitted based on local investigator discretion.

Hospitalized patients with an O_2 or PPV requirement will be evaluated for influenza A infection. Enrollment in this study requires ongoing treatment within 24 hours of hospital admission with one of the following:

- any PPV or
- any supplemental O_2 to maintain oxygen saturation (SpO_2) > 92% (Section 3.3.2)

Patients on PPV should not exceed *approximately* 45% of the total patients enrolled *in the study*.

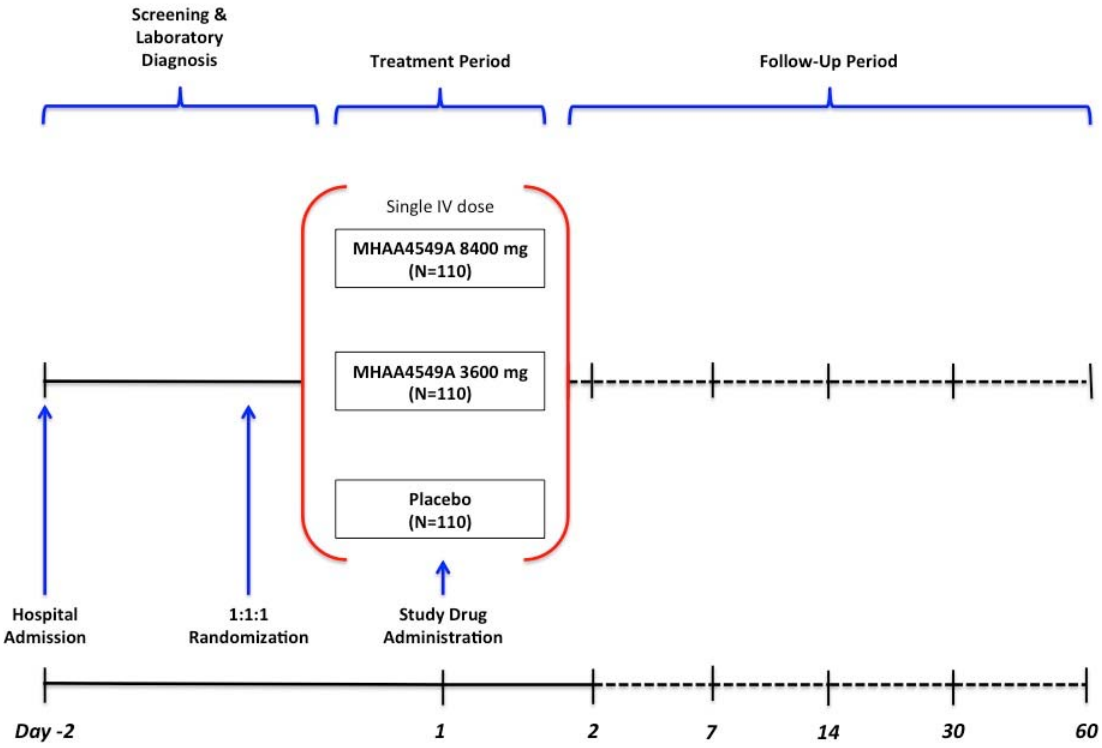
[redacted]

Safety evaluations will also be provided by an IMC and SOC, as defined in the IMC and SOC agreement (see Section 3.1.2). If after review of available study data, the IMC and SOC conclude that there is a significant toxicity or worsening disease associated with MHAA4549A, they may recommend stopping further enrollment in the study.

An additional safety cohort of the first 30 patients, or patients from the first influenza season (whichever occurs first), will be assessed by the IMC and SOC. A review of chemistry laboratory test results, AEs, SAEs, vital signs, and deaths will be assessed.

A schedule of *activities* is provided in Appendix 1a and Appendix 1b. A diagram of the study design is presented in Figure 1.

Figure 1 Phase 2b Study Design (GV29216)



3.1.2 Internal Monitoring Committee and Scientific Oversight Committee

A combined approach with both an IMC and a SOC is proposed to enhance patient safety. The IMC consists of Sponsor representatives from the following functions: Clinical Science, Drug Safety, Biostatistics, and Statistical Programming and Analysis, *and may invite representatives from other functional areas on an ad-hoc basis when additional expertise is required (e.g., Clinical Pharmacology, Research, etc)*. The IMC members will be unblinded to patient treatment and assignment. The Clinical Science representative on the IMC (IMC Chair) will be a person other than the Study Medical Monitor and will not be involved in the conduct of the study or have any contact with study investigators or site staff. The Study Medical Monitor will remain blinded to individual treatment assignments, unless, in exceptional cases, specific circumstances require Study Medical Monitor unblinding after IMC Chair approval. The Drug Safety Scientist on the IMC will also not be involved in the conduct of the study or have any contact with the study investigators. The Biostatistician and Statistical Programmer are the only IMC members involved in the conduct of the study; however, they do not have any contact with study investigators, and all discussion within the IMC are kept

confidential. All other Sponsor and Contract Research Organization personnel involved in the conduct of the study will remain blinded to individual treatment assignments.

The two SOC members are external experts in the field and will be unblinded to treatment allocation. The SOC may be further expanded by the IMC during the course of the study to include additional external experts if the need arises.

A detailed description of the procedures, data flow, and meeting schedule of the IMC and SOC will be provided in a separate IMC and SOC agreement.

3.1.3 End of Study

The end of study is defined as the first day when all patients have had a study completion visit or early termination visit or have otherwise been discontinued from the study.

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Study Design

Hospitalized influenza A infection represents a high unmet need, which, when left untreated, may progress to a more serious disease that may result in significant morbidity and mortality in otherwise healthy adults as well as in vulnerable populations.

This study is designed to estimate the improvement in outcome of a combination regimen of MHAA4549A with oseltamivir compared to a standard of care arm of placebo with oseltamivir. The study population will include hospitalized patients with influenza A requiring $ongoing$ O_2 support and/or PPV support within 24 hours of hospital admission.

Study GV29216 will be a Phase 2b study involving approximately 330 patients. The sample size was determined based on an expected clinically meaningful difference of $1-2$ days improvement in time to normalization of respiratory function between the control and treatment arms, assuming a 5 day median time to the time to normalization of respiratory function in the standard of care arm (Blackwood et al. 2011; Premier Inc, Charlotte, NC).

This design ensures that all patients in the trial will receive the current NAI treatment, oseltamivir, as standard of care at a minimum, and will evaluate the clinical benefit of combining MHAA4549A with this standard of care regimen. Therefore, this study aims to identify a regimen that could deliver maximum benefit in this high unmet need disease, while still treating all enrolled patients with the currently accepted standard of care.

3.2.2 Rationale for Patient Population and Primary Endpoint

Severe influenza, for the purpose of this study, is defined as requiring one of the following treatments: any supplemental O_2 to maintain an $SpO_2 > 92\%$ or PPV. PPV is

defined as any mechanical positive pressure device to maintain oxygenation; this can include positive pressure mask and intubation.

This patient population was chosen based on the rationale that respiratory failure is a hallmark of influenza and a major driver of morbidity and mortality, as well as hospitalization. The recovery from ventilator support has been shown to be directly proportional to time spent in the ICU (Blackwood et al. 2011; Premier Inc, Charlotte, NC). Based upon an analysis of morbidity and mortality, the patient population that requires supplemental O_2 or ventilation on their first day of admission was determined to have a high unmet medical need as they have an estimated mortality of 9%-32%, and 27% require admission to the ICU, according to analysis of a database of over 70,000 hospitalized patients in the U.S. from 2005-2012 (Premier Inc, Charlotte, NC).

The proposed primary efficacy outcome measure in this study is "Time to normalization of respiratory function," defined as oxygen saturation ≥ 95% without oxygen supplementation. Support for use of a respiratory endpoint in this population comes from recently published data demonstrating that a composite endpoint that captured respiratory rate, fever, heart rate, and blood pressure resolution was primarily driven by the respiratory component of the endpoint (Marty et al. 2014). Given that influenza infections generally do not cause systemic infections and influenza disease is restricted to the respiratory tract, the Sponsor believes that the primary endpoint represents a clinically meaningful outcome in this patient population (as shown by analysis of PREMIER database) and measures an important physiologically relevant pharmacodynamic response parameter of MHAA4549A. This endpoint is a measure of patient function, measures a symptom that represents a serious consequence of influenza, and is consistent with clinically relevant endpoints discussed in the US Food and Drug Administration (FDA) Guidance, "Influenza: Developing Drugs for Treatment and/or Prophylaxis" (FDA 2011).

3.2.3 Rationale for Control Group and Treatment Window

In this study, the standard of care regimen for the control or comparator group *(hospitalized influenza A patients)* is oseltamivir, an NAI. In the treatment groups, MHAA4549A will be dosed in addition to oseltamivir. *Oseltamivir* for a minimum of 5 days is permitted following treatment with MHAA4549A. Treatment for longer than 5 days is permitted based on local investigator discretion (WHO 2005; Fiore et al. 2011; *CDC 2016*). The oseltamivir dosing regimen is listed in Table 2. This control treatment was based on consideration of safety, ethics, and efficacy for treatment of severe influenza and is consistent with guidelines for antiviral treatment of hospitalized patients with influenza (Harper et al. 2009; Fiore et al. 2011).

Table 2 Oseltamivir Dosing Regimen

Neuraminidase Inhibitor	Dosing Regimen	Duration of Therapy
Oseltamivir	75 mg or 150 mg oral twice daily [a]	5 days [b]

[a] 75 mg or 150 mg dose at the discretion of the investigator, and dose must be documented. Capsules can be opened and the granules administered via nasogastric tube, if required. For renal dose adjustments, follow local standard of care practice/local package insert and document in the eCRF.

[b] Longer treatment times are at the discretion of the investigator (WHO 2005; Fiore et al. 2011; CDC 2016).

If oseltamivir resistance is highly suspected or identified or oseltamivir route of administration challenges are encountered, then following discussion with the Sponsor *Medical Monitor*, an alternative NAI to oseltamivir may be used. *For renal dose adjustments, local standard-of-care practice/local package insert should be followed and documented in the eCRF. Capsules other than 75 mg (for 75 mg twice a day [BID] or 150 mg BID regimens) cannot be provided through the study Interactive Voice and Web Response System (IxRS). In these instances, the study site may supply the appropriate dose and be reimbursed by the Sponsor.*

From a safety standpoint there are no expected drug interactions between MHAA4549A, a monoclonal antibody, and any NAI, which are small molecule drugs that bind to a different viral protein than MHAA4549A. In the Phase 2a challenge study, all subjects that were dosed with MHAA4549A also received a 5-day course of oseltamivir starting on Day 7. There were no safety effects attributable to the combination when the drugs were present concurrently. *In the Phase 2a challenge study, MHAA4549A treatment did not appear to impact the exposure* of oseltamivir and its *active metabolite oseltamivir carboxylate. There was no suggestion of PK drug-drug* interaction *between* MHAA4549A *and oseltamivir.*

For this Phase 2b study, a combination of MHAA4549A and oseltamivir was determined to be the most clinically feasible treatment regimen, both from an ethical as well as a practical perspective. The treatment of all patients with oseltamivir ensures that all patients will receive the standard of care. Given the high morbidity and mortality of hospitalized patients with influenza A along with guidelines from Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) it is recommended that NAIs are the standard of care for hospitalized patients with influenza A (Harper et al. 2009; *CDC 2016*). Furthermore, pre-clinical efficacy data from a study using MHAA4549A and oseltamivir in combination showed a potential synergistic effect of both compounds which may be due to the different and potentially complementary mechanisms of action, i.e. targeting viral HA and neuraminidase (NA).

Dosing of MHAA4549A is confined to a treatment window designed for best expected treatment success and to ensure that any observed effects can be attributed to the study

drug with high confidence. MHAA4549A shall only be dosed within 5 days of onset of symptoms (including fever, chills, malaise, dry cough, loss of appetite, myalgias, coryza, or nausea), no later than 48 hours after admission to the hospital, and if a subject has taken less than a total of 6 doses (3 doses for peramivir) of approved anti-influenza therapy from onset of symptoms. This proposed window is supported by data demonstrating that hospitalized influenza patients benefit from NAI treatment even at 5 days from onset of symptoms (Louie et al. 2012). The patient must start standard-of-care oseltamivir no later than 12 hours after completion of MHAA4549A administration.

3.2.4 Rationale for MHAA4549A Dosage

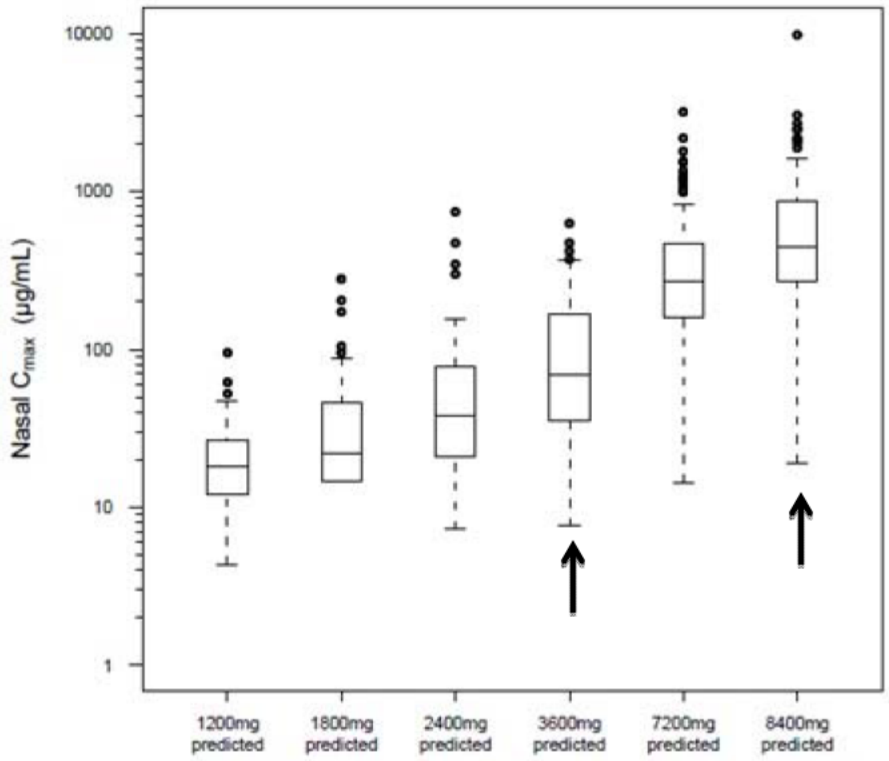
Single IV doses of 3600 and 8400 mg were selected to assess the safety, efficacy, and pharmacokinetics of MHAA4549A and to provide data for further clinical development. The selection of dose in this study was based on nonclinical efficacy data from the in vivo mouse influenza A infection models, the pharmacokinetics in clinical studies, and the relationship between the pharmacokinetics, pharmacodynamics, and efficacy observed in the Phase 2a challenge study in influenza A (GV28985).

The dose of 3600 mg is based on the Phase 2a challenge study (GV28985), which demonstrated both a significant decrease in viral shedding in the upper respiratory tract and a decrease in the AUC of symptoms scores in patients who received the 3600-mg dose of MHAA4549A as compared to patients who received placebo (see Section 1.2.4). An exploratory exposure-response analysis of this group demonstrated that subjects with nasal viral loads greater than the median viral load had shorter time to resolution of viral shedding as compared with the placebo group (median: 75.8 hours vs. 113.7 hours), whereas subjects with nasal viral loads less than the median viral load had similar time to resolution of viral shedding compared with the placebo group (median: 112.1 hours vs. 113.7 hours). Thus, at higher viral loads, higher doses of MHAA4549A are expected to be more efficacious.

The 8400-mg dose was selected based on the hypothesis that severely ill patients hospitalized with influenza infection (the target population of MHAA4549A) are likely to have high viral loads and longer durations of viral shedding and require increased doses of MHAA4549A. Simulations from a semi-quantitative pharmacokinetic model developed from the Phase 2a challenge study (GV28985) suggest that 8400 mg is the minimum dose that will show a separation of nasal exposure from a dose of 3600 mg (Figure 2).

Both the 3600- and 8400-mg doses of MHAA4549A are expected to be safe based on previous clinical Phase 1 Phase 2a studies.

Figure 2 Semi-Quantitative Pharmacokinetic Model of Nasal Exposure



Note: The bottom and top of the box represent the 25th and 75th percentile, and the band inside the box is the median *(n =100 per dose level)*. The upper whisker is the 1.5 interquartile range (IQR) of 75th percentile and the lower whisker is the 1.5 IQR of 25th percentile. *Single dots represent outliers. Simulation assumes PK can be extrapolated at doses above 3600 mg and that the PK profile in acute uncomplicated influenza A infection is similar to the PK profile of severely ill patients.*

3.2.5 Rationale for Biomarker Assessments

[redacted]

[redacted]

[redacted]

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- AEs and clinical laboratory abnormalities
- Vital signs, physical findings, ATAs, and clinical laboratory results during and following administration of MHAA4549A

3.3.2 Primary Efficacy Outcome Measures

The primary efficacy outcome measure for this study *is* as follows:

- Time to normalization of respiratory function defined as:
  - The time to cessation of O_2 support resulting in a stable $SpO_2 \geq 95\%$ (see Appendix 2 for details)

3.3.3 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- *Clinical status of patient at Days 1–7, 14, and 30. This is an ordinal outcome with six mutually exclusive categories:*
  1. *Death;*
  2. *In the ICU;*
  3. *Non-ICU hospitalization, requiring supplemental oxygen;*
  4. *Non-ICU hospitalization, not requiring supplemental oxygen;*
  5. *Not hospitalized, but unable to resume normal activities; or*
  6. *Not hospitalized with full resumption of normal activities*
- Clinical failure after 24 hours post-infusion of study drug; defined as:
  - Progression to increased O_2 requirement defined by an increase in oxygen supplementation from low flow oxygen (i.e., 2–6 L/min) to high flow oxygen

*(i.e., >*6 L/min) or from oxygen supplementation alone to any PPV or extracorporeal membrane oxygenation (ECMO)

  - Progression to ICU
  - Prolonged ventilation or O_2 support defined by $>$2 weeks, or
  - Death
- Time to clinical resolution of *abnormal* vital signs (3/5 criteria must be met):
  - $SpO_2 \geq 95\%$ without supplemental O_2
  - Respiratory rate $<$ 24 breaths per minute without supplemental O_2
  - Core temperature $<$ 37.2°C immediately prior to receipt of any antipyretic drug, and at least 6-8 hours from the last dose of antipyretic or core temperature $>$ 36°C in patients who are initially hypothermic
  - Heart rate (HR) $<$ 100 beats/minute
  - Systolic blood pressure (SBP) $>$ 90 mmHg
- All-cause mortality at Day 14, Day 30, and Day 60
- Influenza A viral load in nasopharyngeal samples
  - AUEC (qPCR)
  - Peak viral load (qPCR)
  - *Duration* of *viral shedding* (qPCR)
- Duration of hospitalization
- Duration of ICU stay
- Antibiotic usage for respiratory infections
- Complications of influenza:
  - Pneumonia (HAP/VAP)
  - Exacerbations of chronic lung disease
  - Myocarditis
  - ARDS
  - Otitis media
  - Other related complications
- All-cause readmission at Day 30 and Day 60
- Duration of ventilation

3.3.4 Pharmacokinetic Outcome Measures

The primary PK outcome measures for this study are as follows:

- PK parameters for MHAA4549A in serum including total exposure (i.e., AUC), maximum observed concentration (C_{max}), clearance, half-life, and volume of distribution, when appropriate, as data allow

The exploratory PK outcome measures for this study are as follows:

[redacted]

3.3.5 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

This study aims to enroll approximately 330 men and women and is designed to assess the safety and clinical activity of a single IV administration of 3600 mg MHAA4549A or a single IV administration of 8400 mg MHAA4549A in adult patients hospitalized with severe influenza A.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Hospitalized men or women ≥ 18 years of age on the day of signing the informed consent or obtaining surrogate consent from an authorized representative
- Diagnosis of influenza A where a Sponsor-approved influenza test is used as an aid in diagnosis. A Sponsor-approved influenza test includes:
  - Influenza antigen test –OR–
  - Influenza PCR test
- One of the following markers of severity within 24 hours of hospital admission:
  - Requirement for PPV –OR–
  - Requirement for O_2 supplementation to maintain $SpO_2 > 92\%$ *(Source documentation should show that the patient's SpO_2 was less than 92% off oxygen. Source documentation may consist of either a SpO_2 off oxygen with a value below 92% or a documentation of the Investigator's rationale in lieu of this SpO_2 documentation.)*
- A negative urine or serum pregnancy test for women of child-bearing potential
- Patients of reproductive potential must agree to use reliable means of contraception as described below as a minimum (adherence to more stringent local requirements may be required):
  - For women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use two adequate methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment period and for at least 120 days after the dose of study drug

    Abstinence is only acceptable if it is in line with 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.

    Barrier methods must always be supplemented with the use of a spermicide.

Examples of contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, hormonal implants, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.

Male partners who have had a vasectomy should have the appropriate post-vasectomy documentation available of the absence of sperm in the ejaculate. The vasectomized male partner should be the sole partner for that patient.

- For men: agreement to remain abstinent or use a condom during the treatment period and for at least 30 days after the dose of study drug and agreement to refrain from donating sperm during this same period

  Men with a pregnant partner must agree to remain abstinent or use a condom for the duration of the pregnancy.

  Abstinence is only acceptable if it is in line with 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.

- Non-reproductive potential is defined below (but could be superseded by local definitions, if they are more stringent):

  Women who are postmenopausal *(≥12 months of non-therapy-induced* amenorrhea*)*

  Women who are surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)

  Men who are surgically sterile (i.e., castration)

4.1.2 Exclusion Criteria

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

- Pregnant or lactating, or intending to become pregnant during the study
  - Women who are not postmenopausal (postmenopausal defined as ≥12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative pregnancy test result within 2 days prior to initiation of study drug.
- Hypersensitivity to monoclonal antibodies or to any *constituents (sodium succinate, sucrose, polysorbate 20)* of MHAA4549A study drug
- Hypersensitivity to the active substance or to any excipients of oseltamivir
- Investigational therapy within the 30 days prior to study treatment
- Received prior therapy with any anti-influenza monoclonal antibody therapy (including MHAA4549A) *within* 8 months prior to study treatment
- Current treatment (within 7 days of dosing) with probenecid, amantadine, or rimantidine

- Patients who have taken more than a total of 6 doses (3 doses of peramivir) of anti-influenza therapy (e.g., oseltamivir, zanamivir, *laninamivir,* peramivir) in the period from onset of symptoms and prior to study treatment
- Admission > 48 hours prior to study treatment
- Onset of influenza symptoms (including fever, chills, malaise, dry cough, loss of appetite, myalgias, coryza, or nausea) > 5 days prior to study treatment
- Positive influenza B or influenza A + B infection within 2 weeks prior to study treatment
- High probability of mortality in the next 48 hours as determined by the investigator
- Patient requiring home or baseline oxygenation therapy
- Patient with history of chronic lung disease *with a documented* $SpO_2 < 95\%$ *off oxygen*
- Patient on a chronic dose of corticosteroids exceeding 10 mg/day of prednisone or equivalent steroid dose for a duration of greater than 14 days within 30 days of entry into study
- Creatinine clearance ≤ 10 mL/min
- Patients who received nasally administered influenza A vaccine within 7 days *prior to screening*
- Patients with the following significant immune suppression:
  - Bone marrow or solid organ transplant in the previous 12 months
  - Cancer chemotherapy in the previous 12 months
  - HIV infection with most recent CD4 < 200 cells/mL
  - Other significant immune suppression as determined by the investigator in discussion with the Sponsor Medical Monitor
- Patient on ECMO at time of randomization
- Any disease or condition that would, in the opinion of the site investigator or Sponsor, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The randomization of patients will be managed by a central Interactive Voice and Web Response System (IxRS) through use of a dynamic hierarchical algorithm which includes a random component. The treatment assignments will be unblinded to selected Sponsor personnel to facilitate ongoing monitoring of safety and tolerability, including members of the IMC and SOC.

All patients will be randomly assigned to receive 3600 mg MHAA4549A, 8400 mg MHAA4549A, or placebo at a 1:1:1 ratio stratified by country, whether patient is on PPV versus supplemental O_2 at randomization, and whether the patient has suspected or

confirmed bacterial pneumonia vs no bacterial pneumonia at randomization. Initially GV29216 randomly assigned patients to receive either 3600 mg MHAA4549A, or placebo at a 1:1 ratio. The updated randomization scheme takes into account the numbers already allocated to these two arms and strata prior to allocating to the three arm design so that by the end of the study there will be an approximate 1:1:1 allocation between the three arms.

All patients will receive oseltamivir (as described in Table 2) for a minimum of 5 days. Treatment for longer than 5 days is permitted based on local investigator discretion.

Unblinded personnel (i.e., unblinded site pharmacist or other designated, qualified unblinded study personnel) at each study site will prepare the IV infusions of study drug, as described in Section 4.3.3. The Sponsor will provide masking bags and blinded study personnel will administer the study drug. The other parties who are involved in the conduct of the study (i.e., patients and blinded site personnel) will remain blinded to patient-specific treatment assignments until the final database lock after the completion of the study.

Bioanalytical laboratory personnel responsible for performing PK assays will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed. Samples from patients assigned to the comparator arm will not be analyzed except by request (e.g., to evaluate a possible error in study drug administration).

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this trial.

If unblinding is necessary for patient management (e.g., in the case of an SAE for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code in IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study drug for any other reason, they should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to an SAE).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all suspected unexpected serious adverse reactions (SUSAR) (see Section 5.4) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 MHAA4549A and Placebo

MHAA4549A *will be supplied by the Sponsor in a sterile, preservative-free liquid solution in a single-use 15-mL USP/Ph. Eur. Type 1 glass vials filled to deliver 10 mL (500 mg) of MHAA4549A solution.*

MHAA4549A placebo *will be provided as a clear, colorless, sterile, preservative-free liquid solution and has the same vial configuration as the drug product.*

For information on the formulation and handling of MHAA4549A, see the *pharmacy manual* and the *Investigator's* Brochure.

4.3.1.2 Oseltamivir (Tamiflu®)

Oseltamivir (Tamiflu®) is an influenza NAI indicated for treatment of acute, uncomplicated influenza. The Sponsor will provide *75-mg capsules of* oseltamivir for up to a 10-day treatment course *(for 75- or 150-mg BID regimens). For renal dose adjustments, follow local standard-of-care practice/local package insert and document in the eCRF. Capsules other than 75 mg (for 75- or 150-mg BID regimens) cannot be provided through the study IxRS. In these instances, the study site may supply the appropriate dose and be reimbursed by the Sponsor.*

For information on the formulation, packaging, and handling of oseltamivir; see the local prescribing information for oseltamivir.

Storage: Capsules should be stored at 25°C (77.7°F); excursions are permitted to 15°C to 30°C (59°F to 86°F).

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 MHAA4549A and Placebo

Administration of MHAA4549A or placebo will be performed in a setting with emergency medical equipment and personnel who are trained to monitor for and respond to medical emergencies. A qualified physician *or medically qualified designee* will be on site during study drug administration for all patients.

A single dose of MHAA4549A or placebo will be delivered by IV infusion following dilution in 0.9% normal saline over approximately 120 minutes. Study drug should be delivered using a 0.*20- to 0.22-*μm in-line filter. Compatibility testing has shown that MHAA4549A is stable when diluted in 0.9% normal saline in a polyvinylchloride bag, polyolefin bag, or ethylene vinyl acetate bag (EVA), at concentrations of 0.24 mg/mL up to 27.0 mg/mL. Study drug must be administered within the treatment window outlined in Section 3.1.1. Further detailed instructions for preparation of study drug can be found in the Pharmacy Manual.

Subjects who experience a moderate-to-severe infusion-related reaction should have their infusion stopped. The infusion should not be restarted. The infusion will be discontinued in the event that the subject experiences a serious reaction and further dosing of subjects will be halted until the safety of the drug is assessed.

There are no recommended dosage modifications for MHAA4549A since it is a single infusion. Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. General supportive measures will be taken to manage any AEs associated with overdose. Patients experiencing such AEs will be followed up clinically until the event has resolved.

Trained clinical site staff responsible for adequate and accurate study drug administration, accounting, and management will administer study drugs to patients. Study drug preparation and dosing instructions will be provided to each site. The exact times of study drug administration will be recorded in the relevant dispensing/administration logs and patient's source notes. Any noncompliance or problems with study drug administration will be recorded in the patient's source notes and reported to the Sponsor if appropriate.

4.3.2.2 Oseltamivir-Neuraminidase Inhibitor (NAI)

The Sponsor will supply *75-mg* oseltamivir (Tamiflu®) *capsules* for this study for up to a 10-day course *(for 75-* or 150-mg *BID regimens). Oseltamivir* will be administered twice daily as described in Section 3.1.1. Capsules can be opened and the granules administered via nasogastric tube, if required. Doses should be captured in the eCRF. *For renal dose adjustments, follow local standard-of-care practice/local package insert and document in the eCRF. Capsules other than 75 mg (for 75- or 150-mg BID regimens) cannot be provided through the study IxRS. In these instances, the study site may supply the appropriate dose and be reimbursed by the Sponsor.*

Any overdose or incorrect administration of oseltamivir should be noted on the oseltamivir Administration eCRF. AEs associated with an overdose or incorrect administration of oseltamivir should be recorded on the Adverse Event eCRF.

Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary, empty (used) oseltamivir packets and unused oseltamivir capsules to the study site at the next follow up visit. Patients will record the date and time when each oseltamivir capsule is administered.

4.3.3 Investigational Medicinal Product Accountability

Investigational medicinal products (IMPs) required for completion of this study (i.e., MHAA4549A and *75-mg* oseltamivir *capsules*) will be provided by the Sponsor. The

study site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMP will be stored in a secure pharmacy or locked area with access limited to authorized personnel, in accordance with the details provided in the Investigator's Brochure and Pharmacy Manual. Upon receipt, MHAA4549A and placebo vials must be refrigerated at 2°C to 8°C until use. MHAA4549A does not contain antimicrobial preservatives; therefore, care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation. Dilute under appropriate aseptic conditions using 0.9% normal saline. The solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use should not exceed 24 hours at 2°C to 8°C and/or 4 hours at ambient temperature (18°C – 24°C). If the dose solution is stored at 2°C – 8°C, it should be removed from refrigeration and allowed to reach room temperature prior to administration. If the infusion is interrupted and the combined ambient temperature storage and interruption time exceeds 4 hours, prepare a new dose solution to resume the infusion (see the Pharmacy Manual). Protect dose solutions from heat and intense light.

The total duration from the preparation of dose solutions to the end of infusion should not exceed 24 hours. Vials are intended for single use only; therefore, any remaining solution should be discarded (see the Pharmacy Manual).

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

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

4.4 POST-TRIAL ACCESS TO MHAA4549A

As this is single dose administration, Genentech does not intend to provide MHAA4549A to patients after the conclusion of the study or any earlier withdrawal. Patients may or may not be eligible for any potential subsequent trials of MHAA4549A under a separate protocol.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:
http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.5 CONCOMITANT THERAPY AND FOOD

Concomitant medication includes any medication (e.g., prescription drugs, over the counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 30 days prior to screening to the study completion/*early* discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. For any NAIs (e.g., oseltamivir, peramivir, zanamivir, laninamivir) that have been taken prior to study drug therapy, the number of doses and duration of therapy must be recorded.

4.5.1 Permitted Therapy

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

All therapies required for management of the patient's acute illness are permitted except for those listed below in Section 4.5.2.

4.5.2 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 7 days prior to study treatment, unless otherwise specified below: probenecid, amantadine, or rimantidine.

Use of other NAIs, including but not limited to oseltamivir, zanamivir, *laninamivir,* and peramivir, are prohibited during the study, but allowed up to a total of 6 doses (3 doses for peramivir) in the period from onset of symptoms and prior to study treatment as outlined in the exclusion criteria. Patients must start standard-of-care oseltamivir no later than *12* hours after completion of MHAA4549A administration. If oseltamivir resistance is highly suspected or identified or if oseltamivir route of administration challenges are encountered then, following discussion with the Sponsor's *Medical Monitor*, an alternative NAI to oseltamivir may be used.

4.5.3 Prohibited Food

There are no prohibited foods for this study.

4.6 STUDY ASSESSMENTS

Please see Appendix 1a and Appendix 1b for the schedule of activities performed during the study.

4.6.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-*related procedures.* Informed consent by authorized representatives may be obtained only if allowed by and in accordance with local regulations and Independent Review Board (IRB)/Independent Ethics Committee (IEC)

policies and procedures. Informed Consent Forms (ICF) 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 randomization. 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.

4.6.2 Diagnostic Testing for Enrollment

All hospitalized patients with severe influenza A must be assessed for disease confirmation prior to and enrollment into the study. A Sponsor-approved influenza test is required as an aid in the diagnosis of influenza A infection. This requires a nasopharyngeal swab be introduced into one nostril. *A lower respiratory tract sample may be used if appropriate for the Sponsor-approved local PCR test.* Note that the influenza antigen test or influenza PCR test result must be available within the 48-hour screening window.

4.6.3 Medical History and Demographic Data

Medical history includes clinically significant diseases and procedures, including chronic respiratory disease, infections, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days prior to the screening visit. A careful assessment of the patient's baseline SpO_2 will be made especially if the patient has a history of severe chronic lung disease.

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

4.6.4 Priority of Assessments

When events warrant, or in the opinion of the investigator, safety issues become paramount, safety assessments will always have priority over all other measurements and procedures. Under routine circumstances, however, PK, nasal virological, and biomarker serum/plasma samples have priority over other measurements. The timing and number of safety measurements may be modified based on clinical evaluations.

Assessments on Day 1 must be concluded prior to dosing as specified in Appendix 1a. Any screening assessments completed prior to consent as standard of care do not need to be repeated if done within the screening period.

4.6.5 [redacted]

[redacted]

[redacted]

4.6.6 [redacted]

[redacted]

4.6.7 Physical Examinations

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

At protocol designated visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed which include, at a minimum, evaluation of general appearance, dermatological examination of the injection sites, evaluations directed by patient-reported symptoms, and any other evaluations that the investigator deems clinically relevant. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as AEs, if appropriate, on the adverse event eCRF.

Day 1 physical examination is optional if already completed on Day -1 or -2.

4.6.8 Vital Signs

Vital signs will include measurements of respiratory rate, *heart* rate, temperature, and systolic and diastolic blood pressures after the patient has been in a seated or supine position for >5 minutes. *Temperature should be measured using the same methodology throughout the study and should be measured prior to administration of any antipyretic drugs.* Patients in intensive care may have vital signs assessed following local procedures, but those procedures should be captured in the eCRF in accordance with the eCRF instructions.

4.6.9 Oxygen Saturation Measurements

To ensure that the respiratory status is well recorded, the following daily measurements will be performed. *All* patients will have their SpO_2 and corresponding respiratory

assessments recorded daily in the morning between 6:00 a.m. and 12:00 noon local time. *Unless clinically contraindicated*, patients* on low flow O_2 will have a daily trial of their SpO_2 while on and off the supplementation, as outlined in *Appendix 2, and both values will be recorded. If a patient is clinically able to be removed from oxygen outside the time window above (6:00 a.m. to 12:00 noon), the trial-off data should be recorded as an unscheduled visit.*

If the patient is on oxygen supplementation, SpO_2 measured by pulse oximetry and the corresponding respiratory assessments (e.g., FiO_2, flow rate) will be recorded. If the patient is on PPV, partial pressure of arterial O_2 (PaO_2) and the corresponding respiratory assessments (e.g., FiO_2, ventilator mode, ventilator respiratory rate, positive end expiratory pressure) will be recorded. If clinically appropriate (i.e., the patient is on non-invasive PPV), the conversion table in Appendix 11 may be used for PaO_2.

**If a patient has an SpO_2 <95% while on oxygen supplementation, he/she shall be considered to be "clinically contraindicated" from requiring a trial off oxygen; however, corresponding respiratory assessments should be recorded.*

4.6.10 Laboratory, Biomarker, and Other Biological Samples

Samples for the laboratory tests listed in Table 3 and Table 4 will be sent to the study site's local laboratory for analysis at screening and during the study, respectively.

Table 3 Laboratory Tests at Screening

Hematology:	**Clinical Chemistry:**
Hemoglobin	Thyroid stimulating hormone (optional)
Hematocrit	
Erythrocyte count (RBC)	**Serology:**
Leukocytes (WBC)	HIV Serology
Neutrophils *(*segmented *and* bands *if clinically indicated)*	
Lymphocytes	**Misc:**
Monocytes	Pregnancy Test (urine or serum; women of child-bearing potential)
Eosinophils	
Basophils	
Platelets	

Note: Investigators must document their review of each laboratory report by signing (or initialing) and dating each report.

Table 4 Laboratory Tests during the Study

Hematology:	**Clinical Chemistry (Blood):**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Bicarbonate
Leukocytes (WBC)	Chloride
Neutrophils *(*segmented *and* bands *if clinically indicated)*	Calcium
Lymphocytes	Phosphorus
Monocytes	Magnesium
Eosinophils	Glucose
Basophils	Urea nitrogen (BUN) or urea
Platelets	Creatinine
	Total cholesterol
	Total protein
Coagulation:	Albumin
Activated partial thromboplastin time (APTT)	Total bilirubin
Prothrombin time (PT)	Alkaline phosphatase
International Normalized Ratio (INR)	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
Urinalysis:	Amylase
pH	Gamma-glutamyl transpeptidase (GGT) (if clinically indicated)
Specific gravity	
Glucose	C-reactive protein (CRP) (optional)
Protein	Erythrocyte Sedimentation Rate (ESR) (optional)
Ketones	
Blood	
Bilirubin	**Misc:**
Nitrite	Pregnancy Test (*urine or serum;* if clinically indicated)
Leukocyte esterase	
Microscopic examination (if clinically indicated)	

Note: Investigators must document their review of each laboratory report by signing (or initialing) and dating each report.

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

- [redacted]
- Serum samples for ATA testing (see Appendix 1a and Appendix 1b)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

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

4.6.11 Electrocardiograms

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

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

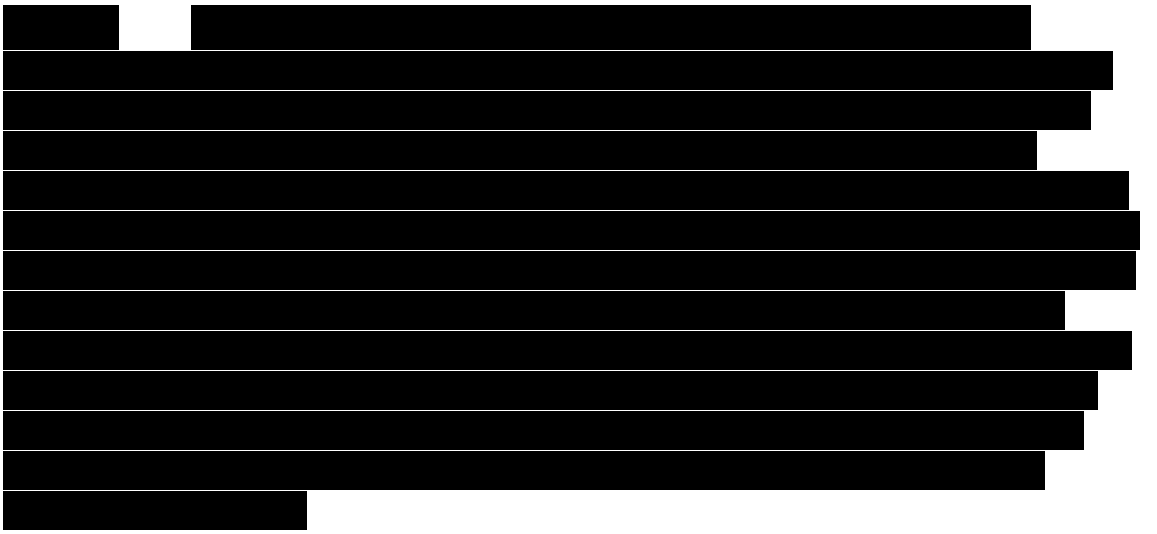
For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The following should be recorded in the appropriate eCRF: HR, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF *(or QTcB if*

QTcF is not available) based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean *corrected QT interval* is > 500 ms and/or > 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until *the corrected* QT interval has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard of care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on discontinuation should be made, as described in Section 4.9.2. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, medications known to prolong the QT interval, severe bradycardia).

4.6.12 [redacted]

[redacted]



4.7 APACHE AND SOFA SCORES

Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) scores are for patients that are admitted into the ICU. These assessments are not required for study conduct or entry but should be collected if available. The initial scores for APACHE and SOFA should be taken within 24 hours of entry into the ICU and at the time points specified in Appendix 1a.

For the calculation of the initial APACHE and SOFA scores, the worst values in the first 24 hours of ICU admission should be used. SOFA scores are only for patients admitted into the ICU that have available data for calculation (i.e., partial pressure of arterial oxygen/fraction of inspired oxygen [PaO_2/FiO_2] in mmHg). See Appendix 7 for SOFA score calculation.

4.8 OSELTAMIVIR MEDICATION DIARY

Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary, empty (used) oseltamivir packets, and unused oseltamivir capsules to the study site at the next follow up visit.

Patients will record the date and time when each oseltamivir capsule is administered.

4.9 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.9.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.9.2 Study Treatment Discontinuation

Patients must discontinue MHAA4549A infusion and therefore treatment if they experience any of the following:

- Life threatening infusion-related reactions

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

- Pregnancy
- Serious skin/hypersensitivity reactions

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

The IMC and SOC may recommend to permanently discontinue dosing for all patients within one or both study arms in the event of a general safety concern.

4.9.3 Study Completion/Early Discontinuation Visit

Patients who complete all study visits through Day 60 are considered to have completed study. All patients who discontinue from the study early will be asked to complete all assessments for the early discontinuation visit. Please see Schedule of *Activities* provided in Appendix 1a for assessments performed at the Study Completion/Early Discontinuation visit.

4.9.4 Study and Site Discontinuation

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

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

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study. The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

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

4.10 *ASSAY METHODS*

[redacted]

[redacted]

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

MHAA4549A is not approved and is currently in clinical development. Thus, the entire safety profile is not known at this time. The safety plan for this study is based upon preclinical data and the previous Phase 1 and Phase 2a studies and is designed to ensure patient safety. It will include specific eligibility criteria and monitoring assessments as detailed below and in Section 4.1.

The investigator, in consultation with the Sponsor, is responsible for assuring the safety of study participants who have entered this study and for taking appropriate action concerning any event that seems unusual, even if this event may be considered to be an unanticipated benefit to the study participant. The investigator will be responsible for a clinical assessment of the study participants before discharge from the study, and for the establishment of a discharge plan, if needed.

During the study, the incidence and nature of adverse events, serious adverse events, and laboratory abnormalities will be assessed. An ongoing blinded review of safety will be carried out by the Medical Monitor and a drug safety scientist. An unblinded review of safety will be performed on an ongoing regular basis by the IMC and SOC as described in the IMC and SOC agreement.

5.1.1 *Risks Associated with MHAA4549A*

There are no known risks associated with MHAA4549A based on completed Phase 1 (GV28916 and GV29609) and Phase 2a (GV28985) studies.

5.1.1.1 *Immunogenicity*

MHAA449A is a monoclonal antibody-based therapeutic. As with any recombinant monoclonal antibody, MHAA4549A may elicit an immune response in patients with the development of antibodies against MHAA4549A. Subjects will be closely monitored for any potential immune response to MHAA4549A. Screening, confirmatory, and characterization assays with appropriate sensitivity and therapeutic tolerance will be employed to assess ATAs before and after treatment with MHAA4549A.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

Adverse events will be monitored throughout the entire study (enrollment through Day 60 or Early Discontinuation).

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug

- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events [DAIDS]; see Section 5.3.3, Appendix 8, and Appendix 9); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Non-serious adverse events of special interest (AESI) are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study 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 (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below
- Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Adverse events associated with suspected cases of infusion-related reactions (IRR) which occur within 24 hours of study drug administration and may show the following signs and symptoms (for guidance on reporting AEs associated with IRR, see Section 5.3.5.1):
  - Fever and/or shaking chills
  - Flushing and/or itching
  - Alterations in heart rate and blood pressure
  - Dyspnea or chest discomfort
  - Back or abdominal pain

- Nausea, vomiting, and/or diarrhea
- Various types of skin rashes
- Anaphylaxis

Anaphylaxis due to IV drugs most often presents with the following signs and symptoms:

- Cutaneous symptoms: flushing, itching, urticaria, and/or angioedema (usually of face, eyelids, or lips)
- Respiratory symptoms: repetitive cough, sudden nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and or change in voice quality due to laryngeal edema
- Cardiovascular symptoms: faintness, tachycardia (or less often bradycardia), tunnel vision, chest pain, hypotension, sense of impending doom, and/or loss of consciousness
- Gastrointestinal symptoms: such as nausea, vomiting, abdominal cramping, and diarrhea

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until *study completion at* the Day 60 visit or *until an* Early Discontinuation visit. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

Investigators will seek information on adverse events and serious adverse events at each patient contact. All adverse events, and serious adverse events, whether reported by the patient or noted by authorized study personnel, will be recorded.

The adverse event grading (severity) scale in the DAIDS v1.0 will be used for assessing adverse event severity (see Table 5).

Table 5 Adverse Event Grading (Severity) Scale

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical AE NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

AE = adverse event; DAIDS = Division of Acquired Immunodeficiency Syndrome.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 6 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than *an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than* a diagnosis of *infusion-related* reaction or *anaphylactic* reaction*)*.

Other Adverse Events

For adverse events other than infusion-related reactions, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is

subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF, unless the severity increases. If a persistent adverse event becomes more severe, it should be recorded as a separate event on the Adverse Event eCRF. The initial (less severe) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became more severe. If a persistent adverse event becomes serious, it should be recorded as a separate event on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The initial (non-serious) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became serious.

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

5.3.5.4 Abnormal Laboratory Values

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

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment (laboratory abnormalities should be repeated at the first opportunity and only considered clinically significant if they persist on repeat assessment)

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event. Investigators should promptly repeat any abnormal assessment or clinically significant laboratory result. Only those findings that remain clinically significant upon a repeat assessment will be considered adverse events.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin $5\times$ upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

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

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.6 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.4) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of severe influenza or any related co-morbidities should be recorded on the Study Completion/Early Discontinuation eCRF. All other on

study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF, and immediately reported to the Sponsor as an SAE (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

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

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of Influenza A Infection

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

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
    - The patient has not experienced an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Adverse Events Associated with an Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No clinical safety data related to overdosing of MHAA4549A are available, however, overdoses with a monoclonal antibody theoretically could cause volume overload that can result in edema and/or heart failure.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (see Section 5.4.2 for further details)
- Non-serious adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

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

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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

[redacted] *24-Hour Safety Hotline*

- *North America:* [redacted]
- *EMEA/APAC:* [redacted]
- *Latin America:* [redacted]

Genentech Medical Monitor contact information for all sites if above *contact* cannot be reached:

Medical Monitor:	[redacted]
Telephone Nos.:	US Office [redacted]
	US Mobile [redacted]
Email Address:	[redacted]

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. A paper *Clinical Trial* Serious Adverse Event / Adverse Event of Special Interest Reporting Form should be completed and faxed or scanned and emailed to the Sponsor's Safety Risk Management department or its designee immediately (i.e., no more than 24 hours after learning of the event), using the contact information below per region:

Region	Fax Number	Email Address
Asia Pacific	[redacted]	[redacted]
Europe	[redacted]	[redacted]
Latin America	[redacted]	[redacted]
North America	[redacted]	[redacted]

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until the patient *completes the study* at Day 60 or *discontinues early*. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper *Clinical Trial* Serious Adverse Event/Adverse Event of Special Interest Reporting Form should be completed and faxed or scanned and emailed to *the Sponsor* or its designee immediately (i.e., no more than 24 hours after learning of the event), using the contact information provided to investigators (see Section 5.4.2.1). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 120 days of study drug *administration*. A *paper Clinical Trial* Pregnancy *Reporting Form* should be completed *and submitted to the Sponsor or its designee* immediately (i.e., no more than 24 hours after learning of the pregnancy*), either by faxing or by scanning and emailing the form using* the *fax number or email address provided in Section 5.4.2.1*. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the

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

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant *during the study or* within 30 days of study drug *administration.* A *paper Clinical Trial* Pregnancy *Reporting Form* should be completed *and submitted to* the *Sponsor or its designee* immediately (i.e., no more than 24 hours after learning of the pregnancy*), either by faxing or by scanning and emailing* the *form using the fax number or email address provided in Section 5.4.2.1.* Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. *After* the authorization has been signed, the investigator will *submit a paper Clinical Trial* Pregnancy *Reporting Form when updated* information on the course and outcome of the pregnancy *becomes available*. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 60 days after the dose of study drug), if the event is believed to be related to prior study drug treatment. *These events should be reported through the use of the Adverse Event eCRF and submit the report via the EDC system. However, if the EDC system is not available, the* investigator should report these events directly to *the Sponsor* or its designee, either by faxing or by scanning and emailing *a paper Clinical Trial* Serious Adverse Event / Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators (refer to site binder).

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

The Sponsor will promptly evaluate all serious adverse events including suspected unexpected serious adverse reactions (SUSARs) and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, IECs, and applicable health authorities based on applicable legislation.

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

- MHAA4549A Investigator's Brochure
- Local prescribing information for oseltamivir

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

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

Certain adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting. These anticipated events include, but are not limited to, the following:

- Asymptomatic elevations of ALT, AST, and or amylase without corresponding elevations of bilirubin have been shown to be increased during influenza A infection (Polakos et al. 2006; Yingying 2011)
- Influenza associated disease and or complications of influenza

An IMC and SOC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

All efficacy analyses will be conducted according to the intent-to-treat principle and will include all patients who meet the following condition with patients allocated to the treatment arm to which they were randomized:

- Randomized patients who have confirmed influenza A infection as confirmed by a central PCR test from Day 1 samples

Safety analyses will include all patients who were included in the randomization and who received at least one dose of study medication, with patients allocated to the treatment arm associated with the regimen actually received.

No formal hypothesis testing will be done in this study. As a result, no adjustment for a type 1 error will be made to account for the multiplicity of analyses.

Results will be presented both for the MHAA4549A 3600 mg and 8400 mg treatment groups separately and combined for the purpose of comparison to standard of care.

Final efficacy and safety analyses of the total study population will be conducted at the end of the study after all patients have completed all study assessments and the database has been cleaned and closed. Further details of the analyses, including analysis of the exploratory endpoints, will be contained in the statistical analysis plan (SAP) which will be prepared and finalized before the first optional interim analysis (see Section 6.10) or the final efficacy and safety analysis, if no interim analysis takes place.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is estimation of the effect size and hypothesis generation regarding the effect of MHAA4549A on the time to normalization of respiratory function relative to the standard of care rather than hypothesis testing. Point and interval estimates will be obtained. Approximately 330 patients will be enrolled. It is assumed that the median time to normalization of respiratory function in the control arm is 5 days. This sample size (approximately 110 patients per arm) provides 71% power to detect a

treatment difference of 1 day for the primary endpoint in both MHAA4549A arms assuming a 2-sided alpha of 0.2 and no difference in efficacy between the two active arms. If the 3600-mg dose shows a treatment difference of 1 day and the 8400-mg dose shows a treatment difference of 1.5 days or more then this sample size provides $>$ 86% power assuming a 2-sided alpha of 0.2.

Operating characteristics (power) under other possible assumptions for 2-sided alpha of 0.2 and true differences of 0.5 to 2 days are provided in Table 7.

Table 7 Operating Characteristics for Proposed Study Design for Several Possible True Underlying Median Values

	True Underlying Median for MHAA4549A							
	3600 mg	8400 mg	3600 mg	8400 mg	3600 mg	8400 mg	3600 mg	8400 mg
	4 days	4 days	4 days	3.5 days	4 days	3 days	4.5 days	4 days
Hazard Ratio	0.8	0.8	0.8	0.7	0.8	0.6	0.9	0.8
Power of log-rank test [a]	71.4%		86.6%		98.8%		56.2%	

Note: Operating characteristics are based on the following assumptions: 330 evaluable patients, event times are exponentially distributed, median time to normalization of respiratory function in the control arm is 5 days, and patients are followed for 60 days.

[a] Two-sided $\alpha = 0.20$.

It should be noted that the study is underpowered for detection of minimally clinically meaningful differences at a 2-sided alpha of 0.05 such as a true hazard ratio of 0.80 in both MHAA4549A arms.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue (early discontinuation of treatment or early termination from the study), and complete the study will be tabulated by treatment group using descriptive statistics. Reasons for early discontinuation of treatment or early termination from the study will be listed and summarized by treatment group. Any eligibility criteria exceptions and other protocol deviations will also be summarized by treatment group.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics of the patient will be summarized for all randomized patients by treatment group by use of descriptive statistics. Baseline is defined as the last available value prior to study drug administration.

During the study patient disposition, concurrent treatment, and compliance with study treatment and visits will be summarized on the safety analysis population using descriptive statistics.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized patients who are confirmed to be influenza A infected, with patients grouped according to the treatment assigned at randomization.

Time to event data will be *analyzed* using Kaplan-Meier methodology and stratified Cox proportional hazards models and will be summarized using n, median when estimable, hazard ratios, and 95% confidence intervals. Patients who are lost to follow-up (while event free) will be censored at the time that they are last known to be event free.

The ordinal outcomes will be analyzed using a proportional odds model. To supplement the overall summary odds ratio, separate odds ratios will be estimated for each dichotomized definition of improvement that can be formulated from the components of the ordinal outcome. A test for the proportionality assumption will also be made. Patients discharged from the hospital to a rehabilitation facility will be included in category 5. Patients discharged from the hospital to a nursing home will also be included in category 5, unless the patient lived in a nursing home prior to admission to the hospital, in which case the patient will be characterized based on resumption of normal activities.

Estimation of the treatment difference of proportions and *the corresponding* 95% confidence interval*s* will be calculated using stratum-adjusted Mantel-Haenszel methodology (Koch et al. 1989). For continuous endpoints, Analysis of Covariance methods (after appropriate transformation of data) will be used to estimate treatment differences and 95% confidence intervals.

Other than censoring in the time to event analyses, no other imputation for missing data will be performed.

6.4.1 Primary Efficacy Endpoint

- Median time to normalization of respiratory function.

6.4.2 Secondary Efficacy Endpoints

- *Clinical status at Days 1-7, 14, and 30 categorizing proportion of patients in each of the 6 pre-defined categories*
- Proportion of patients with clinical failure after 24 hours post-infusion of study drug
- Median time to clinical resolution of vital signs
- Hazard ratio for mortality at Day 14, Day 30, and Day 60
- Mean and median AUC of viral load

- Mean and median peak viral load
- Median duration of viral shedding in nasopharyngeal samples
- *Proportion of patients with detectable infection*
- Median duration of hospitalization
- Median duration of ICU stay
- Proportion of patients requiring antibiotics for respiratory indications during study
- Proportion of patients with influenza secondary complications
- Median duration of ventilation
- Proportion of patients who are readmitted by Day 30 and Day 60

6.4.3 Subgroup Analyses

Subgroup analyses will be performed to examine the consistency of the treatment estimates with use of the primary and selected secondary endpoints. Subgroups will include the stratification factors as well as patients who are identified at baseline as influenza A positive by the upper, lower, or both airways and by patients with bacterial co-infections at admission as well as by the influenza season during which the patient was randomized. Additional subgroups may be added following assessment of baseline characteristics as exploratory analyses.

6.5 SAFETY ANALYSES

The safety analyses will include all randomized patients who received study drug, with patients grouped according to the treatment actually received. Safety parameters to be evaluated include AEs (including deaths, SAEs, discontinuations due to AEs, and the incidence and severity of AEs), clinical laboratory tests, vital signs (including SpO_2 measurements), and ECGs.

All collected AE event data will be listed by study site and patient number. All AEs that occur on or after treatment on Day 1 will be summarized for each treatment group by mapped term, appropriate thesaurus levels, body system, and event within each body system, and toxicity grade. In addition, all SAEs, including deaths, will be listed separately and summarized. SAEs caused by a protocol mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) that occur between consent and first dose of study medication will be listed separately.

Laboratory data with values outside of the normal ranges will be identified. In addition, select laboratory data will be summarized by treatment group using descriptive summary statistics.

The absolute and percentage changes from baseline in vital sign parameters will be computed, and changes deemed clinically significant by the Investigator will be noted. Appropriate descriptive summary statistics will be provided for all vital sign parameters

6.6 *PHARMACOKINETIC* ANALYSES

Individual and mean serum MHAA4549A concentration versus time data will be tabulated and plotted. The serum pharmacokinetics of MHAA4549A will be summarized by estimating total serum drug exposure (i.e., AUC), C_{max}, C_{min}, total serum clearance, half-life, and volume of distribution, as data allow. Estimates for these parameters will be tabulated and summarized (e.g., mean, standard deviation, coefficient of variation). Interpatient variability will be evaluated. MHAA4549A serum concentration–time data may be compared with available data from other MHAA4549A clinical studies.

[redacted]

6.7 *IMMUNOGENICITY ANALYSES*

The immunogenicity analyses will include patients with at least one predose and one postdose ATA assessment, with patients grouped according to treatment received.

The numbers and proportions of ATA-positive patients and ATA-negative patients during the treatment and follow-up periods will be summarized by treatment group. Patients are considered to be ATA positive if they are ATA negative at baseline but develop an ATA response following study drug administration (treatment-induced ATA response), or if they are ATA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., ≥0.60 titer units) than the titer of the baseline sample (treatment-enhanced ATA response). Patients are considered to be ATA negative if they are ATA negative at baseline and all post-baseline samples are negative, or if they are ATA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ATA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

6.8 *BIOMARKER ANALYSES*

[redacted]

[redacted]

[redacted]

6.9 *EXPLORATORY PHARMACOKINETICS ANALYSES*

[redacted]

6.10 OPTIONAL INTERIM ANALYSES

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

If conducted, an interim analysis would be for administrative purposes only (i.e., internal planning or decision making) and would not impact the conduct of the current study in any way. A nominal type I error penalty of 0.0001 will be taken.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent

directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

The Sponsor's sample ICFs (and ancillary sample ICFs) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The

Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/IEC submission. The final IRB/IEC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's authorized representative as applicable and in accordance with local regulations, and IRB/IEC policies, before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments (see Section 9.1).

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

8.4 CONFIDENTIALITY

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

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

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

Given the exploratory nature of the biomarker analyses, data derived from exploratory biomarker specimens 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 Sponsor policy on study data publication (see Section 9.5).

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate, financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the

course of the study and for 1 year after completion of the study (i.e., last patient, last visit [LPLV]).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/IEC in accordance with established IRB/IEC policies and procedures.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

Genentech, Inc., a member of the Roche group, is the Sponsor of this study. A clinical research organization (CRO) may provide clinical operations oversight, including but not limited to project management, clinical monitoring and site management, data quality support, medical monitoring, and some safety reporting and regulatory activities as specified in study management plans. Genentech will provide CRO oversight, develop the database and randomization scheme, and conduct statistical programming and analysis. An IMC and SOC will provide safety monitoring for the study in addition to the ongoing review of safety by the Medical Monitor and Safety Scientist.

EDC will be utilized for this study. An IxRS will be used to assign patient numbers, randomize patients into study through use of a dynamic hierarchical algorithm, and manage site drug supply. A central laboratory will be used for sample management and storage until shipment to specialty laboratories or Genentech for analysis.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information from the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website: http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

Approval must be obtained from the IRB/IEC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to

eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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Appendix 1a
Schedule of *Activities*

Notes: Unless otherwise indicated, **all assessments on Day 1 should be performed prior to study drug administration**; x's within parentheses, i.e., (x), indicate optional assessments. Please refer to Follow-up Period table for visits to be completed after patient is discharged from hospital prior to Day 60. Any screening assessments completed prior to consent as standard of care do not need to be repeated if done within the screening period. If a patient is unable to be present at the site for a follow-up visit, a telephone visit is *encouraged*.

Hospitalized Days (only to be completed while patients are hospitalized																					
	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11-13	D14	D15-19	D20	D21-24	D25	D26-29	D30	Hospital Discharge[a]	D60 Study Completion or Early Discontinuation while hospitalized	Unscheduled
Informed consent[b]	x																					
Sponsor-approved influenza test[c]	x																					
Inclusion/exclusion criteria	x																					
Medical history and demographic	x																					

Appendix 1a
Schedule of Activities (cont.)

Hospitalized Days (only to be completed while patients are hospitalized																						
	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11-13	D14	D15-19	D20	D21-24	D25	D26-29	D30	Hospital Discharge[a]	D60 Study Completion or Early Discontinuation while hospitalized	Unscheduled
data																						
Pregnancy test [d]	x																					(x)
Confirm O_2 requirement [e]	x																					
Respiratory Assessment [f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)
Concomitant medications [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)
Vital signs [h]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)
APACHE score [i]		(x [j])											(x)						(x)	(x)	(x)	(x)
SOFA score [k]		(x [j])						(x)					(x)						(x)	(x)	(x)	(x)
Electrocardiogra		x				x							x						x	x	x	(x)

Appendix 1a
Schedule of Activities (cont.)

Hospitalized Days (only to be completed while patients are hospitalized																					
	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11-13	D14	D15-19	D20	D21-24	D25	D26-29	D30	Hospital Discharge[a]	D60 Study Completion or Early Discontinuation while hospitalized	Unscheduled
m (12-lead)[l]																						
Randomization		x																				
MHAA4549A administration[m]		x																				
Oseltamivir administration[n]		x	x	x	x	x	(x)	(x)	(x)	(x)	(x)											
Complete physical examination[o]	x	(x)																				(x)
Limited, symptom-directed physical examination[p]			x	x	x	x							x						x	x	x	(x)
Weight & height[q]	x	x				x							x						x	x	x	(x)

Appendix 1a
Schedule of Activities (cont.)

Hospitalized Days (only to be completed while patients are hospitalized																						
	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11-13	D14	D15-19	D20	D21-24	D25	D26-29	D30	Hospital Discharge[a]	D60 Study Completion or Early Discontinuation while hospitalized	Unscheduled
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)
Hematology [r]	x		x			x							x						x	x	x	(x)
Chemistry panel [r]	(x) [s]	x	x			x							x						x	x	x	(x)
Coagulation panel [r]		x				x							x						x	x	x	(x)
Erythrocyte sedimentation rate		(x)	(x)			(x)							(x)						(x)	(x)	(x)	(x)
C-reactive protein		(x)	(x)			(x)							(x)						(x)	(x)	(x)	(x)
Urinalysis [r, t]		x	x			x							x						x	x	x	(x)
Serology (HIV) [r, u]	x																					

Appendix 1a
Schedule of Activities (cont.)

Hospitalized Days (only to be completed while patients are hospitalized																					
	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11-13	D14	D15-19	D20	D21-24	D25	D26-29	D30	Hospital Discharge[a]	D60 Study Completion or Early Discontinuation while hospitalized	Unscheduled
[redacted]		x	x	x	x	x	x	x	x	x	x		x		x		x		x	x	x	(x)
[redacted]		x	x	x	x	x	x	x	x	x	x		x		x		x		x	x	x	(x)
Flu antibodies (HAI) [x]		x											x						x	x	x	(x)
[redacted]		x																	x	x	x	(x)
Serum for MHAA4549A PK measurements [y]		x	x	x		x		x					x						x	x	x	(x)
[redacted]		x				x														(x)		(x)

Appendix 1a
Schedule of Activities (cont.)

Hospitalized Days (only to be completed while patients are hospitalized																					
	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11-13	D14	D15-19	D20	D21-24	D25	D26-29	D30	Hospital Discharge[a]	D60 Study Completion or Early Discontinuation while hospitalized	Unscheduled
[redacted]																				aa		
[redacted]		x	x	x		x		x			x		x		x		x		x	x	x	(x)
[redacted]		x	x	x		x		x			x		x		x		x		x	x	x	(x)
[redacted]		x																	x	x	x	(x)
[redacted]		x																	x	x	x	(x)
[redacted]		x																	x	x	x	(x)
[redacted]		x																	x	x	x	(x)
[redacted]																				x		

Appendix 1a
Schedule of Activities (cont.)

Hospitalized Days (only to be completed while patients are hospitalized																					
	D -2,-1	D1 (Randomization)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11-13	D14	D15-19	D20	D21-24	D25	D26-29	D30	Hospital Discharge[a]	D60 Study Completion or Early Discontinuation while hospitalized	Unscheduled
Oseltamivir medication diary [dd]																				x		
Clinical status assessment[ee]		x	x	x	x	x	x	x					x						x			

Appendix 1a
Schedule of Activities (cont.)

[redacted]; AE = adverse event; APACHE = Acute Physiology and Chronic Health Evaluation; ATA = Anti-therapeutic antibodies; D = day; Dx = diagnostics; eCRF = electronic Case Report Form; ECG = electrocardiogram; HAI = hemagglutinin inhibition; [redacted]; ICU = Intensive Care Unit; IRB/IEC = Independent Review Board/Independent Ethics Committee; NAI = neuraminidase inhibitor; O_2 = oxygen; PaO_2/FiO_2 = partial pressure of oxygen/fraction of inspired oxygen; PCR = polymerase chain reaction; PD = pharmacodynamics; PK = pharmacokinetic; PPV = positive pressure ventilation; qPCR = quantitative Polymerase Chain Reaction; RBCs = red blood cells; SOFA = Sequential Organ Failure Assessment; SpO_2 = oxygen saturation measured by pulse oximetry; WBCs = white blood cells.

[a] Assessments to be performed irrespective of day of discharge. Assessments on discharge day will supersede assessments for matching day except for the study completion/early discontinuation visit (e.g., If a patient is discharged from the hospital on Day X, use assessments under "hospital discharge" column instead of the Day X column and record under the hospital discharge folder in the eCRF. If a patient discontinues from the study early on Day X, complete all assessments under the "early discontinuation" column and record under the early discontinuation folder in the eCRF.

[b] Informed consent must be obtained from all patients. For patients who are unable to consent, an authorized representative may be used if allowed by local regulations and IRB/IEC policy.

[c] Sponsor-approved influenza test using a nasopharyngeal swab in one nostril *or lower respiratory tract sample (if appropriate for the sponsor-approved local PCR test)*. A Sponsor-approved influenza test includes influenza antigen test or influenza polymerase chain reaction (PCR) test. Result must be available within the 48-hour screening window.

[d] A urine *or serum* pregnancy test should be collected only for women considered by the investigator to be of childbearing potential, see exclusion criteria. This result must be available within 2 days prior to study treatment. If urine testing is not available at the site, blood already collected from an existing sample may be tested for pregnancy.

[e] Confirm patient requires supplemental O_2 or PPV within 24 hours of hospital admission.

[f] *Unless clinically contraindicated, all* patients will have their on-study SpO_2 and corresponding respiratory assessments recorded daily in the morning between 6:00 a.m. and 12:00 noon local time; screening SpO_2 may be taken outside this window. From Day 1 onward post-study drug administration, patients on low flow O_2 should have a daily trial of their SpO_2 while on and off the supplementation and both values will be recorded. If the patient is on oxygen supplementation, SpO_2 measured by pulse oximetry and the corresponding respiratory assessments (e.g., FiO_2, flow rate) will be recorded. If the patient is on PPV, PaO_2 and the corresponding respiratory assessments (e.g., FiO_2, ventilator mode, ventilator respiratory rate, positive end-expiratory pressure) will be recorded. If clinically appropriate (i.e., the patient is on non-invasive PPV), the conversion table in Appendix 11 may be used.

[g] Concomitant medications should be recorded for 30 days prior to screening, through the study completion/early discontinuation visit. See exclusion criteria in Section 4.5.2 for prohibited therapies.

Appendix 1a
Schedule of Activities (cont.)

[h] Vital signs will be collected within 1 hour before MHAA4549A infusion and within 1 hour after completion of MHAA4549A infusion and include temperature, respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure. Temperature should be measured using the same methodology throughout the study and should be measured prior to administration of any antipyretic drugs. In patients who have multiple vital signs taken during any day, the most abnormal value should be recorded from that 24-hour period. Temperature, blood pressure, respiratory rate, and heart rate will be completed after the patient has been in a seated or supine position for > 5 minutes. The worst/most abnormal value from the last 24-hour period should be recorded for patients who are in the ICU.

[i] APACHE scores are optional and only for patients that are in the ICU. For calculation of the screening APACHE score, the worst values in the *first* 24 hours should be used. APACHE scores are not required for study conduct or entry but should be collected if available.

[j] Assessment to be conducted based on entry into ICU; may vary from patient to patient.

[k] SOFA scores are *optional and* only for patients in the ICU that have available data such as PaO_2/FiO_2 (mmHg). See Appendix 7 for SOFA score calculation.

[l] Patient should rest in a supine position for 10 minutes prior.

[m] Patient will be a resident for at least 24 hours following administration of MHAA4549A.

[n] Oseltamivir must be given for a minimum of 5 days. Treatment longer than 5 days is permitted based on the discretion of the investigator [indicated by (x)].

[o] Complete physical examination includes evaluations of general appearance of head, eye*s*, ear*s*, nose, and throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as AEs, if appropriate. Day 1 physical examination is optional if *already completed* on Day -1 or -2.

[p] Limited, symptom-directed physical examination includes, at a minimum, evaluation of general appearance, dermatological examination of the injection sites, evaluations directed by patient-reported symptoms, and any other evaluations that the investigator deems clinically relevant. Changes from any prior examination should be recorded. New or worsened abnormalities should be recorded as AEs, if appropriate.

[q] Height will be obtained at screening only. Weight will be obtained at all indicated visits. Height and weight will be recorded in centimeters and kilograms, respectively.

[r] Local laboratory measurements should be utilized.

[s] For optional thyroid stimulating hormone test.

[t] Urinalysis includes pH, specific gravity, glucose, protein, ketones, blood, bilirubin, nitrite, and leukocyte esterase. Microscopic examination (e.g., sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) will be performed if clinically indicated.

[u] HIV serology result not needed for randomization and a positive result does not require patient discontinuation.

Appendix 1a
Schedule of Activities (cont.)

[redacted]

[redacted]

[redacted]

[y] Day 1 serum PK samples are to be drawn 30 (±5) minutes pre-dose of MHAA4549A, 60 (± 15) minutes after the end of infusion. Serum PK samples on Day 2 and after are to be drawn immediately before oseltamivir dosing. PK samples will be drawn from the contralateral arm from that used for drug infusion and must be labeled with the exact time of draw.

[redacted]

[aa] If patient is discharged on or before Day 5, the oseltamivir PK samples are to be taken on the discharge day.

[redacted]

[redacted]

[dd] Patients who are discharged from the hospital with oseltamivir will be required to complete a medication diary and return the medication diary, empty (used) oseltamivir packets and unused oseltamivir capsules to the study site at the next follow up visit. Patients will record the date and time when each oseltamivir capsule is administered.

Appendix 1a
Schedule of Activities (cont.)

[ee] *Indicate which clinical status the patient is categorized under: death; in the ICU; non-ICU hospitalization, requiring supplemental oxygen; non-ICU hospitalization, not requiring supplemental oxygen; not hospitalized, but unable to resume normal activities; or not hospitalized with full resumption of normal activities*

Appendix 1b
Schedule of *Activities*: Follow-Up Period

- If a patient is discharged prior to Day 14, he/she will need to complete the following assessments for Day 14, Day 30, and Day 60 below.
- If a patient is discharged after Day 14 but prior to Day 30, he/she will need to complete the following assessments for Day 30 and Day 60 below.
- If a patient is discharged after Day 30, but prior to Day 60, he/she will need to complete the following assessments for Day 60 below.
- If patient is hospitalized for Day 14, Day 30, and/or Day 60, please refer to Appendix 1a.

Day (D)	D14 ± 1 (If discharged BEFORE Day 14)	D30 ± 4 (If discharged BEFORE Day 30)	Day 60 ± 7 (Study Completion) or Early Discontinuation
Concomitant medications [a]	x	x	x
Vital signs [b]	x	x	x
Electrocardiogram (12-lead) [c]	x	x	x
Weight, BMI [d]	x	x	x
Adverse events	x	x	x
Hematology [e]	x	x	x
Chemistry panel [e]	x	x	x
Coagulation panel [e]	x	x	x
Urinalysis [e]	x	x	x
Flu antibodies (HAI)	x	x	x
[redacted]		x	x
Serum for MHAA4549A PK measurements [f]	x	x	x
[redacted]	x	x	x
[redacted]	x	x	x
[redacted]		x	x
[redacted]		x	x
[redacted]		x	x

Appendix 1b
Schedule of Activities: Follow-Up Period (cont.)

Day (D)	D14 ± 1 (If discharged BEFORE Day 14)	D30 ± 4 (If discharged BEFORE Day 30)	Day 60 ± 7 (Study Completion) or Early Discontinuation
[redacted]		x	x
Clinical status assessment[h]	*x*	*x*	

[redacted]; ATA = Anti-therapeutic antibodies; BMI = body mass index; D = day; Dx = diagnostics; eCRF = electronic Case Report Form; ECG = electrocardiogram; HAI = hemagglutinin inhibition; [redacted] PD = pharmacodynamics; PK = pharmacokinetic.

[a] Concomitant medications should be recorded for 30 days prior to screening, through the study completion/early discontinuation visit. See exclusion criteria in Section 4.1.2 for prohibited therapies.

[b] Vital signs include temperature, respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure. Temperature should be measured using the same methodology throughout the study and should be measured prior to study drug administration of any antipyretic drugs. In patients who have multiple vital signs taken during any day, the most abnormal value should be recorded from that 24-hour period. Temperature, blood pressure, respiratory rate, and heart rate will be completed after the patient has been in a seated or supine position for > 5 minutes.

[c] ECG should be recorded after the patient has rested in a supine position for 10 minutes.

[d] Weight will be recorded in kg.

[e] Local laboratory measurements should be used.

[f] PK samples must be labeled with the exact time of draw.

[redacted]

[h] *Indicate which clinical status the patient is categorized under: death; in the ICU; non-ICU hospitalization, requiring supplemental oxygen; non-ICU hospitalization, not requiring supplemental oxygen; not hospitalized, but unable to resume normal activities; or not hospitalized with full resumption of normal activities*

Appendix 2
Time to Normalization of Respiratory Function

For the purposes of this study, the time to normalization of respiratory function will be defined as the time to removal of the patient from O_2 supplementation in order to maintain an $SpO_2 \geq 95\%$.

Unless clinically contraindicated, patients* who are on low flow O_2 (*i.e.,* 2-6 L/min) should receive a daily trial off O_2 in the morning between 6:00 a.m. and 12:00 noon as described below.

1. Patient should be resting or sitting.
2. Patient should be fitted with pulse oximeter, and their SpO_2 should be checked once while on O_2 and then again 3 – 5 minutes after turning off O_2 supplementation. *Clinical judgment should be used to determine when the SpO_2 result is stable to record.*
3. If the $SpO_2 \geq 95\%$, then the time and reading should be recorded. Notify the study doctor so that he/she can make a clinical judgment to determine whether the O_2 can be removed.
4. The recorded time for the endpoint corresponds with the initial discontinuation of O_2 and reading.

If a patient is clinically able to be removed from oxygen outside the time window above (6:00 a.m. and 12:00 noon), the trial off data should be recorded as an unscheduled visit.

** If a patient has an SpO2 <95% while on oxygen supplementation, he/she shall be considered to be "clinically contraindicated" from requiring a trial off oxygen; however, corresponding respiratory assessments should be recorded.*

Appendix 3

[redacted]

Appendix 4

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 5

[redacted]

Appendix 6

[redacted]

Appendix 7
SOFA Score Calculation

Variables	SOFA Score				
	0	**1**	**2**	**3**	**4**
Respiratory (PaO_2/FiO_2, mmHg)	>400	≤ 400	≤ 300	≤ 200[a]	≤ 100[a]
Coagulation (Platelets x $10^3/\mu L$)[b]	>150	≤ 150	≤ 100	≤ 50	≤ 20
Liver (Bilirubin, mg/dL)[b]	<1.2	$1.2-1.9$	$2.0-5.9$	$6.0-11.9$	>12.0
Cardiovascular (Hypotension)	No hypotension	MAP <70 mmHg	Dop ≤ 5 or dob (any dose)[c]	Dop >5, epi ≤ 0.1, or norepi ≤ 0.1[c]	Dop >15, epi >0.1, or norepi >0.1[c]
Central Nervous System (Glasgow Coma Score Scale)	15	$13-14$	$10-12$	$6-9$	<6
Renal (Creatinine, mg/dL or urine output, mL/day)[d]	<1.2	$1.2-1.9$	$2.0-3.4$	$3.5-4.9$ or <500	>5.0 or <200

Norepi = norepinephrine; Dob = dobutamine; Dop = dopamine; Epi = epinephrine; FiO_2 = fraction of inspired oxygen; MAP = mean arterial pressure; PaO_2 = partial pressure of arterial oxygen.

[a] Values are with respiratory support.

[b] To convert bilirubin from mg/dL to μmol/L, multiply by 17.1.

[c] Adrenergic agents administered for at least 1 hour (doses given are in μg/kg per minute).

[d] To convert creatinine from mg/dL to μmol/L, multiply by 88.4.

References for Appendix 7:

Ferreira FL, Bota DP, Bross A et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001; 286(14):1754–1758

Vincent JL, de Mendonca A, Cantraine F et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;26(11): 1793–1800.

Appendix 8
DAIDS Toxicity Grading Tables for Clinical Abnormalities

From the FDA Guidance document 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials' (September 2007)

Vital Signs [a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) [b] (°F)*	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40.0 102.1 – 104.0	>40 >104
Tachycardia – beats per minute	101- 115	116 – 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia – beats per minute [c]	50 – 54	45 – 49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) – mmHg	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mmHg	91 – 95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mmHg	85 – 89	80 – 84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	>25	Intubation

[a] Subject should be at rest for all vital sign measurements.

[b] Oral/tympanic temperature; no recent hot or cold beverages or smoking.

[c] When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Appendix 8 (cont'd)
DAIDS Toxicity Grading Tables for Clinical Abnormalities

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/ vomiting	No interference with activity or 1 – 2 episodes/ 24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 g/ 24 hours	4 – 5 stools or 400 – 800 g/ 24 hours	5 or more watery stools or > 800 g/ 24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity no requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Appendix 9
DAIDS Toxicity Grading Tables for Laboratory Abnormalities

Adapted from Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007 DRAFT and FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials

Abbreviations used in the table:
[redacted]; CPK = creatine phosphokinase; Dec = Decreased; IV = Intravenous; LLN = Lower limit of normal; Mod = Moderate; Req = Required; Rx = Therapy; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = Upper limit of normal.

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 – 10.5 g/dL	8.0 – 9.4 g/dL	6.5 – 7.9 g/dL	<6.5 gm/dL
Absolute Neutrophil Count	1,000 – 1,500/mm^3	750 – 999/mm^3	500 – 749/mm^3	<500/mm^3
*Platelets	125,000 – 140,000/mm^3	100,000 – 124,999/mm^3	25,000 – 99,999/mm^3	<25,000/mm^3
WBCs	11,000 – 13,000/mm^3	13,000 – 15,000/mm^3	15,000 – 30,000/mm^3	>30,000 or <1,000/mm^3
*Lymphocytes Decrease – cell/mm^3	750 – 1,000	500 – 749	250 – 499	<250
*Eosinophils – cell/mm^3	650 – 1500	1501 – 5000	>5000	Hypereosinophilic
Abnormal Fibrinogen	Low: 100 – 200 mg/dL High: 400 – 600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: <50 mg/dL	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20 – 40 mcg/mL	41 – 50 mcg/mL	51 – 60 mcg/mL	>60 mcg/mL
Prothrombin Time (PT)	1.01 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin Time (APTT)	1.01 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3 x ULN	>3 x ULN
Methemoglobin	5.0 – 9.9%	10.0 – 14.9%	15.0 – 19.9%	>20.0%

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

Appendix 9 (cont'd)
DAIDS Toxicity Grading Tables for Laboratory Abnormalities

CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130 – 135 mEq/L	123 – 129 mEq/L	116 – 122 mEq/L	<116 mEq/L or abnormal sodium with mental status changes or seizures
Hypernatremia	146 – 150 mEq/L	151 – 157 mEq/L	158 – 165 mEq/L	>165 mEq/L or abnormal sodium with mental status changes or seizures
Hypokalemia	3.0 – 3.4 mEq/L	2.5 – 2.9 mEq/L	2.0 – 2.4 mEq/L or intensive replacement therapy or hospitalization required	<2.0 mEq/L or abnormal potassium with paresis ileus or life-threatening arrhythmia
Hyperkalemia	5.6 – 6.0 mEq/L	6.1 – 6.5 mEq/L	6.6 – 7.0 mEq/L	>7.0 mEq/L or abnormal potassium with life-threatening arrhythmia
Hypoglycemia	55 – 64 mg/dL	40 – 54 mg/dL	30 – 39 mg/dL	<30 mg/dL or abnormal glucose with mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 – 160 mg/dL	161 – 250 mg/dL	251 – 500 mg/dL	>500 mg/dL or abnormal glucose with ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 – 7.8 mg/dL	7.7 – 7.0 mg/dL	6.9 – 6.1 mg/dL	<6.1 mg/dL or abnormal calcium with life threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6 – 11.5 mg/dL	11.6 – 12.5 mg/dL	12.6 – 13.5 mg/dL	>13.5 mg/dL or abnormal calcium with life-threatening arrhythmia
Hypomagnesemia	1.4 – 1.2 mEq/L	1.1 – 0.9 mEq/L	0.8 – 0.6 mEq/L	<0.6 mEq/L or abnormal magnesium with life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 – <1.25 x ULN	1.25 – <1.5 x ULN	1.5 – 1.75 x ULN	>1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 – <1.5 x ULN	1.5 – <2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Appendix 9 (cont'd)
DAIDS Toxicity Grading Tables for Laboratory Abnormalities

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 × ULN	2.0 - <3.0 × ULN	3.0 – 8.0 × ULN	>8.0 × ULN
ALT (SGPT)	1.1 - <2.0 × ULN	2.0 - <3.0 × ULN	3.0 – 8.0 × ULN	>8.0 × ULN
GGT	1.1 - <2.0 × ULN	2.0 - <3.0 × ULN	3.0 – 8.0 × ULN	>8.0 × ULN
Alkaline Phosphatase	1.1 - <2.0 × ULN	2.0 - <3.0 × ULN	3.0 – 8.0 × ULN	>8.0 × ULN
Amylase	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.1 – 5.0 × ULN	>5.1 × ULN
Lipase	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.1 – 5.0 × ULN	>5.1 × ULN
*CPK – mg/dL	1.25 – 1.5 × ULN	1.6 – 3.0 × ULN	3.1 – 10.0 × ULN	>10 × ULN

* From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg – 1 g loss/day	2-3+ or 1-2 g loss/day	4+ or 2-3.5 g loss/day	Nephrotic syndrome or >3.5 g loss/day
Hematuria	Microscopic only <10 RBC/hpf	Gross, no clots >10 RBC/hpf	Gross, with or without clots, OR red blood casts	Obstructive or required transfusion
*Glucose	Trace	1+	2+	Hospitalization for hyperglycemia

From the FDA Guidance document 'Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials'

Appendix 10
Anaphylaxis Precautions and Management

Administration of MHAA4549A will be performed in a setting with emergency medical equipment and personnel who are trained to monitor for and respond to medical emergencies. A qualified physician *or medically qualified designee* will be on site during study drug administration for all patients.

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Airway management equipment
- O_2
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion.
- Maintain an adequate airway.
- Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix 11
Respiratory Conversion Table for PaO_2

Estimating PaO_2 from a given oxygen saturation

Oxygen Saturation (%)	PaO_2 (mmHg)
80	44
81	45
82	46
83	47
84	49
85	50
86	52
87	53
88	55
89	57
90	60
91	62
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145

From The Extended Study of Prevalence of Infection in Intensive Care:
http://www.intensive.org/epic2/Documents/Estimation%20of%20PO2%20and%20FiO2.pdf

Appendix 12
Clinical Status Assessment

Clinical status will be assessed on Days 1-7, 14, and 30. Assessment should be collected at a consistent time throughout the study. Indicate the patient's clinical status for the day:

1. *Death;*
2. *In the ICU;*
3. *Non-ICU hospitalization, requiring supplemental oxygen;*
4. *Non-ICU hospitalization, not requiring supplemental oxygen;*
5. *Not hospitalized, but unable to resume normal activities; or*
6. *Not hospitalized with full resumption of normal activities*