Official Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial of MHAA4549A, a Monoclonal Antibody, Administered as Monotherapy for the Treatment of Acute Uncomplicated Seasonal Influenza A Infection in Otherwise Healthy Adults

NCT Number: **NCT02623322**

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PROTOCOL

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY, ADMINISTERED AS MONOTHERAPY FOR THE TREATMENT OF ACUTE UNCOMPLICATED SEASONAL INFLUENZA A INFECTION IN OTHERWISE HEALTHY ADULTS**
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FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	13-May-2016 21:01:46

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PROTOCOL AMENDMENT, VERSION 3: RATIONALE

This Version 3 amendment revises the study design to address health authority feedback:

- Reduces the inclusion criteria enrollment window (from ≤120 hours) to "≤72 hours (3 days) between onset of influenza-like illness (as determined by the investigator) and start of study treatment"
- Revision of a typographical error in Section 3.1.3

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

This Version 2 amendment revises the study design to address operational constraints associated with patient enrollment and follow up:

- Expands the inclusion criteria enrollment window (from ≤72 hours) to "≤120 hours (5 days) between onset of influenza-like illness (as determined by the investigator) and start of study treatment"
- Telephone visits to assess safety (e.g., symptoms, adverse events) at Day 30 and Day 100 instead of in-clinic visits

In addition, Version 2 also contains revisions to support the changes discussed above as well as updates to sections to be consistent with current company standards

- Update background section with final data for the GV29609 Phase 1 high dose study
- Remove the language "Sponsor-approved" from diagnostic inclusion criteria since sites can use their local diagnostic tests
- Revised the Stopping Rules (Section 3.1.4) to make the criteria more simple and clear
- Updated objectives and outcomes to be consistent with company protocol template
- Added "identification of pro-inflammatory lipid mediators in urine" as an exploratory outcome measure
- Updated procedure for reporting persistent or recurrent adverse events (Section 5.3.5.4) to be consistent with current company standards
- Updated Emergency Medical Contacts (Section 5.4.1)
- Updated Safety sections (Section 5) to be consistent with current company standards
- Update Schedule of Activities to be consistent with changes made to the study design
- Addition of question to adult patient symptom diary (Appendix 6) to capture potential fevers between time points

- Updated language/rearranged sections to be consistent with company protocol template standard

PROTOCOL AMENDMENT, VERSION 3: SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

GLOBAL CHANGE

Changes made to Sections 3.1.1, 3.2, and 4.1.1 and Appendix 1 in Version 2 regarding the inclusion criteria enrollment window have been eliminated in Version 3. That is, the inclusion criteria enrollment window has been changed throughout the protocol from $\leq$120 hours to $\leq$72 hours (3 days) between onset of influenza-like illness (as determined by the investigator) and start of study treatment. This change reverts to the enrollment window specified in Version 1.

SECTION 3.1.3: Internal Monitoring Committee and Scientific Oversight Committee

Change made to Section 3.1.3 in Version 2 in error has been corrected in Version 3. Text remains as it was in Version 1, as follows.

> As a result, the IMC/SOC may recommend *stopping* further enrollment in the study or other protocol modifications.

FIGURE 1: Study Design

Figure 1 has been revised to reflect the changes to the protocol.

PROTOCOL AMENDMENT, VERSION 2 & VERSION 3:
SUMMARY OF CHANGES

The Summary of Changes below includes all changes made since Version 1 except those changes discussed separately in the Summary of Changes for Version 3 above.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.1: BACKGROUND ON INFLUENZA

However, influenza can also cause serious complications requiring hospitalization such as pneumonia leading to acute respiratory failure, secondary bacterial respiratory infections, and death. *Annually,* seasonal influenza ~~yearly~~ results in approximately three to five million cases of severe illness and up to 500,000 deaths worldwide (WHO 2014). ~~Influenza caused an estimated yearly average of 19,100 deaths between 1997 and 2009 in the United States (Matias et al. 2014). A comparable mortality and morbidity has been reported for European countries (Snacken et al. 2012).~~ Thus, a significant unmet medical need still exists in those at high-risk of developing influenza-complications, including children, the elderly, pregnant women, and those with underlying chronic medical conditions or weakened immune systems.

SECTION 1.2.1: Nonclinical Background

MHAA4549A is a human monoclonal IgG1 antibody that binds to the influenza A virus. MHAA4549A was 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 ~~genome entry into the host cell~~*replication*.

SECTION 1.2.2: Clinical Safety Background

To date, MHAA4549A has been shown to be safe and well tolerated in three *completed* clinical studies, which altogether enrolled 136 healthy volunteers. In addition, *an ongoing global* Phase 2b Study (GV29216)*,* in *24 countries across North America, Europe, Latin America, and Asia-Pacific, is currently enrolling* hospitalized patients with severe influenza infection *and* has shown no clinically significant drug-related safety signals.

SECTION 1.2.2.1: Phase 1 Entry-into-Human Study (GV28916)

No serious adverse events or dose-limiting toxicities were reported. Two clinical laboratory values were considered TEAEs (an increase in ALT in one 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 serious adverse events or dose-limiting toxicities were reported.~~

No safety issues were observed with respect to vital signs or ECG measurements. Overall, no relevant differences in mean values or deviations from baseline over time were observed in subjects receiving MHAA4549A as compared to placebo for all lab values. 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 or MHAA4549A at 8,400 mg *(Cohort A)* or 10,800 mg *(Cohort B) and followed for 120 days*.

~~In a follow up period of 120 days, an unblinded safety data analysis demonstrated that these doses of MHAA4549A were safe and well tolerated. Headache was the most commonly reported adverse event in the study~~

~~In subjects who received 8400 mg MHAA4549A (N=4), 3 subjects reported 14 TEAEs~~

- ~~Six TEAEs were reported as related to MHAA4549A: 3 headaches, 1 pruritus, 1 peripheral swelling, and 1 nasal congestion~~

~~In subjects who received 10800 mg MHAA4549A (N=4), 4 subjects reported 8 TEAEs~~

- ~~Three TEAEs were reported as related to MHAA4549A: 1 nausea, 1 headache, and 1 asthenia~~

~~In subjects who received placebo (N=6), 5 subjects reported 11 TEAEs~~

- ~~One TEAE was reported as related to placebo: 1 headache~~

~~All TEAEs were reported as mild except for an unrelated moderate TEAE of a >10x upper limit of normal (ULN) increase in creatinine kinase on Day 15 in one subject who received 10800 mg MHAA4549A. There were no serious adverse events and no subjects discontinued the study for any reason. Based on these data in healthy volunteers, MHAA4549A is considered safe and well tolerated at doses up to 10800 mg. None of the subjects in the study developed treatment induced ATAs. One subject tested positive for ATA at baseline.~~

A total of 34 TEAEs were reported by 12 (85.7%) of the 14 subjects who received one dose of the study medication or placebo (safety population). Twenty-four (24) of these TEAEs were reported by 7 (87.5%) of the 8 subjects who had received MHAA4549A and 10 TEAEs were reported by 5 (83.3%) of the 6 subjects who received placebo. TEAEs were reported by 3 of the 4 subjects receiving 8,400 mg MHAA4549A and 4 of 4 subjects receiving 10,800 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, reported by 4 subjects who received MHAA4549A (3 subjects in Cohort A and 1 subject in Cohort B), and

nasopharyngitis, reported by three subjects who received MHAA4549A (1 subject in Cohort A and 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 one subject who received 8400 mg MHAA4549A, and elevations of blood CK, observed twice in one subject who received 10,800 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)

Adverse events were collected from time of influenza A inoculation (Day 0). There was no evidence of a dose-related pattern of TEAEs in MHAA4549A-treated subjects, an observation that is consistent with *all of* the Phase 1 studies (GV28916 and GV29609) *conducted to date.*

SECTION 1.2.3: Clinical Pharmacokinetics

In the Phase 1 high-dose study (GV29609), MHAA4549A showed linear PK with a mean half-life ($t_{1/2}$) of approximately 21.5 days (range 21.4–21.6 days). For the 8,400-mg and 10,800-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) are consistent with that observed in the Phase 1 study (GV28916) and Phase 2a study (GV28985).

SECTION 1.3: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The primary goal of this exploratory Phase 2 Study (GV29893) is to demonstrate safety and tolerability of MHAA4549A in otherwise healthy patients with naturally ~~infected~~*acquired* acute uncomplicated seasonal influenza A. The study will also assess the potential ability of MHAA4549A to reduce the severity and/or duration of clinical signs and symptoms, and [redacted] related to acute *uncomplicated* influenza. Other measures, such as influenza reinfection rate, frequency of secondary complications, hospital admissions, ~~and~~ mortality*, PK, immunogenicity, and biomarkers* will also be assessed.

P~~Other p~~otential risks of MHAA4549A include immunogenicity and infusion-related reactions. Theoretically, any biological 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 preclinical 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.

Antibody-dependent enhancement (ADE) of ~~infection~~*disease* has been suggested as a potential risk of antiviral antibodies as therapeutic interventions for influenza (Khurana et al. 2013). ADE of viral uptake might occur when non-neutralizing antiviral antibodies facilitate virus entry into host cells, leading to enhanced viral ~~shedding and~~ replication *and shedding* (Takada and Kawaoka 2003; Whitehead et al. 2007; Dejnirattisai et al. 2010; Crowe 2013).

SECTION 2.1: PRIMARY OBJECTIVE

- To evaluate the safety and tolerability of a single IV dose of MHAA4549A as compared to placebo when administered in otherwise healthy patients with acute uncomplicated seasonal influenza A, focusing on the following:

  Nature, frequency, and severity of serious and non-serious adverse events

  ~~Immunogenicity assessment~~

  Effects on laboratory values, vital signs, ECG parameters, and other safety biomarkers

SECTION 2.2: Secondary Objectives

- To examine the time to alleviation of clinical signs and symptoms of influenza A infection
- To examine the severity of clinical signs and symptoms of influenza A infection
- To measure hospital admission rate
- *To measure* ~~and length~~*duration* of *hospital* stay
- To measure antibiotic usage for secondary bacterial respiratory infections
- To measure the frequency, severity and development of secondary complications of influenza (pneumonia, exacerbation of chronic lung disease, myocarditis, acute respiratory distress syndrome, acute otitis media, other related complications)
- *To measure the incidence of death*
- To measure influenza re-infection rate

SECTION 2.3: EXPLORATORY OBJECTIVES

- [redacted]

- [redacted]

SECTION 3.1.1: Overview of Study Design

Patients who are eligible for enrollment will be randomized in a 1:1:1 ratio into three treatment groups: a single IV dose of 3600 mg MHAA4549A, a single IV dose of 8400 mg MHAA4549A, or a single IV dose of placebo. Study drug administration will begin within 72 hours (3 days) of onset of influenza-like illness (as defined in the inclusion criteria, Section 4.1.1) and all patients will be followed for a minimum of 100 days from randomization.…

~~A Sponsor approved~~ rapid PCR test or rapid antigen test will be used as an aid in the diagnosis of influenza A infection and serve as the basis for satisfying study entry requirements.

… A ~~Sponsor approved~~ rapid PCR test or rapid antigen test will be performed as soon as possible, preferably within 72 hours of influenza symptom onset. [redacted] If the patient tests negative by rapid antigen testing, the results will be confirmed by PCR. The patient will follow the assessments in Appendix 2, until a negative PCR result for influenza is confirmed. Such patients will not be re-dosed with study treatment, but local standard of care anti-influenza treatments including neuraminidase inhibitors will be permitted and recorded. These patients must still complete *telephone* follow-up visits at Days 30 and 100 from initial randomization.

A schedule of ~~assessments~~*activities* is provided in Appendix 1.

SECTION 3.1.2: Safety Monitoring Committee

The incidence and nature of any adverse events, serious adverse events, and laboratory abnormalities will be assessed on an ongoing basis by Investigators *in conjunction with a Safety Monitoring Committee (SMC).*~~, If an event is identified as a suspected dose limiting adverse event (DLAE; see Section), the Sponsor will convene a meeting of the Safety Monitoring Committee (SMC) within 24 hours to assess whether the event meets the criteria of a confirmed DLAE. The SMC may also meet to assess the significance of other adverse events or safety findings at any time following a request from either an Investigator or the Sponsor.~~

The SMC will consist of designated Sponsor representatives from clinical science (including the Sponsor's Medical Monitor), safety science, biostatistics, clinical pharmacology, as well as the lead Principal Investigator (PI) and any other individuals whom the Sponsor requires to assist with such assessments. When necessary, a SMC member may be replaced at any meeting by a designee.

If an Investigator determines that an event potentially meets Stopping Criteria (see Section 3.1.4), the Investigator will immediately contact the Sponsor and a meeting of the SMC will be convened within 24 hours. If, after a review of the blinded study data, the SMC unanimously agrees with the Investigator's original assessment that the event potentially meets Stopping Criteria, the patient will be unblinded to the SMC. If the patient actually received active MHAA4549A, then the SMC will consult with the IMC and SOC (see Section 3.1.4) to determine the impact upon the study.

In addition to events that potentially satisfy Stopping Criteria, the SMC may also meet to assess the significance of other adverse events or safety findings at any time following a request from either an Investigator or the Sponsor. Regardless of whether any specific events require assessment, the SMC will evaluate overall safety at a minimum of every 4 weeks.

SECTION 3.1.3: Internal Monitoring Committee and Scientific Oversight Committee

To provide additional assurance of *patient* safety, safety evaluations will also be ~~provided~~*conducted* by an IMC and SOC, as defined in a separate IMC/SOC agreement. In contrast to the SMC, which will ~~rapidly~~*continuously* evaluate ~~suspected DLAEs and other AEs of interest~~*blinded adverse events*, the IMC and SOC will periodically evaluate all available unblinded ~~study~~ data to assess whether the study data in its entirety suggest~~s~~ a significant toxicity or worsening disease associated with MHAA4549A. As a result, ~~they~~*the IMC/SOC* may recommend stopping further enrollment in the study or other protocol modifications.

~~An IMC and SOC will provide additional assurance of 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 all patient treatment and assignment. The Clinical Science representative on the IMC will serve as the IMC Chair and will be a person other than the study Medical Monitor. The IMC Chair *and the drug safety scientist on the IMC* will not be involved in the conduct of the study or have any contact with the study investigators or site staff. ~~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.~~ *Although* the ~~clinical pharmacologist,~~ biostatistician and statistical programmer ~~are the only IMC~~ members *of the IMC will be* involved in the conduct of the study~~; however~~, they ~~do~~*will* not have any contact with study investigators, and all discussion within the IMC ~~are~~*will be* 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 SOC members will consist of *at least* two external experts in the field ~~who will also be unblinded to treatment allocation.~~*, but* additional experts may be added to the SOC

by the IMC during the course of the study ~~if the need arises~~. *SOC members will also be unblinded to study treatment assignments.*

SECTION 3.1.4: *Stopping Rules*~~Definition of Dose Limiting Adverse Event~~

Further dosing in a treatment arm or in the entire study will be suspended if any of the following criteria is met:

- If a*ny* patient experiences ~~any one of the following adverse events while enrolled in the study and the~~ *a life-threatening* adverse event *related to MHAA4549A*
- *If a single serious adverse event* is deemed related to ~~blinded study drug by the Investigator, then that~~ *MHAA4549A*
- *If a* patient ~~will be considered to~~*experiences a persistent post-dose QTcF >500 ms and/or >60 ms longer than the baseline value related to MHAA4549A*
- If ≥2 patients out of all patients who have ~~experienced a suspected dose limiting adverse event (DLAE):~~received MHAA4549A to date (including this or any other study) experience similar adverse events that meet causality criteria (see Section 5.3.4):

  ~~Any serious adverse event~~

  An unexpected worsening of influenza inconsistent with the usual course of disease

  Any ~~other~~ intolerable systemic reaction that results in a significant compromise in the ability to conduct activities of daily living

  A suspected systemic immunological reaction to study drug

  ~~Adverse events that are graded at least severe and are deemed related to MHAB5553A~~

If a patient *in the blinded study* experiences any of the above ~~suspected DLAEs~~ (e.i, ~~an event~~*conditions* of sufficient severity that risk would exceed benefit ~~if the AE were actually the result of treatment by MHAA4549A~~), the Investigator must *immediately* notify the Sponsor*, who will suspend all dosing in the study and convene a meeting of the SMC* within 24 hours ~~of~~*following* knowledge of the event. ~~Further dosing within the entire study must be held until the SMC, in consultation with the IMC and SOC, determines whether it can be resumed or whether it should be discontinued permanently.~~

~~Once the Sponsor is notified, the SMC will meet to evaluate the suspected DLAE as soon as feasible (expected to be within 24 hours of the initial report).~~ If, after a review of the blinded study data, the SMC unanimously agrees with the Investigator's original assessment that the event ~~meets the criteria of a suspected DLAE, the~~ *would meet Stopping Criteria if the* patient *had received active drug, the patient's treatment* will be unblinded to the SMC. If the patient ~~actually received active~~ *did receive* MHAA4549A ~~and~~ *, further dosing within* the ~~DLAE meets causality criteria (Section) then~~*entire study must be suspended until* the ~~DLAE will be considered a confirmed DLAE.~~ *SMC consults with the IMC and SOC.*

~~At a minimum, a confirmed DLAE will be considered dose limiting for patient experiencing that event, but may also be considered as defining a dose level that exceeds the MTD for MHAA4549A. As a result, the SMC will ask the IMC/SOC to meet in an ad hoc session to evaluate all unblinded study data. Following IMC/SOC input, dosing may stop for all patients receiving MHAA4549A at and that dose or for all patients within the study (see Stopping Rules in Section).~~

SECTION 3.1.5: ~~Stopping Rules~~

~~At any meeting of the IMC or SOC, all available clinical and safety data will be evaluated and further dosing in a single patient, one or more treatment arms, or the entire study will be suspended when any of the following are met:~~

- ~~If 2 or more patients out of all patients who have received MHAA4549A to date (including this and other studies) experience~~

  ~~Similar confirmed DLAEs~~

  ~~Adverse events that are graded at least severe and are deemed related to MHAA4549A~~

- ~~If 1 patient experiences a life threatening confirmed DLAE~~
- ~~If a single serious adverse event that is deemed related to MHAA4549A~~

In addition to the above criteria*, dosing will also be halted* if the IMC and SOC conclude there is a clinically significant imbalance in toxicity between ~~arms~~*one or both of the arms receiving* MHAA4549A and *the arm* receiving placebo

Dosing may only resume if the IMC and SOC*, in consultation with the SMC,* unanimously determine~~, upon~~ *that Stopping Criteria have not been met for at least one (or for both) of the dose levels in this study. Any decision on whether Stopping Criteria have been met will always be made following a* review of all ~~available~~ unblinded data from this and ~~all~~*any* previous ~~studies examining~~*study that examined* MHAA4549A.~~, that the events are not causally related to MHAA4549A or do not satisfy severity criteria. Furthermore, based upon their interpretation of the data and in consultation with the SMC, the IMC and SOC may determine that dosing must stop for all dose levels, only for levels at or above the level where the stopping rules were met, or only for the affected individuals.~~

SECTION 3.2: *END OF STUDY AND* LENGTH OF STUDY

The study will consist of the following study periods

- Screening and Enrollment/Randomization: ≤72 hours (3 days) between onset of influenza-like illness (as determined by the investigator) and start of MHAA4549A or placebo
- On-Site Follow-Up: Follow-up study visits at Days 3, 5, *and* 7~~, 30, 100~~ after receiving MHAA4549A or placebo
- Telephone Follow-Up: Telephone follow-up visits at Day 2, 14*, 30, and 100* after receiving MHAA4549A or placebo

Patients who are unable to return to the clinic for on-site follow-up visits should be contacted by phone to: 1) ascertain health status, 2) record adverse event information, and 3) ask that the diary be completed and returned.

SECTION 3.3: ~~END OF STUDY AND LENGTH OF STUDY~~ *RATIONALE FOR STUDY DESIGN*

SECTION 3.3.1: Rationale for MHAA4549A Dose and Schedule

The ~~starting~~ 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 1.2.4.2)….

Both the 3600- and 8400-mg doses of MHAA4549A are expected to be safe based on *data from* previous clinical Phase 1 and Phase 2 studies (see Section 1.2.2).

SECTION 3.3.4: Rationale for *Virologic and* Biomarker Assessments

Influenza causes a wide spectrum of clinical disease and the severity of infection varies among patients. ~~Therefore, all patients may not be equally likely to benefit from treatment with MHAA4549A. To investigate those patients who are most likely to respond to MHAA4549A and~~*To* understand the pharmacological activity of MHAA4549A in patients with influenza A infection, biomarker samples *and measure virological activity and host responses* will be collected prior to and after dosing. Because ~~pharmacodynamics (PD)~~ biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

SECTION 3.4.1: Primary Outcome Measures

Incidence, nature, and severity of adverse events and clinical laboratory abnormalities (graded according to the Division of Acquired Immunodeficiency Syndrome [DAIDS] Toxicity Grading Tables for Clinical Abnormalities) associated with the administration of MHAA4549A to patients with influenza A as measured by changes in vital signs, physical findings, *and* clinical laboratory results~~, and immunogenicity assessment~~

SECTION 3.4.2: Secondary Outcome Measures

- *Incidence of death*

SECTION 3.4.3: Exploratory Outcome Measures

[redacted]

[redacted]

SECTION 4.1.1: Inclusion Criteria

Patients must meet the following criteria for study entry:

- Otherwise healthy adult men or women ≥18 years and ≤65 years of age on the day of signing the informed consent
- Tests positive for influenza A infection using a ~~Sponsor approved~~ rapid PCR test or rapid antigen test as an aid in influenza diagnosis during screening
- ≤72 hours (3 days) between onset of influenza-like illness (as determined by the investigator) and start of study treatment.
- Presence of at least 1 moderate or severe constitutional symptom (e.g., headache, myalgias, fever, chills, fatigue, anorexia, nausea) and 1 moderate or severe respiratory symptom (e.g., cough, sore throat, rhinorrhea) at screening
- ~~All routine laboratory parameters are within normal limits, unless deemed by the investigator to not be clinically significant~~

- Women of childbearing potential, that is women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or who are surgically sterile (absence of ovaries and/or uterus), must have a negative pregnancy test result within 2 days prior to study drug
- For women of childbearing potential: agreement to remain abstinent or use two highly effective methods of contraception (failure rate of <1% per year)*, including vasectomy of a male partner,* for at least 120 days after study drug

SECTION 4.1.2: Exclusion Criteria

- Patients who ~~have been pregnant within 6 months prior to screening, have been breastfeeding within 3 months prior to screening,~~*are currently pregnant, breastfeeding, or* have a positive pregnancy test at screening, or are intending to become pregnant during the study

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization will be stratified by onset of influenza-like illness (≤36 hours and >36 hours) and the type of influenza test used at enrollment (rapid PCR or rapid antigen test). A ~~dynamic hierarchical~~*permuted block* randomization method will be used to obtain an approximate 1:1:1 ratio of patients in the 3600 mg MHAA4549A, 8400 mg MHAA4549A, and placebo strata.

SECTION 4.3: STUDY TREATMENT

The investigational medicinal product (IMP) for this study is MHAA4549A.

SECTION 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. All patients will be monitored for study drug reactions during administration and for at least 30 minutes after completion of study drug administration.

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*–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 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 at half of the initial rate. The infusion will be discontinued in the event that the subject experiences a serious reaction and further dosing of subjects halted until safety of the drug is assessed.

SECTION 4.4.1: Permitted Therapy

Patients with recurrent influenza infection may be given local standard of care anti-influenza treatments including neuraminidase inhibitors.

SECTION 4.4.2: Prohibited Therapy

Use of the following therapies is prohibited throughout the patient's participation in the study (from enrollment to end of study):

- Any influenza antiviral therapy (e.g., oseltamivir, zanamivir, peramivir, amantadine, rimantadine) from onset of influenza-like illness *(except for recurrent influenza as described in Section 3.1.1)*

SECTION 4.5: STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of ~~assessments~~*activities* performed during the study.

SECTION 4.5.1: 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 Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

SECTION 4.5.2: Diagnostic Testing for Enrollment

All patients must be assessed for influenza A disease confirmation prior to enrollment into the study. A ~~Sponsor approved~~ rapid PCR test or rapid antigen test is required for diagnosis of influenza A infection. For the diagnostic test, sample collection may involve a nasal swab or a nasopharyngeal swab, depending on the diagnostic platform ~~approved~~ at the site.

~~It is highly recommended that the rapid PCR test result or the rapid antigen test result be available within 2 hours from the time of sample collection.~~

SECTION 4.5.4: [redacted]

SECTION 4.5.5: Physical Examinations

A complete physical examination *should be performed at screening and* 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 subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. ~~Please refer to Section for details regarding definitions of adverse events and criteria for reporting.~~

SECTION 4.5.6: Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, temperature *(oral),* and systolic and diastolic blood pressures while the patient is in a seated or supine position for at least 5 minutes~~, and temperature~~.

SECTION 4.5.7: Laboratory, Biomarker, and Other Biological Samples

[redacted]

SECTION 4.5.8: Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of ~~assessments~~*activities* (see Appendix 1), 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: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected using Fridericia's formula (QTcF) *(or Bazett's formula [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 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 QTcF 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 study drug discontinuation should be made, as described in Section 3.1.4. 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 4.5.9: Patient Daily Symptom Diary

Patients will use ~~an electronic device (electronic patient reported outcome [ePRO]) or~~ paper diaries ~~(as applicable)~~ to record symptom data (Nicholson et al. 2000; Treanor et al. 2000) (Appendix 6). *The investigator staff will provide* the paper diary ~~PRO device~~ and instructions for completing the symptom diary ~~will be provided by the investigator staff~~. The purpose of the diary is to record any symptoms of influenza-like illness, symptom relief medications and temperature *(oral)*. The symptom diary card, symptom relief medications and temperature should be completed two times daily: when a patient first wakes up in the morning (before getting out of bed) and ~12 hours later up to Day 14 or until resolution of symptoms (defined as a total symptom score of 0–1 for 24 hours without use of symptom relief medications). Temperature should be taken before administration of acetaminophen/paracetamol and/or NSAIDs (see Section 4.4.1 for permitted medications). Patients should be encouraged to stay consistent with the diary schedule and sites should check that patients are able to take their temperature properly. Day 1 entry will be completed within 6 hours prior to start of study infusion.

~~The data from electronic diaries will be transmitted to a centralized database at the ePRO vendor and can be accessed by appropriate study personnel securely via the Internet. See for symptom diary.~~

SECTION 4.5.9: Study Completion/Early Discontinuation

Patients who complete all study visits through Day 100 are considered to have completed the study. All patients who discontinue from the study early will be asked to complete all assessments for the ~~early discontinuation~~*current day. If a patient discontinues after Day 7, only a telephone* visit *is required as the Early Discontinuation*

visit. Please see Schedule of ~~Assessments~~*Activities* provided in Appendix 1 for assessments performed at the Study Completion *and* Early Discontinuation visit.

SECTION 5.1: SAFETY PLAN

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. All patients will be monitored for study drug reactions during administration and for at least 30 minutes after completion of study drug administration.

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 assay with appropriate sensitivity and therapeutic tolerance will be employed to assess *the prevalence of pre-existing* ATAs ~~before, during, and after the treatment with~~*to* MHAA4549A.

SECTION 5.3.1: Adverse Event Reporting Period

After initiation of study drug, all adverse events will be reported until study ~~discharge~~*completion* at the Day 100 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 5.3.5.4: 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~~. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded *on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., ≤24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions).*~~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 even became more severe. Fluctuations in intensity during resolution should not be captured as new events unless they exceed the maximum severity previously recorded for that AE~~ *The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.*

~~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). 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 even became serious.~~

SECTION 5.3.5.8: Deaths

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

SECTION 5.3.5.11: Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as ~~addressed in Sections 5.3.5.9 and 5.3.5.10 and as~~ outlined below.

SECTION 5.3.5.11: *Patient-Reported Outcome Data*

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

SECTION 5.4.1: Emergency Medical Contacts

[redacted] **24-Hour Safety Hotline**

- North America: [redacted]
- EMEA/*APAC:* [redacted]

[redacted] ~~**Medical Monitor contact information**~~:

~~Primary Medical Monitor:~~ [redacted]

~~Telephone Nos.:~~ ~~US Office~~ [redacted]

~~US Mobile~~ [redacted]

~~Email Address:~~ [redacted]

~~Secondary Medical Monitor:~~ [redacted]

~~Telephone Nos.:~~ ~~US Office~~ [redacted]

~~US Mobile~~ [redacted]

~~Email Address:~~ [redacted]

SECTION 5.4.2.1: Events That Occur prior to Study Drug Initiation

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

Region	Fax Number	Email Address
North America	[redacted]	[redacted]
EMEA	[redacted]	[redacted]
Asia Pacific	[redacted]	[redacted]

SECTION 5.4.2.2: Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the patient ~~is discharged from~~*completes* the study at Day 100 or ~~Early Discontinuation~~*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, the *paper Clinical Trial* Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided *in Section 5.4.2.1*~~to investigators~~. 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 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*~~to investigators.~~. 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, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.~~

SECTION 5.4.3.3: 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*~~to investigators~~. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. ~~In order to accomplish this,~~ 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 ~~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.

SECTION 5.6: ~~POST STUDY~~ ADVERSE EVENTS *THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD*

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 100 days after study drug administration), 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. However, if the EDC system is not available,* the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

SECTION 6.4: Primary Safety Analyses

The prevalence (baseline~~) of ATA and incidence (treatment emergent~~) of ATA will be reported and correlation with PK, safety, efficacy, and *biomarker* endpoints will be analyzed as data allow.

SECTION 6.5.2: Exploratory Endpoints

- [redacted]

[redacted]

SECTION 6.7: PHARMACOKINETIC ANALYSES

Individual and mean serum MHAA4549A concentration versus time data will be tabulated and plotted. The serum PK of MHAA4549A will be summarized by estimating total serum drug exposure (i.e., AUC), *maximum* concentration (C_{max}), total serum clearance, half-life, and volume of distribution, as data allow.

SECTION 6.8: EXPLORATORY ANALYSES

[redacted]

SECTION 6.8.1: *Biomarker Analyses*

[redacted]

[redacted]

SECTION 6.9: IMMUNOGENICITY ANALYSES

The immunogenicity analyses will be limited to testing of predose samples from all patients enrolled in the study. No post-dose samples will be collected (except for Day 7 in the case of recurrent influenza).

The number of ATA-positive patients at baseline will be determined, which will provide an estimate of the prevalence of pre-existing ATAs in this patient population. [redacted]

No additional immunogenicity assessments are planned for this study.

SECTION 7.1: DATA QUALITY ASSURANCE

~~If using e PRO devices: ePRO data will be collected through use of an electronic device provided by an ePRO vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The ePRO device data are available for view access only via secure access. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.~~

SECTION 7.3: PATIENT-REPORTED DAILY SYMPTOM DATA

~~Patients will use an ePRO device use paper diaries to record influenza-like symptoms, temperature, and acetaminophen/paracetamol and/or NSAIDs use.~~

~~For ePRO devices, the data will be transmitted to a centralized database at the ePRO vendor. The data can be reviewed by site staff via secure access.~~

~~Once the study is complete, the ePRO data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine readable format on a compact disc.~~

SECTION 7.6: RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ~~ePRO data~~/paper diaries ~~(if applicable)~~, 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.

SECTION 8.4: CONFIDENTIALITY

Given the complexity and exploratory nature of the 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).

SECTION 9.4: ADMINISTRATIVE STRUCTURE

Data reported by patients regarding their symptoms, body temperature, and any use of acetaminophen/paracetamol and/or NSAIDs will be captured using paper diaries ~~or electronically via ePRO devices (as applicable)~~.

FIGURE 1: Study Design

Figure 1 has been revised to reflect the changes to the protocol.

TABLE 5: Probability of Observing Adverse Events at Different Event Rates

Rows for underlying “True Rate” of 2% and 6% have been deleted.

REFERENCES:

~~Matias G, Taylor R, Haguinet F, et al. Estimates of mortality attributable to influenza and RSV in the United States during 1997-2009 by influenza type or subtype, age, cause of death, and risk status. Influenza Other Respir Viruses 2014;8(5):507-15.~~

~~Snacken R, Quinten C, Devaux I, et al. Surveillance of hospitalized severe cases of influenza A (H1N1)pdm09 and related fatalities in nine EU countries in 2010-2011. Influenza Other Respir Viruses 2012;6(6):e93-e96.~~

APPENDIX 1: Schedule of Activities

The Schedule of Assessments has been revised to reflect the changes to the protocol.

APPENDIX 2: Schedule of Activities for Recurrent Influenza

The Schedule of Assessments has been revised to reflect the changes to the protocol.

APPENDIX 5: Anaphylaxis Precautions and Management

The Schedule of Assessments has been revised to reflect the changes to the protocol.

APPENDIX 6: Adult Patient Symptom Diary

The Schedule of Assessments has been revised to reflect the changes to the protocol.

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY, ADMINISTERED AS MONOTHERAPY FOR THE TREATMENT OF ACUTE UNCOMPLICATED SEASONAL INFLUENZA A INFECTION IN OTHERWISE HEALTHY ADULTS**
PROTOCOL NUMBER:	GV29893
VERSION NUMBER:	3
EUDRACT NUMBER:	2016-000425-40
IND NUMBER:	117,318
TEST PRODUCT:	MHAA4549A
MEDICAL MONITOR:	[redacted]
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 retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the CRO.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY, ADMINISTERED AS MONOTHERAPY FOR THE TREATMENT OF ACUTE UNCOMPLICATED SEASONAL INFLUENZA A INFECTION IN OTHERWISE HEALTHY ADULTS**
PROTOCOL NUMBER:	GV29893
VERSION NUMBER:	3
EUDRACT NUMBER:	2016-000425-40
IND NUMBER:	117,318
TEST PRODUCT:	MHAA4549A
INDICATION:	Influenza A
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of MHAA4549A compared with placebo in patients with acute uncomplicated seasonal influenza A. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective

- To evaluate the safety and tolerability of a single IV dose of MHAA4549A as compared to placebo when administered in otherwise healthy patients with acute uncomplicated seasonal influenza A, focusing on the following:
  - Nature, frequency, and severity of serious and non-serious adverse events
  - Effects on laboratory values, vital signs, ECG parameters, and other safety biomarkers

Secondary Objectives

- To examine the time to alleviation of clinical signs and symptoms of influenza A infection
- To examine the severity of clinical signs and symptoms of influenza A infection
- To measure hospital admission rate
- *To measure duration* of *hospital* stay
- To measure antibiotic usage for secondary bacterial respiratory infections
- To measure the frequency, severity and development of secondary complications of influenza (pneumonia, exacerbation of chronic lung disease, myocarditis, acute respiratory distress syndrome, acute otitis media, other related complications)
- *To measure the incidence of death*
- To measure influenza re-infection rate

Pharmacokinetic Objective

- To characterize the PK profile of a single dose of MHAA4549A in serum

Exploratory Objectives

[redacted]

[redacted]

Study Design

Description of Study

This is a randomized, double-blind, placebo-controlled study (GV29893) designed to assess the safety and tolerability, efficacy, and pharmacokinetics of MHAA4549A compared to placebo when administered to approximately 141 otherwise healthy patients with acute uncomplicated seasonal influenza A. This study will inform the safety of MHAA4549A in the natural influenza infection setting.

Patients who are eligible for enrollment will be randomized in a 1:1:1 ratio into three treatment groups: a single IV dose of 3600 mg MHAA4549A, a single IV dose of 8400 mg MHAA4549A, or a single IV dose of placebo. Study drug administration will begin within 72 hours (3 days) of onset of influenza-like illness (as defined in the inclusion criteria) and all patients will be followed for a minimum of 100 days from randomization. All patients will be monitored for study drug reactions during administration and for at least 30 minutes after completion of study drug administration. After study discharge, all drug-related serious adverse events will continue to be reported to the Sponsor. Randomization will be stratified by onset of influenza-like illness ($\leq$36 hours and $>$36 hours) and type of influenza test used for enrollment (rapid polymerase chain reaction (PCR) or rapid antigen test). A permuted block randomization method will be used to obtain an approximate 1:1:1 ratio of patients in the 3600 mg MHAA4549A, 8400 mg MHAA4549A, or placebo groups within each stratum.

A rapid PCR test or rapid antigen test will be used as an aid in the diagnosis of influenza A infection and serve as the basis for satisfying study entry requirements. The intent-to-treat (ITT) population will include all patients randomized who received study medication. A central quantitative PCR test will be performed on Day 1 virology samples to confirm influenza A infection and define the intent-to-treat infected (ITTI) population for analyses.

If a patient develops new symptoms of influenza (as defined the in inclusion criteria) between Days 14 and 100, consistent with recurrent influenza infection (reinfection after initial influenza symptoms completely resolved), he/she should immediately inform site study personnel. A rapid PCR test or rapid antigen test will be performed as soon as possible, preferably within 72 hours of influenza symptom onset. [redacted] If the patient tests negative by rapid antigen test, the results will be confirmed by PCR. The patient will follow the assessments, until a negative PCR result for influenza is confirmed. Such patients will not be re-dosed with study treatment, but local standard of care anti-influenza treatments including neuraminidase inhibitors will be permitted and recorded. These patients must still complete *telephone* follow-up visits at Days 30 and 100 from initial randomization.

Safety evaluations will also be provided by an Internal Monitoring Committee (IMC) and Scientific Oversight Committee (SOC), as defined in a separate IMC/SOC agreement. 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 or other protocol modification.

Number of Patients

This study aims to enroll approximately 141 patients (47 per treatment arm).

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Otherwise healthy adult men or women ≥ 18 years and ≤ 65 years of age on the day of signing the informed consent
- Tests positive for influenza A infection using a rapid PCR test or rapid antigen test as an aid in influenza diagnosis during screening
- ≤ 72 hours (3 days) between onset of influenza-like illness (as determined by the investigator) and start of study treatment.
- Presence of at least 1 moderate or severe constitutional symptom (e.g., headache, myalgias, fever, chills, fatigue, anorexia, nausea) and 1 moderate or severe respiratory symptom (e.g., cough, sore throat, rhinorrhea) at screening
- Women of childbearing potential, that is women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or who are surgically sterile (absence of ovaries and/or uterus), must have a negative pregnancy test result within 2 days prior to study drug
- For women of childbearing potential: agreement to remain abstinent or use two highly effective methods of contraception (failure rate of < 1% per year)*, including vasectomy of a male partner,* for at least 120 days after 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.

  Examples of highly effective contraceptive methods include: bilateral tubal ligation, male partner sterilization, combined (estrogen and progestogen) or progestogen-only hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), intrauterine device (IUD), and intrauterine hormone releasing system (IUS).
- For men: agreement to remain abstinent or use a condom for at least 30 days after study drug administration and agreement to refrain from donating sperm for 90 days after study drug administration.

  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.

Exclusion Criteria

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

- History of major medical conditions from medical history, physical examination, and/or routine laboratory tests that may put the subject at higher risk for influenza related complications as determined by the investigator during screening
- Creatinine clearance ≤ 80 mL/min
- Any abnormal laboratory test or ECG, which is deemed by the investigator to be clinically significant
- Patients who have taken any influenza antiviral therapy (e.g. oseltamivir, zanamivir, peramivir, amantadine, rimantadine) in the period from onset of influenza-like illness and prior to enrollment
- Patients who *are currently pregnant, breastfeeding, or* have a positive pregnancy test at screening, or are intending to become pregnant during the study
- Clinical signs and symptoms consistent with otitis, bronchitis, sinusitis, or pneumonia, or active bacterial infection at any site that requires therapy with antibiotics
- Investigational therapy within 30 days prior to initiation of study treatment or within 5 half-lives of the investigational product, whichever is greater
- Hypersensitivity to any constituents (sodium succinate, sucrose, polysorbate 20) of MHAA4549A

- Prior therapy with any anti-influenza monoclonal antibody, including MHAA4549A
- Received nasally administered influenza A vaccine within 14 days prior to screening
- Positive influenza B or influenza A + B infection within 2 weeks prior to study treatment
- Significant history of tobacco use at any time (≥ 10 pack year history, e.g. one pack a day for 10 years)
- Patients receiving chronic dose of oral corticosteroids exceeding 10 mg/day of prednisone or equivalent steroid dose or inhaled corticosteroids at any dose for a duration of greater than 14 days within 30 days prior to screening
- History or evidence of autoimmune disease or known immunodeficiency of any cause
- Patients taking any medications that suppress the immune system (immunosuppressives)
- History of asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, reactive airway disease, or chronic lung condition of any etiology.

  A history of childhood asthma before the age of 12 is acceptable provided the subject:

  Has no symptoms consistent with asthma

  Is not receiving chronic or acute treatment for asthma.

  Patients with asthma after age 12 but who has not received treatment for asthma in the past 4 years can be included at the investigator's discretion after consultation with the Sponsor.
- Planned medical or surgical procedure during the study
- Known HIV infection with CD4+ T cell count ≤ 200 cells/mL in the past 12 months
- History of illicit drug use or alcohol abuse in the 12 months prior to screening which, in the investigator's judgment, could affect compliance with study requirements
- Serious infection requiring oral or IV antibiotics within 14 days prior to screening
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction

End of Study

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

Length of Study

The total duration of this study for each subject is approximately 14 weeks, including screening, enrollment, treatment, and follow-up.

Investigational Medicinal Products

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.

Test Product (Investigational Drug)

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 at 3600 mg IV, or 8400 mg IV or placebo IV at a 1:1:1 ratio.

Comparator

MHAA4549A placebo will be provided as a clear, colorless, sterile, preservative-free liquid solution and has the same vial configuration as the Drug Product.

Statistical Methods

Primary Analysis

The primary objective of this study is to characterize the safety and tolerability of a single dose of MHAA4549A as compared to placebo when administered in otherwise healthy patients with acute uncomplicated seasonal influenza A. Statistical summaries will be descriptive in nature.

Patients will be grouped according to treatment actually received, and any patients who receive any amount of MHAA4549A or placebo will be included in the analyses.

Determination of Sample Size

The planned sample size for this study is approximately 47 patients per treatment group. A total of approximately 141 patients will be enrolled in this study in order to obtain 120 evaluable patients (an estimated dropout rate of 15%).

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 1 error penalty of 0.0001 will be taken.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ADE	antibody-dependent enhancement
ALT	alanine aminotransferase
ALP	alkaline phosphatase
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
ATA	anti-therapeutic antibody
AUC	area under the curve
AUC0-infinity	area under the curve from zero to infinity
BUN	blood urea nitrogen
CK	creatinine phosphokinase
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CRO	contract research organization
DAIDS	Division of Acquired Immunodeficiency Syndrome
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EIH	entry into humans
ELISA	enzyme-linked immunosorbent assay
E.U.	European Union
EVA	ethylene vinyl acetate
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transferase
GLP	good laboratory practice
HA	hemagglutinin
HAI	hemagglutinin inhibition
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)

Abbreviation	Definition
IQR	interquartile range
IRB	Institutional Review Board
IRR	infusion related reaction
ITT	intent-to-treat
ITTI	intent-to-treat infected
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
IxRS	Interactive voice and web response system
LDH	lactate dehydrogenase
LPLV	last patient, last visit
NA	neuraminidase
NAI	neuraminidase inhibitor
NOAEL	no observed adverse effect level
NSAID	non-steroidal anti-inflammatory drug
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic
PRO	patient-reported outcome
PT	prothrombin time
qPCR	quantitative polymerase chain reaction
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
SAE	serious adverse event
SMC	Safety Monitoring Committee
SOC	Scientific Oversight Committee
$TCID_{50}$	50% tissue culture infectious dose
TEAE	treatment emergent adverse event
T_{max}	Time at which the C_{max} is observed
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON INFLUENZA

Influenza viruses cause annual epidemics during autumn and winter that are associated with significant human disease. Influenza is a respiratory illness with a broad clinical spectrum that typically results in mild symptoms, such as fever and cough, from which most people recover without requiring medical attention. The standard of care therapy for patients with acute uncomplicated influenza consists of administration of neuraminidase inhibitors (NAI) that include, but are not limited to, oseltamivir, zanamivir, and peramivir.

However, influenza can also cause serious complications requiring hospitalization such as pneumonia leading to acute respiratory failure, secondary bacterial respiratory infections, and death. *Annually,* seasonal influenza results in approximately three to five million cases of severe illness and up to 500,000 deaths worldwide (WHO 2014). Thus, a significant unmet medical need still exists in those at high-risk of developing influenza-complications, including children, the elderly, pregnant women, and those with underlying chronic medical conditions or weakened immune systems.

To address this need, the Sponsor is developing a highly-specific anti-influenza A monoclonal antibody therapy (MHAA4549A) for the treatment of hospitalized patients with severe influenza. This study assesses the safety, efficacy, and pharmacokinetics of MHAA4549A in otherwise healthy patients with acute uncomplicated seasonal influenza A infection.

1.2 BACKGROUND ON MHAA4549A

1.2.1 Nonclinical Background

MHAA4549A is a human monoclonal IgG1 antibody that binds to the influenza A virus. MHAA4549A was 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 *completed* clinical studies, which altogether enrolled 136 healthy volunteers. In addition, *an ongoing global* Phase 2b Study (GV29216)*,* in *24 countries across North America, Europe, Latin America, and Asia-Pacific, is currently enrolling* hospitalized patients with severe influenza infection *and* has shown no clinically significant drug-related safety signals.

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 or MHAA4549A at 1.5 mg/kg, 5 mg/kg, 15 mg/kg, 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 4 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 (4 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 versus 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 one 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 or ECG measurements. Overall, no relevant differences in mean values or deviations from baseline over time were observed in subjects receiving MHAA4549A as compared to placebo for all lab values. 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 or MHAA4549A at 8400 mg *(Cohort A)* or 10800 mg *(Cohort B) and followed for 120 days*.

A total of 34 TEAEs were reported by 12 (85.7%) of the 14 subjects who received one dose of the study medication or placebo (safety population). Twenty-four (24) of these TEAEs were reported by 7 (87.5%) of the 8 subjects who had received MHAA4549A

and 10 TEAEs were reported by 5 (83.3%) of the 6 subjects who received placebo. TEAEs were reported by 3 of the 4 subjects receiving 8,400 mg MHAA4549A and 4 of 4 subjects receiving 10,800 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, reported by 4 subjects who received MHAA4549A (3 subjects in Cohort A and 1 subject in Cohort B), and nasopharyngitis, reported by three subjects who received MHAA4549A (1 subject in Cohort A and 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 one subject who received 8400 mg MHAA4549A, and elevations of blood CK, observed twice in one subject who received 10,800 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 24–36 hours after inoculation, 60 subjects received single IV doses of 400 mg, 1200 mg, 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). There was no evidence of a dose-related pattern of TEAEs in MHAA4549A-treated subjects, an observation that is consistent with *all of* the Phase 1 studies (GV28916 and GV29609) *conducted to date.* Expected influenza-related symptoms and adverse events were observed in inoculated subjects; these influenza-related adverse events were similar in subjects who received MHAA4549A or placebo. Of the 101 subjects randomized, 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%) that occurred in a similar pattern across all treatment groups.

Thirty-six of the 86 subjects (42%) experienced ≥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 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 subjects 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%.

1.2.3 Clinical Pharmacokinetics

The Phase 1 EIH study (GV28916) demonstrated that MHAA4549A serum pharmacokinetics *(PK)* was dose proportional with a mean half-life of approximately 23 days (range: 21.9 to 24.6 days). The PK profile appeared consistent with that of a human IgG1 antibody that lacks known endogenous host targets (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 *serum PK*. The group mean maximum observed concentration (C_{max}) increased in a dose-proportional manner of 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 18,100 day*μg/mL for the 400- and 3600-mg dose groups, respectively, and is approximately dose proportional. PK data from the Phase 2a study (GV28985) is consistent with that observed in the Phase 1 study (GV28916), with MHAA4549A demonstrating a mean half-life of approximately 23 days (mean range: 22.5–23.7 days).

In the Phase 1 high-dose study (GV29609), MHAA4549A showed serum linear PK with a mean half-life ($t_{1/2}$) of approximately 21.5 days (range 21.4–21.6 days). For the 8,400-mg and 10,800-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) are consistent with that observed in the Phase 1 study (GV28916) and Phase 2a study (GV28985).

1.2.4 Clinical Efficacy Background

The virologic efficacy analysis for the Phase 2a 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 post-challenge virus inoculation

  Or

- At least two positive detections by any 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 quantitative polymerase chain reaction [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 variability from the challenge model and inter-subject 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. 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	Placebo (N=21)	MHAA4549A 400 mg (N=11) % Reduction (p-value)	MHAA4549A 1200 mg (N=13) % Reduction (p-value)	MHAA4549A 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 (log10 $TCID_{50}$)	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; mg=milligram; mL=milliliter; qPCR=quantitative polymerase chain reaction; vc=viral copies; $TCID_{50}$=50% tissue culture infectious dose.

Note: Comparison of 400 mg, 1200 mg, 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

Two Phase 1 (GV28916, GV29609) studies have demonstrated that MHAA4549A is safe and well tolerated in healthy volunteers at doses up to 10800 mg. Data from the Phase 2a study (GV28985) demonstrated that doses of approximately 3600 mg MHAA4549A are safe, well tolerated, and effective in reducing viral titers and influenza symptoms as compared to placebo in healthy volunteers inoculated with influenza A

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 clinical development of MHAA4549A.

The primary goal of this exploratory Phase 2 Study (GV29893) is to demonstrate safety and tolerability of MHAA4549A in otherwise healthy patients with naturally *acquired* acute uncomplicated seasonal influenza A. The study will also assess the potential ability of MHAA4549A to reduce the severity and/or duration of clinical signs and symptoms, [redacted] related to acute *uncomplicated* influenza. Other measures, such as influenza reinfection rate, frequency of secondary complications, hospital admissions, mortality*, PK, immunogenicity, and biomarkers* will also be assessed.

Potential risks of MHAA4549A include immunogenicity and infusion-related reactions. Theoretically, any biological 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 preclinical 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.

Antibody-dependent enhancement (ADE) of *disease* has been suggested as a potential risk of antiviral antibodies *when used* as therapeutic interventions for influenza (Khurana et al. 2013). ADE of *infection* might occur when non-neutralizing antiviral antibodies facilitate virus entry into host cells, leading to enhanced viral replication *and shedding* (Takada and Kawaoka 2003; Whitehead et al. 2007; Dejnirattisai et al. 2010; Crowe 2013). In the Phase 2a challenge study (GV28985), no signs or symptoms of ADE were observed, including higher viral titers/genomes or increases in clinical symptom scores in subjects receiving MHAA4549A as compared to placebo.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

- To evaluate the safety and tolerability of a single IV dose of MHAA4549A as compared to placebo when administered in otherwise healthy patients with acute uncomplicated seasonal influenza A, focusing on the following:

  Nature, frequency, and severity of serious and non-serious adverse events

  Effects on laboratory values, vital signs, ECG parameters, and other safety biomarkers

2.2 SECONDARY OBJECTIVES

- To examine the time to alleviation of clinical signs and symptoms of influenza A infection
- To examine the severity of clinical signs and symptoms of influenza A infection

- To measure hospital admission rate
- *To measure duration* of *hospital* stay
- To measure antibiotic usage for secondary bacterial respiratory infections
- To measure the frequency, severity and development of secondary complications of influenza (pneumonia, exacerbation of chronic lung disease, myocarditis, acute respiratory distress syndrome, acute otitis media, other related complications)
- *To measure the incidence of death*
- To measure influenza re-infection rate

2.2.1 Pharmacokinetic Objective

- To characterize the PK profile of a single dose of MHAA4549A in serum

2.3 EXPLORATORY OBJECTIVES

[redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a randomized, double-blind, placebo-controlled study (GV29893) designed to assess the safety *and tolerability*, efficacy, and pharmacokinetics of MHAA4549A compared to placebo when administered to approximately 141 otherwise healthy patients with acute uncomplicated seasonal influenza A. This study will inform the safety of MHAA4549A in the natural influenza infection setting.

Patients who are eligible for enrollment will be randomized in a 1:1:1 ratio into three treatment groups: a single IV dose of 3600 mg MHAA4549A, a single IV dose of 8400 mg MHAA4549A, or a single IV dose of placebo. Study drug administration will begin within 72 hours (3 days) of onset of influenza-like illness (as defined in the inclusion criteria, Section 4.1.1) and all patients will be followed for a minimum of 100 days from randomization. After study discharge, all drug-related serious adverse events will continue to be reported to the Sponsor. Randomization will be stratified by

onset of influenza-like illness (≤36 hours and >36 hours) and type of influenza test used for enrollment (rapid PCR or rapid antigen test). A permuted block randomization method will be used to obtain an approximate 1:1:1 ratio of patients in the 3600 mg MHAA4549A, 8400 mg MHAA4549A, or placebo groups within each stratum.

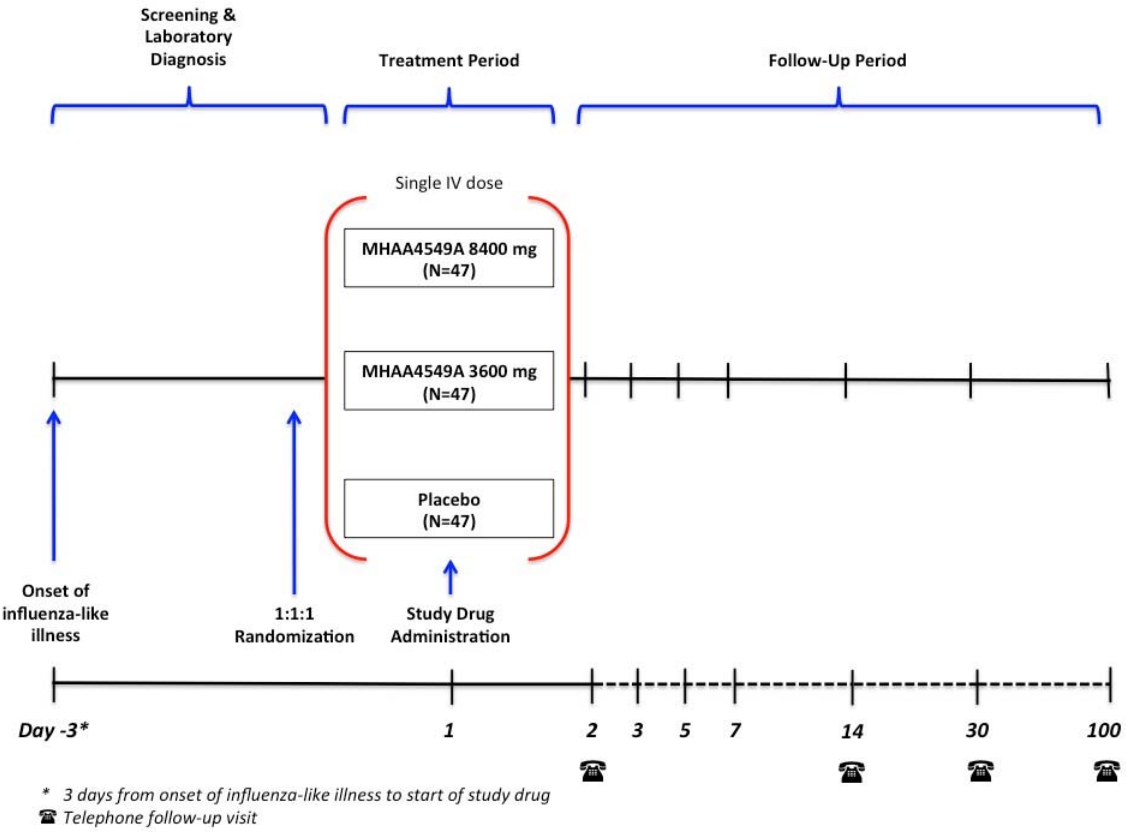
A rapid PCR test or rapid antigen test will be used as an aid in the diagnosis of influenza A infection and serve as the basis for satisfying study entry requirements. The intent-to-treat (ITT) population will include all patients randomized who received study medication. A central quantitative PCR test will be performed on Day 1 virology samples to confirm influenza A infection and define the intent-to-treat infected (ITTI) population for analyses.

If a patient develops new symptoms of influenza (as defined in the inclusion criteria, Section 4.1.1) between Days 14 and 100, consistent with recurrent influenza infection (reinfection after initial influenza symptoms completely resolved), he/she should immediately inform site study personnel. A rapid PCR test or rapid antigen test will be performed as soon as possible, preferably within 72 hours of influenza symptom onset. [redacted] If the patient tests negative by rapid antigen testing, the results will be confirmed by PCR. The patient will follow the assessments in Appendix 2, until a negative PCR result for influenza is confirmed. Such patients will not be re-dosed with study treatment, but local standard of care anti-influenza treatments including neuraminidase inhibitors will be permitted and recorded. These patients must still complete *telephone* follow-up visits at Days 30 and 100 from initial randomization.

Safety evaluations will be provided by an Internal Monitoring Committee (IMC) and Scientific Oversight Committee (SOC), as defined in a separate IMC/SOC agreement. 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 or other protocol modification.

A schedule of *activities* is provided in Appendix 1.

Figure 1 Study Design



3.1.2 Safety Monitoring Committee

The incidence and nature of any adverse events, serious adverse events, and laboratory abnormalities will be assessed on an ongoing basis by Investigators *in conjunction with a Safety Monitoring Committee (SMC).* The SMC will consist of designated Sponsor representatives from clinical science (including the Sponsor's Medical Monitor), safety science, biostatistics, clinical pharmacology, as well as the lead Principal Investigator (PI) and any other individuals whom the Sponsor requires to assist with such assessments. When necessary, a SMC member may be replaced at any meeting by a designee.

If an Investigator determines that an event potentially meets Stopping Criteria (see Section 3.1.4), the Investigator will immediately contact the Sponsor and a meeting of the SMC will be convened within 24 hours. If, after a review of the blinded study data, the SMC unanimously agrees with the Investigator's original assessment that the event potentially meets Stopping Criteria, the patient will be unblinded to the SMC. If the patient actually received active MHAA4549A, then the SMC will consult with the IMC and SOC (see Section 3.1.4) to determine the impact upon the study.

In addition to events that potentially satisfy Stopping Criteria, the SMC may also meet to assess the significance of other adverse events or safety findings at any time following a request from either an Investigator or the Sponsor. Regardless of whether

any specific events require assessment, the SMC will evaluate overall safety at a minimum of every 4 weeks.

3.1.3 Internal Monitoring Committee and Scientific Oversight Committee

To provide additional assurance of *patient* safety, safety evaluations will also be *conducted* by an IMC and SOC, as defined in a separate IMC/SOC agreement. In contrast to the SMC, which will *continuously* evaluate *blinded adverse events*, the IMC and SOC will periodically evaluate all available unblinded data to assess whether the study data in its entirety suggest a significant toxicity or worsening disease associated with MHAA4549A. As a result, *the IMC/SOC* may recommend stopping further enrollment in the study or other protocol modifications.

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 all patient treatment and assignment. The Clinical Science representative on the IMC will serve as the IMC Chair and will be a person other than the study Medical Monitor. The IMC Chair *and the drug safety scientist on the IMC* will not be involved in the conduct of the study or have any contact with the study investigators or site staff. *Although* the biostatistician and statistical programmer members *of the IMC will be* involved in the conduct of the study, they *will* not have any contact with study investigators, and all discussion within the IMC *will be* 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 SOC members will consist of *at least* two external experts in the field*, and* additional experts may be added to the SOC by the IMC during the course of the study. *SOC members will also be unblinded to study treatment assignments.*

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

3.1.4 *Stopping Rules*

Further dosing in a treatment arm or in the entire study will be suspended if any of the following criteria is met:

- If *any* patient experiences *a life-threatening* adverse event *related to MHAA4549A*
- *If a single serious adverse event* is deemed related to *MHAA4549A*
- *If a* patient *experiences a persistent post-dose corrected QT interval >500 ms and/or >60 ms longer than the baseline value related to MHAA4549A*

- *If ≥2 patients out of all patients who* have *received MHAA4549A to date (including this or any other study) experience similar adverse events that meet causality criteria (see Section 5.3.4):*

  An unexpected worsening of influenza inconsistent with the usual course of disease

  Any intolerable systemic reaction that results in a significant compromise in the ability to conduct activities of daily living

  A suspected systemic immunological reaction to study drug

If a patient *in the blinded study* experiences any of the above (i.e., *conditions* of sufficient severity that risk would exceed benefit), the Investigator must *immediately* notify the Sponsor*, who will suspend all dosing in the study and convene a meeting of the SMC* within 24 hours *following* knowledge of the event. If, after a review of the blinded study data, the SMC unanimously agrees with the Investigator's original assessment that the event *would meet Stopping Criteria if the* patient *had received active drug, the patient's treatment* will be unblinded to the SMC. If the patient *did receive* MHAA4549A*, further dosing within* the *entire study must be suspended until* the *SMC consults with the IMC and SOC.*

In addition to the above criteria*, dosing will also be halted* if the IMC and SOC conclude there is a clinically significant imbalance in toxicity between *one or both of the arms receiving* MHAA4549A and *the arm* receiving placebo

Dosing may only resume if the IMC and SOC*, in consultation with the SMC,* unanimously determine *that Stopping Criteria have not been met for at least one (or for both) of the dose levels in this study. Any decision on whether Stopping Criteria have been met will always be made following a* review of all unblinded data from this and *any* previous *study that examined* MHAA4549A.

3.2 *END OF STUDY AND* LENGTH OF STUDY

The study will consist of the following study periods

- Screening and Enrollment/Randomization: ≤72 hours (3 days) between onset of influenza-like illness (as determined by the investigator) and start of MHAA4549A or placebo
- On-Site Follow-Up: Follow-up study visits at Days 3, 5, *and* 7 after receiving MHAA4549A or placebo
- Telephone Follow-Up: Telephone follow-up visits at Day 2, 14*, 30, and 100* after receiving MHAA4549A or placebo

Patients who are unable to return to the clinic for on-site follow-up visits should be contacted by phone to: 1) ascertain health status, 2) record adverse event information, and 3) ask that the diary be completed and returned.

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

The total duration of this study for each subject is approximately 14 weeks, including screening, enrollment, treatment, and follow-up.

3.3 *RATIONALE FOR STUDY DESIGN*

3.3.1 Rationale for MHAA4549A Dose and Schedule

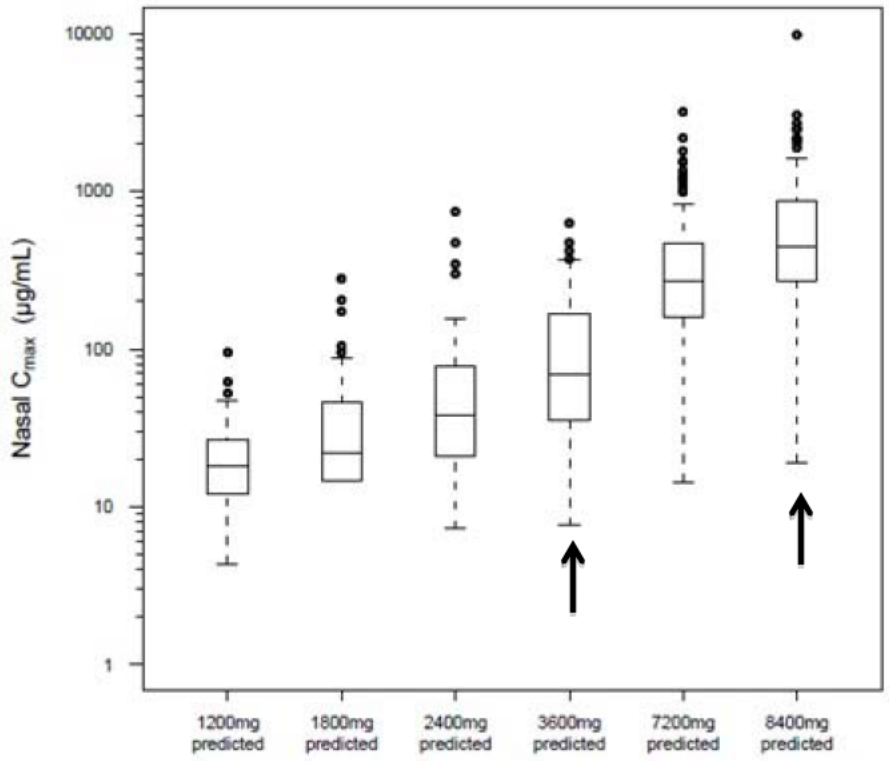
Single IV doses of 3600 mg and 8400 mg were selected to assess the safety, efficacy, and pharmacokinetics of MHAA4549A and to provide data for further clinical development. The selection of dose in this study was based on nonclinical efficacy data from the in vivo mouse influenza A infection models, the pharmacokinetics in clinical studies (see Section 1.2.3), and the relationship between the pharmacokinetics, pharmacodynamics, and efficacy observed in the Phase 2a challenge model 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 1.2.4.2). An MHAA4549A exploratory exposure-response analysis of the Phase 2a study demonstrated that subjects with nasal maximum MHAA4549A concentration (C_{max}) greater than the median nasal C_{max} value 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 C_{max} less than the median nasal C_{max} value 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 *data from* previous clinical Phase 1 and Phase 2 studies (see Section 1.2.2).

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 for each 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.

3.3.2 Rationale for Patient Population

This study will assess the safety, efficacy and pharmacokinetics of MHAA4549A in otherwise healthy patients with acute uncomplicated seasonal influenza A. This population will minimize comorbidities that could confound the interpretation of adverse outcomes in a more severely ill hospitalized population.

3.3.3 Rationale for Control Group

This study will include a placebo treatment arm in order to evaluate the safety, clinical and virologic effects of MHAA4549A on uncomplicated influenza A infection. Although neuraminidase inhibitors are used in this setting, they have not been universally adopted as standard-of-care in this population. In addition the enrollment criteria for this study targets subjects without pre-existing comorbidities to minimize the risk of influenza-related complications.

Patients will be allowed to take over-the-counter medications for symptomatic relief as specified in Section 4.4.1. Site staff will monitor all patients closely for safety and severity of disease.

3.3.4 [redacted]

[redacted]

3.4 OUTCOME MEASURES

3.4.1 Primary Outcome Measures

- Incidence, nature, and severity of adverse events and clinical laboratory abnormalities (graded according to the Division of Acquired Immunodeficiency Syndrome [DAIDS] Toxicity Grading Tables for Clinical Abnormalities) associated with the administration of MHAA4549A to patients with influenza A as measured by changes in vital signs, physical findings, *and* clinical laboratory results

3.4.2 Secondary Outcome Measures

- Time to alleviation of all symptoms (nasal congestion, sore throat, cough, aches, fatigue, headaches, chills/sweats) with resolution maintained for 24 hours (without use of symptom relief medications) as defined by a rating 0 (none) or 1 (mild) for each symptom on a 4-point scale of 0–3. For patients who enroll with mild symptoms, the symptom score must be reduced by 1 point during the study duration.
- Incidence of reinfection or relapse with influenza at 100 days after end of treatment
- Incidence of hospitalization for influenza-related complications at 100 days after end of treatment and length of stay
- Antibiotic usage for secondary bacterial respiratory infections
- Incidence of complications of influenza (e.g., pneumonia, exacerbations of chronic lung disease, myocarditis, acute respiratory distress syndrome (ARDS), otitis media, or other influenza related complications)
- *Incidence of death*

3.4.2.1 Pharmacokinetic Outcome Measure

- PK measurements in serum (including C_{max}, time at which the C_{max} is observed (T_{max}), AUC, systemic clearance, volume of distribution, and half-life as applicable)

3.4.3 Exploratory Outcome Measures

[redacted]

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

This study aims to enroll approximately 141 patients (47 per treatment arm) and is designed to assess the safety, efficacy, and pharmacokinetics of a single IV infusion at two dose levels of MHAA4549A in otherwise healthy adult patients with acute uncomplicated seasonal influenza A versus a comparator arm of placebo. Patients who withdraw/discontinue/are lost to follow-up may not be replaced.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Otherwise healthy adult men or women ≥ 18 years and ≤ 65 years of age on the day of signing the informed consent

- Tests positive for influenza A infection using a rapid PCR test or rapid antigen test as an aid in influenza diagnosis during screening
- ≤72 hours (3 days) between onset of influenza-like illness (as determined by the investigator) and start of study treatment.
- Presence of at least 1 moderate or severe constitutional symptom (e.g., headache, myalgias, fever, chills, fatigue, anorexia, nausea) and 1 moderate or severe respiratory symptom (e.g., cough, sore throat, rhinorrhea) at screening
- Women of childbearing potential, that is women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or who are surgically sterile (absence of ovaries and/or uterus), must have a negative pregnancy test result within 2 days prior to study drug
- For women of childbearing potential: agreement to remain abstinent or use two highly effective methods of contraception (failure rate of <1% per year)*, including vasectomy of a male partner,* for at least 120 days after 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.

  Examples of highly effective contraceptive methods include: bilateral tubal ligation, male partner sterilization, combined (estrogen and progestogen) or progestogen-only hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), intrauterine device (IUD), and intrauterine hormone releasing system (IUS).
- For men: agreement to remain abstinent or use a condom for at least 30 days after study drug administration and agreement to refrain from donating sperm for 90 days after study drug administration.

  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.

4.1.2 Exclusion Criteria

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

- History of major medical conditions from medical history, physical examination, and/or routine laboratory tests that may put the subject at higher risk for influenza related complications as determined by the investigator during screening
- Creatinine clearance ≤80 mL/min
- Any abnormal laboratory test or ECG, which is deemed by the investigator to be clinically significant
- Patients who have taken any influenza antiviral therapy (e.g. oseltamivir, zanamivir, peramivir, amantadine, rimantadine) in the period from onset of influenza-like illness and prior to enrollment

- Patients who *are currently pregnant, breastfeeding, or* have a positive pregnancy test at screening, or are intending to become pregnant during the study
- Clinical signs and symptoms consistent with otitis, bronchitis, sinusitis, or pneumonia, or active bacterial infection at any site that requires therapy with antibiotics
- Investigational therapy within 30 days prior to initiation of study treatment or within 5 half-lives of the investigational product, whichever is greater
- Hypersensitivity to any constituents (sodium succinate, sucrose, polysorbate 20) of MHAA4549A
- Prior therapy with any anti-influenza monoclonal antibody, including MHAA4549A
- Received nasally administered influenza A vaccine within 14 days prior to screening
- Positive influenza B or influenza A+B infection within 2 weeks prior to study treatment
- Significant history of tobacco use at any time ($\geq$10 pack year history, e.g. one pack a day for 10 years)
- Patients receiving chronic dose of oral corticosteroids exceeding 10 mg/day of prednisone or equivalent steroid dose or inhaled corticosteroids at any dose for a duration of greater than 14 days within 30 days prior to screening
- History or evidence of autoimmune disease or known immunodeficiency of any cause
- Patients taking any medications that suppress the immune system (immunosuppressives)
- History of asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, reactive airway disease, or chronic lung condition of any etiology.

  A history of childhood asthma before the age of 12 is acceptable provided the subject:

  Has no symptoms consistent with asthma

  Is not receiving chronic or acute treatment for asthma.

  Patients with asthma after age 12 but who has not received treatment for asthma in the past 4 years can be included at the investigator's discretion after consultation with the Sponsor.
- Planned medical or surgical procedure during the study
- Known HIV infection with CD4+ T cell count $\leq$200 cells/mL in the past 12 months
- History of illicit drug use or alcohol abuse in the 12 months prior to screening which, in the investigator's judgment, could affect compliance with study requirements
- Serious infection requiring oral or IV antibiotics within 14 days prior to screening
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The randomization of patients will be managed by a central Interactive Voice and/or Web Response System (IxRS) through use of a permuted block randomization that includes a random component.

Randomization will be stratified by onset of influenza-like illness ($\leq$36 hours and $>$36 hours) and the type of influenza test used at enrollment (rapid PCR or rapid antigen test). A *permuted block* randomization method will be used to obtain an approximate 1:1:1 ratio of patients in the 3600 mg MHAA4549A, 8400 mg MHAA4549A, and placebo strata.

An unblinded review of safety will be performed on a regular basis by the IMC and SOC as described in the IMC/SOC agreement.

Due to the slight yellow color of MHAA4549A, 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. 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. 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 (i.e., to evaluate a possible error in dosing).

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 by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If a treatment code is broken by a site for any other reason, the investigator must 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 serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is MHAA4549A.

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.

4.3.2 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 at 3600 mg IV, or 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. All patients will be monitored for study drug reactions during administration and for at least 30 minutes after completion of study drug administration.

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*–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 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 halted until safety of the drug is assessed.

There are no recommended dosage modifications for MHAA4549A because 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 adverse events associated with overdose. Patients experiencing such adverse events 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.

4.3.3 Investigational Medicinal Product Accountability

IMPs required for completion of this study (MHAA4549A) 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–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–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. Vials are intended for single use only; therefore, any remaining solution should be discarded.

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 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.

4.3.4 Post-Trial Access to MHAA4549A

As this is single dose administration, the Sponsor 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

4.4 CONCOMITANT THERAPY AND FOOD

Concomitant therapy 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 such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

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

Acetaminophen/paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are allowed for relief of severe influenza symptoms. The patient must record the use of these medications as directed in the patient diary.

Patients with recurrent influenza infection may be given local standard of care anti-influenza treatments including neuraminidase inhibitors.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited throughout the patient's participation in the study (from enrollment to end of study):

- Any influenza antiviral therapy (e.g., oseltamivir, zanamivir, peramivir, amantadine, rimantadine) from onset of influenza-like illness *(except for recurrent influenza as described in Section 3.1.1)*
- Investigational therapy
- Oral/inhaled corticosteroids
- Antitussives or expectorants
- Combination cold or influenza remedies
- Antihistamines
- Herbal medicines for influenza virus infection

4.4.3 Prohibited Food

There are no prohibited foods for this study.

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of *activities* performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-*related procedures*. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before 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.

4.5.2 Diagnostic Testing for Enrollment

All patients must be assessed for influenza A disease confirmation prior to enrollment into the study. A rapid PCR test or rapid antigen test is required for diagnosis of influenza A infection. For the diagnostic test, sample collection may involve a nasal swab or a nasopharyngeal swab, depending on the diagnostic platform at the site.

4.5.3 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.

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

4.5.4 [redacted]

[redacted]

4.5.5 Physical Examinations

A complete physical examination *should be performed at screening and* 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 subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.6 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, temperature *(oral),* and systolic and diastolic blood pressures while the patient is in a seated or supine position for at least 5 minutes.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

Table 2 Laboratory, Biomarker, and Other Biological Samples

Hematology:	**Clinical Chemistry**:
Hemoglobin	Glucose
Hematocrit	Blood urea nitrogen (BUN) or urea
Red blood cell (RBC) count	Creatinine
Platelet count	Total protein
WBC absolute and differential:	Albumin
Total neutrophils (bands & segments, if clinically indicated)	Total bilirubin
Lymphocytes	Alkaline phosphatase (ALP)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Alanine aminotransferase (ALT)
Basophils	Triglycerides
Coagulation:	Amylase (lipase will be reflexively assessed on all samples with amylase > ULN
Prothrombin time (PT)	Calcium
Activated partial thromboplastin time (aPTT)	Phosphorus
Urinalysis:	Sodium
pH	Potassium
Specific gravity	Chloride
Glucose	Bicarbonate
Protein	Lactate dehydrogenase (LDH)
Ketones	Gamma glutamyl transferase (GGT)
Blood	**Misc:**
Bilirubin	Pregnancy test (urine or serum; women of child-bearing potential; at screening only)
Nitrite	
Leukocyte esterase	
Microscopic examination (if clinically indicated)	

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

[redacted]

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

4.5.8 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of *activities* (see Appendix 1), 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: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected using Fridericia's formula (QTcF) *(or Bazett's formula [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 study drug discontinuation should be made, as described in Section 3.1.4. 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).

4.5.9 Patient Daily Symptom Diary

Patients will use paper diaries to record symptom data (Nicholson et al. 2000; Treanor et al. 2000) (Appendix 6). *The investigator staff will provide* the paper diary and instructions for completing the symptom diary. The purpose of the diary is to record

any symptoms of influenza-like illness, symptom relief medications and temperature *(oral)*. The symptom diary card, symptom relief medications and temperature should be completed two times daily: when a patient first wakes up in the morning (before getting out of bed) and ~12 hours later up to Day 14 or until resolution of symptoms (defined as a total symptom score of 0–1 for 24 hours without use of symptom relief medications). Temperature should be taken before administration of acetaminophen/paracetamol and/or NSAIDs (see Section 4.4.1 for permitted medications). Patients should be encouraged to stay consistent with the diary schedule and sites should check that patients are able to take their temperature properly. Day 1 entry will be completed within 6 hours prior to start of study infusion.

Data from paper diaries will be entered into the EDC system by site staff.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 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/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/discontinue/are lost to follow-up may not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment during infusion if they experience any of the following:

- Life-threatening infusion-related reactions

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

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

4.6.3 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
- No study activity (i.e., all patients have completed *the study* and all obligations have been fulfilled)

4.6.4 Study Completion/Early Discontinuation

Patients who complete all study visits through Day 100 are considered to have completed the study. All patients who discontinue from the study early will be asked to complete all assessments for the *current day. If a patient discontinues after Day 7, only a telephone* visit *is required as the Early Discontinuation visit*. Please see Schedule of *Activities* provided in Appendix 1 for assessments performed at the Study Completion *and* Early Discontinuation visit.

4.7 ASSAY METHODS

Serum concentrations of MHAA4549A (pharmacokinetics) will be measured using validated quantitative immunoassays. ATA in serum will be measured using a validated bridging enzyme-linked immunosorbent assay (ELISA). Samples that are positive for ATA may be further characterized, depending on the safety profile and clinical data.

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. In addition, the safety plan is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

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.

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. All patients will be monitored for study drug reactions during administration and for at least 30 minutes after completion of study drug administration.

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/SOC agreement.

5.1.1 Risks Associated with MHAA4549A

There are no known risks associated with MHAA4549A based on *completed* Phase 1 (GV28916, GV29609) and Phase 2 (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. Screening, confirmatory, and characterization assay with appropriate sensitivity and therapeutic tolerance will be employed to assess *the prevalence of pre-existing* ATAs *to* MHAA4549A *in all study participants. Post-dosing ATAs to MHAA4549A will be measured in subjects with recurrent influenza infections*.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting 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 Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- 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 100 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:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the 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* 5.3.5.11)
- 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)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the 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 DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; see Section 5.3.3 and Appendix 4); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). 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 5.3.5.7)
- 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 adverse events 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, urticarial, 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: 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 Sections 5.4, 5.5, and 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 will be reported until study *completion* at the Day 100 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 3).

Table 3 Adverse Event Grading (Severity) Scale

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Estimating Severity Grade				
Clinical adverse events NOT identified elsewhere in this DAIDS Adverse Event Grading Table	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and 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

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 4):

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

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

Table 4 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., cancer diagnosed 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF 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).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded *on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., ≤24 hours after learning that the event became serious; see Section* 5.4.2 *for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.*

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

5.3.5.5 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 is verified by a repeat assessment and meets any of the following criteria:

- Is 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
- Is clinically significant in the investigator's judgment

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 $\times$ 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 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 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 is verified by a repeat assessment and meets any of the following criteria:

- Is 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).

5.3.5.7 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) 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 an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

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 influenza or any related co-morbidities should be recorded only 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 (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.

5.3.5.9 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 beyond that anticipated for the natural course of the condition. 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").

5.3.5.10 Lack of Efficacy or Worsening of Influenza A Infection

Medical occurrences or symptoms of deterioration that are anticipated as part of influenza A should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of influenza 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").

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)

- 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 for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available (e.g., requirement for outpatient care outside of normal outpatient clinical operating hours)

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

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 seriousness 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 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.

5.3.5.13 *Patient-Reported Outcome Data*

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

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)

- 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 Institutional Review Board (IRB)/Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

[redacted] **24-Hour Safety Hotline**

- North America: [redacted]
- EMEA/*APAC:* [redacted]

Genentech Medical Monitor contact information:

Primary Medical Monitor:	[redacted]
Telephone Nos.:	US Office: [redacted]
	US Mobile: [redacted]
Email Address:	[redacted]
Secondary Medical Monitor:	[redacted]
Telephone Nos.:	U.S. Office: [redacted]
	U.S. Mobile: [redacted]
Email Address:	[redacted]

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

Region	Fax Number	Email Address
North America	[redacted]	[redacted]
EMEA	[redacted]	[redacted]
Asia Pacific	[redacted]	[redacted]

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the patient *completes* the study at Day 100 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, the *paper Clinical Trial* Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided *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 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 exposed to study drug or the 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, 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 ADVERSE EVENTS *THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD*

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 100 days after study drug administration), 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. However, if the EDC system is not available,* the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- MHAA4549A Investigator's Brochure

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

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

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

The database will be cleaned and locked when all patients have completed the study (Day 100) or discontinued.

The primary objective of this study is to characterize the safety and tolerability of a single dose of MHAA4549A as compared to placebo when administered in otherwise healthy patients with acute uncomplicated seasonal influenza A. Statistical summaries will be descriptive in nature (e.g., means, standard deviations, and percentiles). Patients will be grouped according to treatment actually received, and any patients who receive any amount of MHAA4549A or placebo will be included in the analyses.

All secondary 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:

- Confirmation of influenza A from Day 1 pre-dose samples using a central PCR (to exclude false positives from local tests)

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

6.1 DETERMINATION OF SAMPLE SIZE

The planned sample size for this study is approximately 47 patients per treatment group. A total of approximately 141 patients will be enrolled in this study in order to obtain 120 evaluable patients (an estimated dropout rate of 15%).

The table below gives the probability of seeing an adverse event with a sample size of 40 per group. If the event occurs at a rate of $\geq 5\%$, the study has a $\geq 87\%$ chance of seeing at least 1 event in the dose group.

Table 5 Probability of Observing Adverse Events at Different Event Rates

Underlying "True Rate"	Probability of Seeing at Least 1 Event	Probability of Seeing at Least 2 Events
1%	33%	6%
5%	87%	60%
10%	99%	92%
15%	99%	98%

Note: Assumes that event rate follows a binomial distribution with p = AE rate and n = 40 patients/arm.

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 PRIMARY 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, 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. Serious adverse events 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.

The prevalence (baseline) of ATA will be reported and correlation with PK, safety, efficacy, and *biomarker* endpoints will be analyzed as data allow.

6.5 SECONDARY EFFICACY ANALYSES

The 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. Efficacy parameters to be evaluated include duration and severity of influenza symptoms, hospitalization, and influenza-related complications.

Time to event data will be analyzed using Kaplan-Meier methodology 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.

6.5.1 Secondary Endpoints

- Median time to alleviation of clinical signs and symptoms of influenza A infection
- Proportion of patients requiring hospitalization
- Median duration of hospitalization
- Proportion of patients with influenza-related deaths
- Proportion of patients requiring antibiotics for respiratory infection
- Proportion of patients with influenza secondary complications
- Proportion of patients with influenza re-infection

6.5.2 Exploratory Endpoints

- [redacted]

[redacted]

6.6 SUBGROUP ANALYSES

Subgroup analyses will be performed to examine the consistency of the treatment estimates with use of the endpoints. Subgroups will include the stratification factors. Additional subgroups may be added following assessment of baseline characteristics as exploratory analyses.

6.7 PHARMACOKINETIC ANALYSES

Individual and mean serum MHAA4549A concentration versus time data will be tabulated and plotted. The serum PK of MHAA4549A will be summarized by estimating total serum drug exposure (i.e., AUC), $maximum$ concentration (C_{max}), 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.

Additional PK analyses, such as population PK, may be conducted as appropriate and reported separately. Potential correlations between relevant PK parameters and safety or efficacy outcomes, as well as other covariates, may also be explored and reported separately.

6.8 EXPLORATORY ANALYSES

[redacted]

[redacted]

6.8.1 ***Biomarker Analyses***

[redacted]

[redacted]

6.9 *IMMUNOGENICITY ANALYSES*

The immunogenicity analyses will be limited to testing of predose samples from all patients enrolled in the study. No post-dose samples will be collected (except for Day 7 in the case of recurrent influenza).

The number of ATA-positive patients at baseline will be determined, which will provide an estimate of the prevalence of pre-existing ATAs in this patient population. [redacted]

No additional immunogenicity assessments are planned for this study.

6.10 INTERIM ANALYSES

6.10.1 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 1 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.

Data from paper diaries will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

At the end of the study, the investigator will receive patient 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 PATIENT-REPORTED DAILY SYMPTOM DATA

Data from paper diaries will be entered into the EDC system by site staff.

7.4 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 7.6.

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/EC review. The study site must also allow inspection by applicable health authorities.

7.5 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.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper diaries, 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 Good Clinical Practice 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. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

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

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative 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/EC-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/EC policy) during their participation in the study. For any updated or revised

Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

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/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

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

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each 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 Informed Consent Form (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 complexity and exploratory nature of the 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/EC 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/EC 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/EC in accordance with established IRB/EC 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/ECs 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, medical monitoring, site management, data quality support, safety reporting, and regulatory activities as specified in the 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 *permuted block* 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.

Data reported by patients regarding their symptoms, body temperature, and any use of acetaminophen/paracetamol and/or NSAIDs will be captured using paper diaries.

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 on 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 Web site:

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/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to 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 1
Schedule of *Activities*

	Screening (-72 hours to 0 hours)	D1[a] (Randomization)	D2	D3	D4	D5	D6	D7 (±1)	D8-13	D14 (±2)	D30 (±7)	*D100 (±7)*	Unscheduled Visit	Early Discontinuation
Informed consent[b]	x													*Complete all assessments for the current day. If a patient discontinues early after Day 7, only a telephone visit is required as the Early Discontinuation visit.*
Rapid PCR test or rapid antigen test[c]	x													
Inclusion/exclusion criteria	x													
Medical history and demographics	x													
Seasonal influenza vaccine history	x													
Confirm onset flu symptoms	x													
Pregnancy screening[d]	x													
Concomitant medications[e]	x	x	x	x	x	x	x	x	x	x	x	x	x	
Vital signs[f]	x	x		x				x					x	
Electrocardiogram (12-lead)[g]	x	x[h]		x				x					*(x)*	
MHAA4549A/Placebo administration[i]		x												
Complete physical examination[j]	x												*(x)*	
Limited, symptom-directed physical examination/symptom assessment[k]		x		x				x					x	
Weight and height[l]	x	x		x				x					(x)	
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	
Hematology[m]	x			x				x					*(x)*	
Chemistry panel[m]	x			x				x					*(x)*	
Coagulation panel [m]		*x*												
Urinalysis [n]	x			x				x					*(x)*	
[redacted]		x		x		x		x					*(x)*	

Appendix 1 (cont'd)
Schedule of *Activities*

	Screening (-72 hours to 0 hours)	D1[a] (Randomization)	D2	D3	D4	D5	D6	D7 (±1)	D8-13	D14 (±2)	D30 (±7)	*D100 (±7)*	Unscheduled Visit	Early Discontinuation
Influenza antibodies (HAI)[p]		x						*x*						*Complete all assessments for the current day. If a patient discontinues early after Day 7, only a telephone visit is required as the Early Discontinuation visit.*
Anti-MHAA4549A antibodies (ATA)[p]		x												
Serum for MHAA4549A PK measurements[q]		x		x		x		x					(x)	
[redacted]		x		x		x		x					(x)	
Telephone visit to assess safety			x							x	*x*	*x*		
Symptom Diary[r]		x	x	x	x	x	x	x	x	x				

AE=adverse event; D=day; HAI=hemagglutinin inhibition; PCR=polymerase chain reaction; PK=pharmacokinetic.

Notes: Days 1, 3, 5, 7, *unscheduled (shaded), and early discontinuation (if applicable)* will be clinic visits.

Xs within parentheses, i.e., (X), indicate optional assessments.

Patients who are unable to return to the clinic should be contacted by phone to: 1) ascertain health status, 2) record adverse event information, and 3) ask that the diary be completed and returned.

[a] All assessments on Day 1 should be performed prior to study drug administration.

[b] Informed consent must be obtained from all patients.

[c] Sample collection may involve a nasal swab or a nasopharyngeal swab, depending on the diagnostic platform *at the site.*

[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 48 hours 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] Concomitant medications should be recorded for 30 days prior to screening, through the study completion/early discontinuation visit. See exclusion criteria for prohibited therapies. Patients should report to study site all concomitant medications taken at home.

[f] Vital signs will be collected within 1 hour before MHAA4549A infusion and within 1 hour after completion of MHAA4549A infusion and include temperature *(oral)*, 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. Temperature, blood pressure, respiratory rate, and heart rate will be completed after the patient has been in a seated or supine position for at least 5 minutes.

[g] Patient should rest in a supine position for 10 minutes prior. If screening ECG is taken within 1-3 hours pre-dose, Day 1 pre-dose ECG does not need to be taken.

[h] On Day 1, ECG must be taken within 1-3 hours pre-dose and 1-3 hours post-dose.

[i] All patients will be monitored for study drug reactions during administration and for at least 30 minutes after completion of study drug administration.

[j] 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.

[k] 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.

[l] Height will be obtained at screening only. Weight will be obtained at all indicated visits (pre-infusion on Day 1). Height and weight will be recorded in centimeters and kilograms, respectively

[m] Local laboratory measurements should be utilized. Hematology *and* chemistry panel at screening must be collected within 36 hours prior to study drug administration. Lipase will be reflexively assessed on all samples with amylase >ULN.

[n] *Urinalysis at screening must be collected within 36 hours prior to study drug administration.* 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. *Screening sample will be collected locally. Day 3, 7 and unscheduled samples will be collected locally and centrally.*

[q] Day 1 serum PK samples are to be drawn *within* 30 (± 5) minutes pre-dose of MHAA4549A, and 60 (± 15) minutes after the end of infusion. On Days 3, *5,* 7 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.

Appendix 1 (cont'd)
Schedule of *Activities*

[r] The symptom diary and temperature *(oral)* should be completed two times daily: when *the study subject* first wake*s* up in the morning (before getting out of bed) and about 12 hours later, up to Day 14 or until resolution of symptoms (defined as a total symptom score of 0-1 for 24 hours without use of symptom relief medications). Temperature should be taken before administration of acetaminophen/paracetamol and/or NSAIDs. Day 1 entry will be completed within 6 hours prior to start of study infusion.

Appendix 2
Schedule of *Activities* for Recurrent Influenza

	Confirm Influenza A Day -3 to Day 1	D1	D2	D3	D4	D5	D6	D7 (±1)	D8-13	D14 (±2)
Rapid antigen test (RAT) or PCR test[a]	x									
Confirm onset of recurrent flu symptoms	x									
Concomitant medications[b]		x	x	x	x	x	x	x	x	x
Vital signs[c]		x		x				x		
Electrocardiogram (12-lead)[d]		x		x				x		
Complete physical examination[e]		x								
Limited, symptom-directed physical examination/symptom assessment[f]				x				x		
Weight[g]		x		x				x		
Adverse events		x	x	x	x	x	x	x	x	x
Hematology[h]		x		x				x		
Chemistry panel[h]		x		x				x		
Coagulation panel[h]		x		x				x		
Urinalysis[i]		x		x				x		
[redacted]		x		x		x		x		
Anti-MHAA4549A antibodies (ATA)								*x*		
Serum for MHAA4549A PK measurements								*x*		
Telephone visit to assess safety			x							x
Symptom Diary[k]		x	x	x	x	x	x	x	x	x

AE=adverse event; D=day; NSAID=non-steroidal anti-inflammatory drug; PCR=polymerase chain reaction; RAT=rapid antigen test; RBC=red blood cell; WBC=white blood cell.

Notes: Days 1, 3, 5, 7 (shaded) will be clinic visits.

Patients with RECURRENT influenza symptoms between Day 14 and Day 100 [defined by at least 1 constitutional symptom (headache, myalgias, fever, chills, fatigue, anorexia, nausea and 1 respiratory symptom (cough, sore throat, rhinorrhea)] will be evaluated for 14 days. These patients must still complete *telephone* follow-up visits at Days 30 and 100 from initial randomization (see Appendix 1):

Appendix 2 (cont'd)
Schedule of *Activities* for Recurrent Influenza

Confirm influenza A (+ or -).

If either the RAT or PCR is positive, the patient will follow the schedule of *activities* and start at Day 1. If the patient tests negative by RAT, the results will be confirmed by RT-PCR. The patient will follow the assessments in Appendix 2, until a negative PCR result for influenza is confirmed.

[a] Sample collection may involve a nasal swab or a nasopharyngeal swab, depending on the diagnostic platform *at the site.*

[b] See exclusion criteria for prohibited therapies

[c] Vital signs include temperature *(oral)*, 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. 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.

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

[e] 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.

[f] 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.

[g] Weight will be recorded in kilograms.

[h] Local laboratory measurements should be utilized, Lipase will be reflexively assessed on all samples with amylase > ULN.

[i] 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. *Day 1, 3, 7 samples will be collected locally and centrally.*

[j] [redacted]

[k] The symptom diary and temperature *(oral)* should be completed two times daily: when you first wake up in the morning (before getting out of bed) and about 12 hours later, up to Day 14 or until resolution of symptoms *(defined as a total symptom score of 0-1 for 24 hours without use of symptom relief medications)*. Temperature should be taken before administration of acetaminophen/paracetamol and/or NSAIDs.

Appendix 3
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 3 (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

g = gram; IV = intravenous.

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 4
DAIDS Toxicity Grading Tables for Laboratory Abnormalities [a]

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 g/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 × ULN	1.26–1.50 × ULN	1.51–3.0 × ULN	> 3 × ULN
Activated Partial Thromboplastin Time (APTT)	1.01–1.66 × ULN	1.67–2.33 × ULN	2.34–3 × ULN	> 3 × ULN
Methemoglobin	5.0–9.9%	10.0–14.9%	15.0–19.9%	> 20.0%

ADL = Activities of Daily Living; CPK = creatine phosphokinase; Dec = Decreased; dl = deciliter; g = gram; IV = Intravenous; LLN = Lower limit of normal; mcg = microgram; mm = millimeter; Mod = Moderate; Req = Required; Rx = Therapy; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = Upper limit of normal.

[a] 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

Appendix 4 (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

Appendix 4 (cont'd)
DAID Toxicity Grading Tables for Laboratory Abnormalities

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1– < 1.25 × ULN	1.25– < 1.5 × ULN	1.5–1.75 × ULN	> 1.75 × 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 × ULN	> 3.0 × ULN

dL = deciliter; L = liter; mEq = milliequivalent; mg = milligram; ULN = upper limit of normal.

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

ALT = alanine transaminase; AST = aspartase transaminase; CPK = creatine phosphokinase; dl = deciliter; GGT = Gamma-glutamyl transferase; mg = milligram; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal.

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

g = gram; hpf = high power field; mg = milligram; RBC = red blood cell.

Appendix 5
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 6
Adult Patient Symptom Diary

This diary will keep track of your flu symptoms and temperature during the study. You should complete it 2 times a day: when you first wake up in the morning (before getting out of bed) and about 12 hours later. Remember to take your temperature before you take any medicines to help your flu symptoms.

Please rate each symptom based on how you feel right now.

Symptom	None 0	Mild 1	Moderate 2	Severe 3
1. Nasal Congestion				
2. Sore Throat				
3. Cough				
4. Aches and Pains				
5. Fatigue (tiredness)				
6. Headache				
7. Chills/sweats (feverish)				

Appendix 6 (cont'd)
Adult Patient Symptom Diary

Temperature:

Please take your temperature now.

What is your temperature right now? (Measure before taking fever medication): _____

(Choose °C or °F)

Did you measure a temperature >38.0°C (100.4°F) in the past 12 hours?

____*Yes*

____*No*

*What was the time and temperature?:*_____

Medications for relief:

Please look at your "allowed medication" wallet card. It shows the most common names of these medications (i.e., acetaminophen/paracetamol, ibuprofen, other NSAIDs)

Have you taken any of these "allowed medications" to help your flu symptoms in the past 12 hours?

____Yes

____No